PO Box 2345, Beijing 100023, China
www.wjgnet.com
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REVIEW

Oncological problems in pancreatic cancer surgery

Akimasa Nakao, Tsutomu Fujii, Hiroyuki Sugimoto, Naohito Kanazumi, Shuji Nomoto, Yasuhiro Kodera, Soichiro Inoue, Shin Takeda

Akimasa Nakao, Tsutomu Fujii, Hiroyuki Sugimoto, Naohito Kanazumi, Shuji Nomoto, Yasuhiro Kodera, Soichiro Inoue, Shin Takeda, Department of Surgery Ⅱ, Nagoya University Graduate School of Medicine, Nagoya, Japan
Correspondence to: Professor Akimasa Nakao, MD, PhD, FACS, Professor and Chairman of Department of Surgery II, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. nakaoaki@med.nagoya-u.ac.jp
Telephone: +81-52-7442232 Fax: +81-52-7442255
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Abstract

Despite the development of more sophisticated diagnostic techniques, pancreatic carcinoma has not yet been detected in the early stage. Surgical resection provides the only chance for cure or long-term survival. The resection rate has increased due to recent advances in surgical techniques and the application of extensive surgery. However, the postoperative prognosis has been poor due to commonly occurring liver metastasis, local recurrence and peritoneal dissemination. Recent molecular-biological studies have clarified occult metastasis, micrometastasis and systemic disease in pancreatic cancer. Several oncological problems in pancreatic cancer surgery are discussed in the present review.

Key words: Pancreatic cancer; Extended resection; Molecular diagnosis; Micrometastasis; Adjuvant therapy

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INTRODUCTION

Over the past 30 years, the number of deaths in Japan due to pancreatic carcinoma has steadily increased from 4400 to 19 000[1] (Figure 1). It is the fifth most common cause of death due to malignant neoplasms (Figure 1). Regional pancreatectomy for carcinoma of pancreatic head region, introduced by Fortner[2] in 1973, has impressed many Japanese pancreatic surgeons. Consequently, the resection rate has gradually improved, but the postoperative prognosis is still poor in spite of the development of diagnostic modalities such as CT-scan, EUS, MRI and PET. In 1980, the Japan Pancreas Society (JPS) published the first edition of its "General Rules for Surgical and Pathological Studies on Cancer of the Pancreas". The fifth edition was published in 2002. The second English edition was published in 2003[3]. The JPS also started a registration system for pancreatic carcinoma in 1981. According to the data of JPS, the 5-year survival of invasive ductal carcinoma of the pancreas after pancreatectomy is only 13.4%[4] (Figure 2). JPS and UICC stage of invasive cancer and survival after pancreatectomy are shown in Figure 3[4]. Comparison of survival curves according to the stage reveals that stratification is much better in the JPS classification than in UICC classification.

In 1981, we developed an antithrombogenic bypass catheter for the portal vein to decompress portal congestion or prevent hepatic ischemia caused by simultaneous resection of portal vein and hepatic artery[5]. Since then, we have been aggressively performing extensive surgical resections including portal vein resection by the non touch isolation technique[7,8] using this bypass method. The resection rate has been elevated and operative mortality has remarkably decreased. However, the postoperative prognosis is still poor due to high recurrence rate. The problems of surgical therapy for pancreatic cancer are discussed in this review.

ONCOLOGICAL PROBLEMS

Intrapancreatic carcinoma development

The indications for total pancreatectomy or pancreatoduodenectomy in pancreatic head cancer are one of the key problems in pancreatic cancer surgery. It is very important to know how the carcinoma has developed from the pancreatic head to the body or tail. A high incidence of development or multicentricity of the carcinoma of the pancreatic head to the body or tail has been reported[9,10]. However, recent histopathological and immunocytochemical analysis of total pancreatectomy specimens have clarified that carcinoma development from head to body or tail is continuous[11-13]. Therefore, intraoperative quick histopathological diagnosis combined with immunohistochemical staining using frozen section can diagnose intrapancreatic carcinoma development more precisely[14,15].

