

## ONCOLOGICAL PROBLEMS IN PANCREATIC CANCER SURGERY

AKIMASA NAKAO

*Department of Surgery II, Nagoya University School of Medicine*

### ABSTRACT

Despite the development of more sophisticated diagnostic techniques, it remains difficult to detect pancreatic carcinoma in the early stage. The resection rate has been increasing 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. Recent molecular-biological studies have been clarifying occult liver metastasis and systemic disease in pancreatic cancer. This paper will review our experience and several problems in pancreatic cancer surgery.

Key Words: pancreatic cancer, surgery, pancreatoduodenectomy, *K-ras*, isolated pancreatectomy

### INTRODUCTION

Pancreatic cancer is the fifth most common cause of death by malignant neoplasm in Japan.<sup>1)</sup> The number of deaths in Japan due to pancreatic cancer has steadily increased, reaching 17,000 in 1996.<sup>1)</sup> After the first successful pancreatoduodenectomy by Whipple et al.,<sup>2)</sup> many kinds of reconstruction of the alimentary tract after pancreatoduodenectomy have been reported.<sup>3-5)</sup> However, the resection rate and prognosis in cases of pancreatic cancer have been very low and poor. The regional pancreatectomy introduced by Fortner<sup>6)</sup> impressed many Japanese pancreatic surgeons. Consequently, the resection rate has gradually improved, but the postoperative prognosis is still poor. This paper introduces our experience and recent advances in molecular-biological studies in pancreatic cancer.

#### Isolated Pancreatectomy

In 1981, we developed an antithrombogenic bypass catheter for the portal vein to decompress portal congestion or prevent hepatic ischemia caused by portal vein resection or simultaneous resection of the hepatic artery.<sup>7,8)</sup> Since then, we have been aggressively performing extensive surgical resections, including portal vein resection by the non-touch isolation technique<sup>9,10)</sup> using this bypass method accompanied by extensive lymph node dissection and extrapancreatic nerve plexus dissection.

From 1981 to 1998, 182 patients with duct cell carcinoma of the pancreas underwent surgical resection. Portal vein resection was performed in 126 (69%) of these 182 cases. The cumulative survival rates including operative and hospital deaths according to conclusive stage<sup>11)</sup> are shown in Figure 1. Postoperative prognosis of stage I and II is relatively good, but that of

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All correspondence to: Akimasa Nakao, Department of Surgery II, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan, TEL 052-744-2232, FAX 052-744-2255

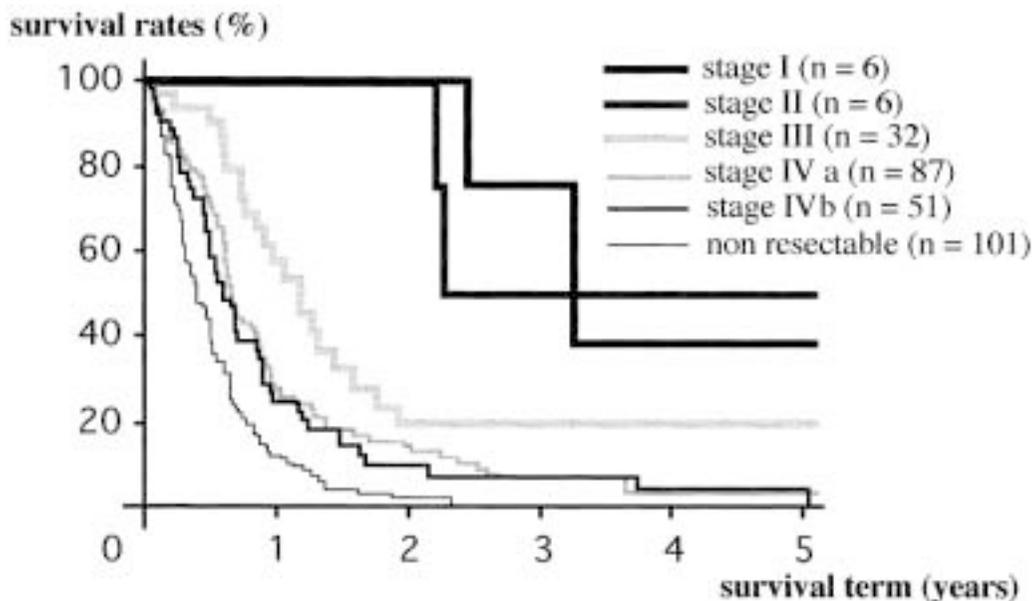


Fig. 1. Survival rate for pancreatic cancer after surgical resection according to Japan Pancreas Society staging classification

stages IVa and IVb is poor in spite of aggressive surgery. The most important problem is that the 75% of the resected cases belong to the advanced stages IVa or IVb.