Table 1 Comparative studies of extended versus standard operation for pancreatic cancer

Author	Yr	Results
Ishikawa *et al*[24]	1988	Retrospective study [standard (n = 37): 9%, 5-Y-S extended (n = 22): 28%, 5-Y-S
Mukaiya *et al*[25]	1998	Retrospective study 77 institutions, 501 patients: NS
Henne-Bruns *et al*[26]	2000	Retrospective study [standard (n = 26) extended (n = 46)] NS
Pedrazzoli *et al*[27]	1998	RCT [standard (n = 40) extended (n = 41) overall survival: NS survival of node positive patients: extended > standard
Yeo *et al*[28]	2002	RCT [standard (n = 146) extended (n = 148) mortality: NS, morbidity: extended > standard, survival: NS

RCT: Randomized controlled test; NS: Not significant.

Lymph node metastasis

Lymph node dissection is one of the important components in pancreatic cancer surgery. The high incidence of 56%[16], 70.5%[17], 73%[18], 76%[19], 77%[20], and 86.4%[21] in resected specimen of pancreatic cancer is the reason for wide dissection of lymph nodes in pancreatic cancer surgery. There are few reports about precise para-aortic lymph node metastasis. The incidence of para-aortic lymph node metastasis for pancreatic head carcinoma is reported to be 16% (7/44)[17] and 26% (23/90), respectively[20]. The incidence of pancreatic body and tail carcinoma is 13% (4/30)[22] and 17% (4/27)[21], respectively. The lymphatic flow from the pancreatic head tumor to the para-aortic lymph node via the posterior surface of the pancreatic head and around the superior mesenteric artery has been suspected[17,18,23].

The efficacy of extended lymph node dissection in pancreatic cancer surgery has been suggested in a retrospective study[24]. However, the efficacy of extended lymph node dissection has not been clarified in retrospective studies[25,26] or in recent prospective randomized controlled tests for pancreatic cancer surgery (Table 1)[27,28].

The incidence of perigastric lymph node metastasis in pancreatic cancer is relatively low[20]. Therefore, pylorus preserving pancreatoduodenectomy (PPPD) is indicated for pancreatic head carcinoma, although its advantage over the classic Whipple operation has not been clarified[29,30].

Vascular invasion

Portal vein resection is another problem in pancreatic cancer surgery. To prevent portal congestion in portal vein resection and hepatic ischemia in simultaneous resection of portal vein and hepatic artery, we developed a catheter-bypass procedure[5,6] in our department in 1981 using antithrombogenic catheter, and isolated pancreatectomy combined with portal vein resection has thus been established[8]. During the past 30 years, the operative mortality rate of pancreatoduodenectomy combined with portal vein resection has decreased, and portal vein resection in pancreatic cancer surgery has become a safe operative procedure. The reported mortality rate is 7.4% (2/27)[31], 10% (6/63)[32], 5% (3/58)[33], 0% (0/31[34], 0/14[35], 0/34[36], 0/24[37]), and 3.2% (1/31)[38]. From 1981 to 2003, 250 of 391 (63.9%) patients with pancreatic carcinoma underwent tumor resection in our department. Portal vein resection was performed in 171 of these 250 (68.4%) resected cases, and the mortality rate was 4.4% (11/250)[39]. The indication and contraindication for portal vein resection have not yet been clarified in pancreatic cancer surgery. There are many reports about the benefit[33,34,40] or no benefit[41] of portal vein resection for curative resection or survival. The most important indication for portal vein resection in pancreatic cancer is the ability to obtain cancer-free surgical margins[39].

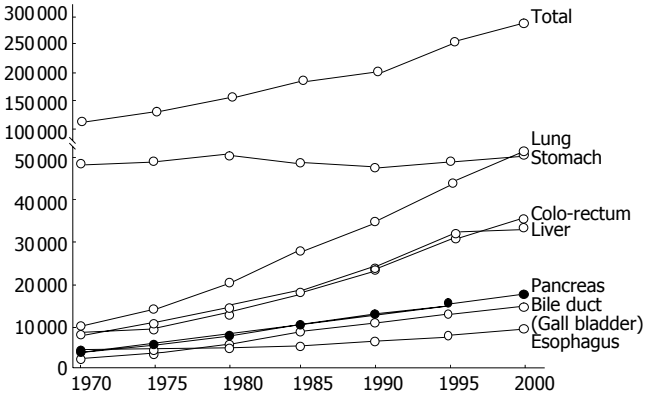

Figure 1 Trends in death due to malignant neoplasms in Japan.

In severe portal invasion cases, it is difficult to obtain cancer-free surgical margins, so the prognosis is poor[39,42-44]. A recent diagnostic modality using intraportal endovascular ultrasonography provides precise information about the relationship between the pancreatic cancer and the portal vein wall, and planning of the operative procedure[45-47].

Extrapancreatic nerve plexus invasion

Pancreatic carcinoma often invades the extrapancreatic nerve plexus[48-51]. There is continuity of the intrapancreatic neural invasion into the extrapancreatic nerve plexus[48]. The grade of intrapancreatic neural invasion correlates with the extrapancreatic nerve plexus invasion[50,51] and the manner of neural invasion has no relationship with the behavior of lymph node metastasis[50].

In pancreatic head carcinoma, complete dissection of extrapancreatic nerve plexus , especially the second portion of pancreatic head nerve plexus and nerve plexus around the superior mesenteric artery, is sometimes necessary to obtain a carcinoma-free surgical margin. However, complete resection of the nerve plexus around

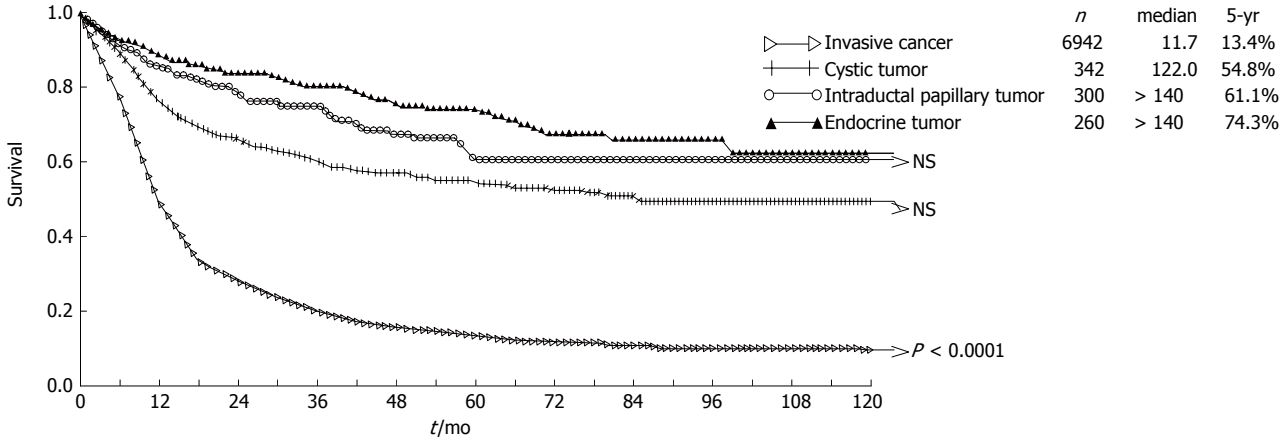

Figure 2 Histology and survival after pancreatectomy. Survival of patients who underwent pancreatectomy is shown. NS, not significant.