#### Histopathological and Immunohistochemical Studies of Resected Specimens

Indication for total pancreatectomy or pancreatoduodenectomy in pancreatic head cancer is one of the key problems in pancreatic cancer surgery. It is very important to know how the carcinoma developed from the pancreatic head to the body or tail. However, it is very difficult to diagnose intrapancreatic carcinoma development before an operation. Thus, the operative quick pathological diagnosis using frozen sections is very important. However, due to poor fixation and abundant fibrous connective tissues, an intraoperative quick pathological diagnosis using conventional H&E staining of fresh frozen sections cannot always detect small cancer nests. In our series using total pancreatectomized specimens of pancreatic head carcinoma, carcinoma development from head to body or tail was clarified as continuous by the conventional pathological diagnosis using H&E staining combined with immunohistochemical staining using anticarcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9.<sup>12,13</sup> Intraoperative quick immunostaining<sup>14,15</sup> combined with conventional quick pathological diagnosis can diagnose intrapancreatic carcinoma development more precisely. We have been trying to preserve the pancreatic body and tail if intrapancreatic carcinoma development from head to body or tail is not observable.<sup>10</sup>

The cumulative survival rates according to lymph node metastasis are shown in Figure 2. The survival rates of the negative lymph node metastasis ( $n_0$ ) group were significantly higher than those of the positive lymph node metastasis groups ( $n_1$ ,  $n_2$ , and  $n_3$ ). The incidence of paraaortic lymph node metastasis was 26%<sup>16</sup> in pancreatic head carcinoma and 13%<sup>17</sup> in pancreatic body and tail carcinoma. Perigastric lymph node metastasis in pancreatic head carcinoma

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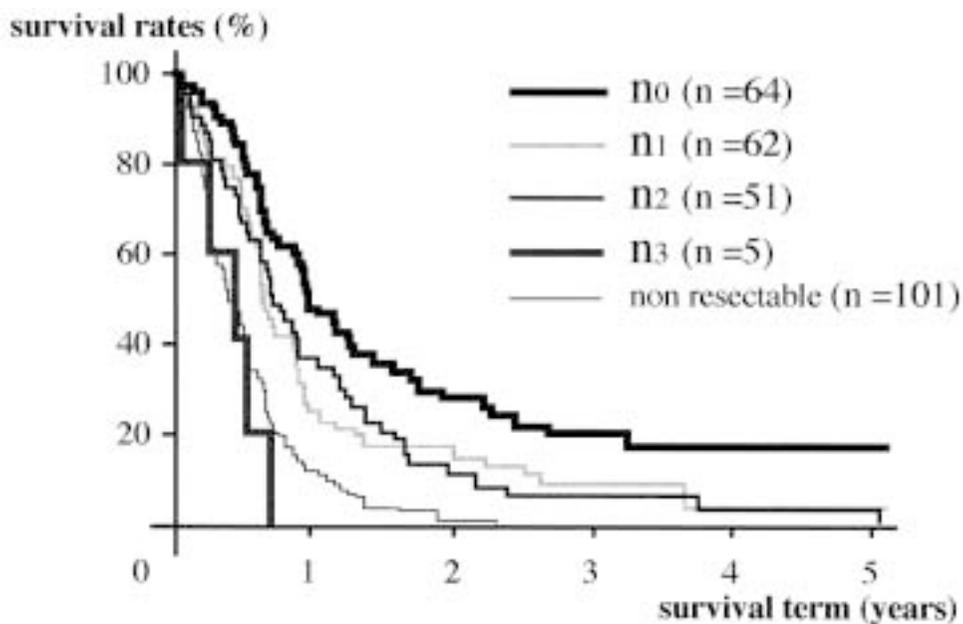


Fig. 2. Survival rate for pancreatic cancer after surgical resection according to the lymph node metastasis