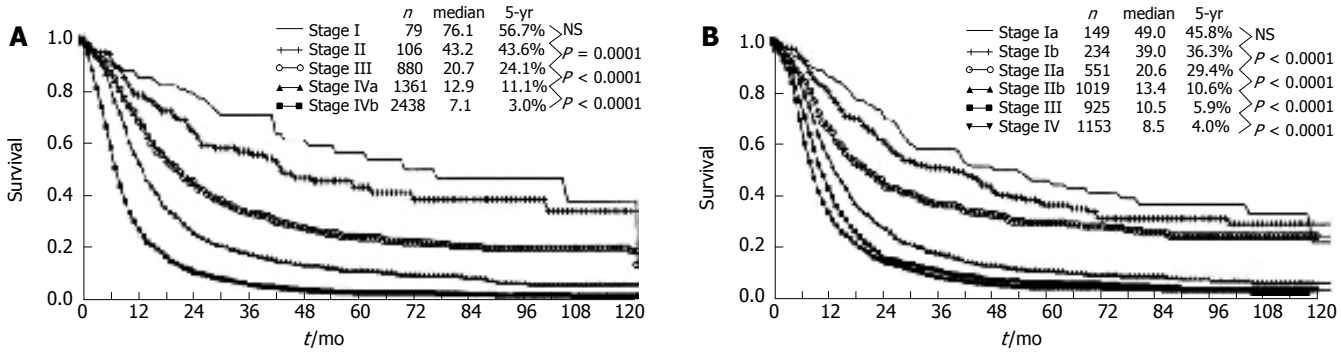

Figure 3 Survival after pancreatectomy according to JPS stage (**A**) and UICC stage (**B**). NS, not significant.

the superior mesenteric artery causes severe diarrhea after surgery, and the prognosis of positive carcinoma invasion to the extrapancreatic nerve plexus cases is very poor[39,50,51]. The greatest cause of carcinoma-positive surgical margin is extrapancreatic nerve plexus carcinoma invasion[39,48,50]. Recently, carcinoma invasion to the second portion of the pancreatic head nerve plexus can be diagnosed using intraportal endovascular ultrasonography[45-47,52]. In our department, if patients have no carcinoma invasion to the second portion of the pancreatic head nerve plexus, the left semi-circular nerve plexus around the superior mesenteric artery is preserved to prevent postoperative diarrhea.

Postoperative recurrence

Even in extended surgery, a high incidence of postoperative liver metastasis, local recurrence, and peritoneal metastasis has been observed with a poor postoperative prognosis (Table 2)[53-57]. The precise diagnosis of recurrence type is difficult even if modern diagnostic modalities are used. However, the local recurrence was 100% and the liver metastasis was 80% in 25 autopsy cases[55]. The first cause of poor postoperative prognosis in pancreatic cancer is liver metastasis. Although occult liver metastasis may be suspected on the basis of extensive clinical data, no criteria have been definitely determined. Surgical therapy combined with effective adjuvant therapy is necessary in view of these types of recurrence.

Adjuvant therapy

Surgical therapy currently offers the only potential cure for pancreatic cancer. However the recurrence rate is very high and the long-term survival is poor.

The potential benefit of adjuvant therapy after resection of pancreatic cancer was first recognized by the randomized trial conducted by the Gastrointestinal Tumor Study Group (GITSG) using chemoradiotherapy almost 20 years ago[58,59]. Since then, few randomized trials have shown a benefit of adjuvant treatment (Table 3)[60-65]. The study of the European Study Group for Pancreatic Cancer (ESPAC-1) concluded that postoperative chemotherapy with fluorouracil plus leucovorin confers a benefit in terms of survival, whereas postoperative chemoradiotherapy has a deleterious effect on survival[64]. The current study by Neuhaus *et al*[65] indicates that the treatment with gemcitabine in patients with resected pancreatic cancer can result in improved disease-free survival as compared to observation.

A new and more effective adjuvant therapy must be established by prospective randomized trials using newly developed drugs[66,67] or therapeutic modalities[68]. Nevertheless, the individualized adjuvant therapy is very important in pancreatic cancer treatment[69,70].

Occult metastasis and micrometastasis

Recent progress in immunohistochemistry and molecular biological studies has made it possible to clarify the occult metastasis and micrometastasis in pancreatic cancer. The

Table 2 Incidence of postoperative recurrence in pancreatic cancer

Author	Yr	Cases (*n*)	Liver (%)	Local (%)	Peritoneal (%)	Bone (%)	Lung (%)	Other (%)
Westerdahl *et al*[53]	1993	74	92	86.5				
Kayahara *et al*[54]	1993	30	60	83.3	40			
Takahashi *et al*[55]	1995	25	80	100	56	24	56	
Sperti *et al*[56]	1997	78	62	72	6			
Nakao *et al*[57]	1997	76	57	34	41	3	1	1

Table 3 Randomised controlled trials of adjuvant treatment for pancreatic ductal adenocarcima

Trial	Comparison	Adjuvant treatment	Number of patients	Conclusions
GITSG, 1985[58], 1987[59]	CRT *vs* OBS	2 × (20 Gy in 10 fractions + 500 mgm^{-2} 5FU d 1-3) + weekly 5FU to recurrence	49 pancreatic patients randomised	Significant increase in median survival (20 *vs* 11 mo, $P = 0.035$) in 43 eligible patients
Norway, 1993[60]	CT *vs* OBS	AMF (40 mgm^{-2} doxorubicin, 6 mgm^{-2} mytomycin C, 500 mgm^{-2} 5FU) once every 3 wk for six courses	61 patients (47 pancreatic, 14 ampullary) randomised 46 additional nonrandomised patients	Significant increase in median survival (23 *vs* 11 mo, $P = 0.02$) in 60 pancreatic and ampullary patients combined
EORTC, 1999[61]	CRT *vs* OBS	2 × (20 Gy in 10 fractions + 25 $mgkg^{-1}$ 5FU/FA d 1-5)	218 patients (120 pancreatic, 93 ampullary) randomised	NS increase in median survival (25 *vs* 19 mo, $P = 0.21$) in 207 eligible patients NS increase in median survival in 114 eligible pancreatic patients (17 *vs* 13 mo, $P = 0.099$)
Japan, 2002[62]	CT *vs* OBS	6 mgm^{-2} mytomycin C d 1 + 310 mgm^{-2} 5FU d 1-5 and d 15-20 followed by 100 mgm^{-2} oral 5FU daily until recurrence	508 patients (173 pancreatic, 335 bile duct/gallbladder/ ampullary) randomised	Significant survival benefit in gallbladder No difference in 158 eligible pancreatic patients No difference in 48 eligible ampullary patients
ESPAC1, 2001[63], 2004[64]	CRT *vs* no CRT CT *vs* no CT	2 × (20 Gy in 10 fractions + 500 mgm^{-2} 5FU/FA d 1-3) (20 mgm^{-2} FA + 425 mgm^{-2} 5FU d 1-5) × six cycles	289 pancreatic patients randomised	NS decrease in survival for CRT ($P = 0.05$) in 289 patients Significant increase in survival for CT ($P = 0.009$) in 289 eligible patients
CONKO-001, 2005[65]	CT *vs* OBS	1 gm^{-2} GEM, d 1, 8, 15, every 4 wk for 6 mo	368 pancreatic patients randomised	Significant increase in median DFS (14.2 *vs* 7.5 mo, $P < 0.05$) in 356 eligible patients

CRT: Chemoradiotherapy; CT: Chemotherapy; OBS: Observation; NS: Not significant; DFS: Disease-free survival.

Table 4 Incidence of pancreatic cancer cells in peripheral blood, bone marrow, and liver tissue

Author	Yr	Incidence
Tada *et al*[71]	1993	Peripheral blood, K-*ras* 2/6 (33%)
Juhl *et al*[72]	1994	Bone marrow, immunostaining: 15/26 (58%)
Inoue *et al*[73]	1995	Liver tissue, K-*ras*: 13/17 (76%)
Nomoto *et al*[74]	1996	Peripheral blood, K–*ras*: postoperative period 10/10 (100%)
Funaki *et al*[75]	1996	Peripheral blood, CEAmRNA: 3/9 (33%)
Aihara *et al*[76]	1997	Peripheral blood, Keratin 19m RNA: 2/38 (5%)
Miyazono *et al*[77]	1999	Peripheral blood, CEAmRNA: 13-21 (61.9%)
Uemura *et al*[78]	2004	Peripheral blood, K-*ras*: 9/26 (35%)

Table 5 Reports of occult lymph node metastasis

Author	Yr	Results
Tian *et al*[79]	1992	HE: 8/56 (14%) Cytokeratin: 17/56 = (30%)
Ando *et al*[80]	1997	K-*ras*: paraaortic lymph nodes: 42/101 (42%)
Demeure *et al*[81]	1998	K-*ras*: Stage I (T1-2, N0, M0) 16/22 (73%)
Yamada *et al*[82]	2000	K-*ras* (-) has a better prognosis than K-*ras* (+)
Bogoevski *et al*[83]	2004	Ber–EP4: immunostaining 56/148 (37.8%)

Table 6 Incidence of occult peritoneal dissemination

Author	Yr	Results
Lei *et al*[84]	1994	Peritoneal washings, conventional cytology, 3/36 (8%), 1/11 (9%) with ascites
Juhl *et al*[72]	1994	Immunostaining (CEA, CA19-9,…, cytokeratin bone marrow 58%, peritoneal washings 58%
Vogel *et al*[85]	1999	Peritoneal washings 39%, bone marrow 38%, one of them positive: died within 19 mo, both negative: 5 y.s. 30% ($P < 0.0001$)
Castillo *et al*[86]	1995	Laparoscopy 16/94 (17%)
Leach *et al*[87]	1996	4/60 (7%)
Nomoto *et al*[88]	1997	Conventional: 0/18 (0%), immunostaining (CEA, CA19-9): 2/18 (11%)
Nakao *et al*[89]	1999	Conventional: 5/66 (8%), immunostaining 14/66 (22%) prognosis between cytology positive and negative: NS

high incidence of K-*ras* point mutation of codon 12 in pancreatic cancer has been observed. Occult pancreatic cancer cells have been detected in peripheral blood, bone marrow and liver by studies of K-*ras*, CEA mRNA, keratin 19 mRNA, along with immunocytochemical staining (Table 4)[71-78].

Occult lymph node metastasis in pancreatic cancer has been also detected by the studies of K-*ras* and immunostaining of cytokeratin or Ber-FP4 (Table 5)[79-83].

The incidence of cancer cells from abdominal washing cytology is shown in Table 6[84-89]. The incidence using conventional staining is 0%-17% (Table 6)[84,86-89]. However

a high incidence of 58%[72], 39%[85], and 22%[89] by immunocytochemical staining using monoclonal antibodies against tumor-associated antigens and cytokeratins has been reported. The difference in prognosis between positive and negative occult metastases remains controversial.

CONCLUSION

Surgical techniques for pancreatic cancer have been developed, and the resection rate has increased in Japan over the past 30 years. However, the prognosis of stage IV patients with pancreatic cancer is still poor even after aggressive surgery because of its high recurrence rate. Occult metastasis and micrometastasis have been more precisely diagnosed by immunocytochemical and molecular biological studies. On the basis of such data, adjuvant multimodal therapies targeting occult metastasis and micrometastasis with radical surgery are recommended. The effectiveness of these adjuvant multimodal therapies must be clarified and more effective adjuvant therapies must be developed.

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