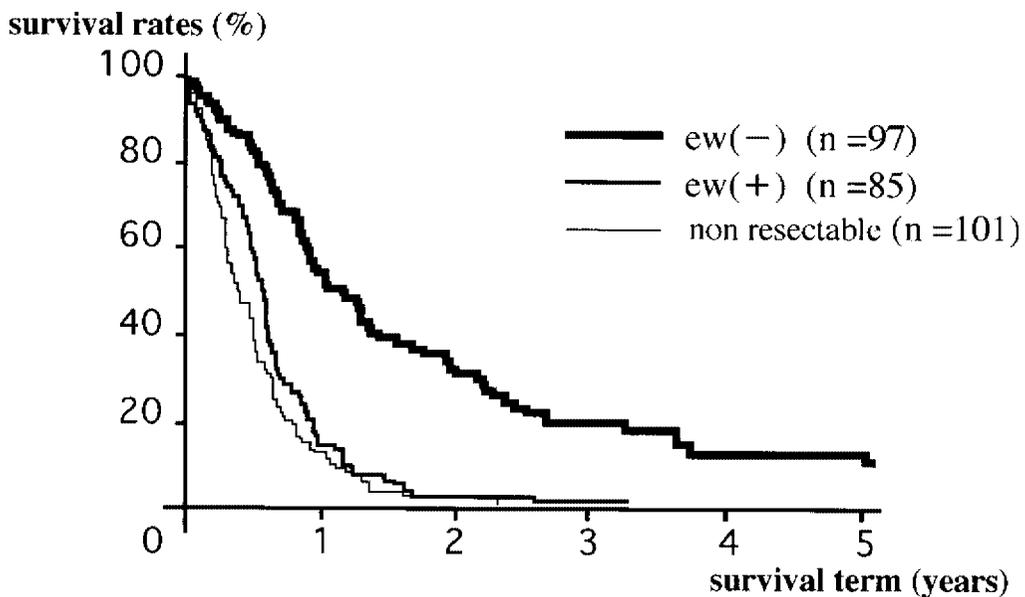


Fig. 3. Survival rate for pancreatic cancer after surgical resection according to the carcinoma invasion to the dissected peripancreatic tissue (ew)

was observed only in infrapyloric lymph nodes, and the incidence was 14%.<sup>16)</sup> Based on these data, pylorus-preserving pancreatoduodenectomy will be indicated if the cancer has no perigastric lymph node metastasis and no serosal or duodenal invasion.

The cumulative survival rates according to the invasion of surgical margins are shown in Figure 3. Survival for more than two years after operation was seen in the carcinoma-free surgical margins (ew(-)) group. A portal vein resection is necessary to obtain a carcinoma-free surgical margin in pancreatic cancer surgery.<sup>18,19)</sup> Recently, a more accurate diagnosis of portal vein invasion using intraportal ultrasonography has been developed.<sup>20,21)</sup>

Pancreatic carcinoma often invades the extrapancreatic nerve plexus. The prognosis with positive carcinoma invasion to this group is extremely poor compared with the negative carcinoma invasion group.<sup>22)</sup> In pancreatic head carcinoma, complete dissection of the extrapancreatic nerve plexus, especially the nerve plexus around the superior mesenteric artery, causes severe diarrhea after surgery. Recently, it has become possible to diagnose carcinoma invasion to the second portion of the pancreatic head nerve plexus using intraportal ultrasonography.<sup>23)</sup> In our department, if patients have no carcinoma invasion to the second portion of the pancreatic head nerve plexus, the left semicircular nerve plexus around the superior mesenteric artery is preserved to prevent postoperative diarrhea.

#### Postoperative Recurrence

Even in extended surgery with an isolated pancreatectomy, a high incidence of postoperative liver metastasis, local recurrence, and peritoneal metastasis has been observed with a poor postoperative prognosis (Table 1).<sup>24-27)</sup> The first cause of a poor postoperative prognosis in pancreatic cancer is liver metastasis. Although occult liver metastasis may be suspected on the bases 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.

Table 1. Incidence of postoperative recurrence in pancreatic cancer

Author	Year	Cases	Liver	Local	Peritoneal	Bone	Lung	Other
Kayahara et al. <sup>24)</sup>	1993	30	60%	83.3%	40%			
Takahashi et al. <sup>25)</sup>	1995	25	80%	100%	56%	24%	56%	
Sperti et al. <sup>26)</sup>	1997	78	62%	72%	6%			
Nakao et al. <sup>27)</sup>	1997	76	57%	34%	41%	3%	1%	1%

Table 2. Incidence of pancreatic cancer cells in peripheral blood, bone marrow, and liver tissue

Author	Year	Incidence
Tada et al. <sup>33)</sup>	1993	peripheral blood, K-ras 2/6 (33%)
Juhl et al. <sup>32)</sup>	1994	bone marrow, immunostaining: 15/26 (58%)
Inoue et al. <sup>38)</sup>	1995	liver tissue, K-ras: 13/17 (76%)
Nomoto et al. <sup>34)</sup>	1996	peripheral blood, K-ras: postoperative period 10/10 (100%)
Funaki et al. <sup>35)</sup>	1996	peripheral blood, CEAmRNA: 3/9 (33%)
Aihara et al. <sup>36)</sup>	1997	peripheral blood, Keratin 19mRNA: 2/38 (5%)
Miyazono et al. <sup>37)</sup>	1999	peripheral blood, CEAmRNA: 13/21 (61.9%)

### Occult and Micrometastasis

Recent progress in immunohistochemistry and molecular biological studies has been clarifying the occult and micrometastasis in pancreatic cancer. The incidence of cancer cells from abdominal washing cytology using conventional staining has been 0–17%.<sup>28-31)</sup> However, an incidence as high as 57% by immunocytochemical staining using monoclonal antibodies against tumor-associated antigens and cytokeratins was reported.<sup>32)</sup> The high incidence of *K-ras* point mutation of codon 12 in pancreatic cancer has also been observed. Occult pancreatic cancer cells have been detected in peripheral blood,<sup>33-37)</sup> bone marrow,<sup>32)</sup> and liver<sup>38)</sup> by studies of *K-ras*, CEA mRNA, Keratin 19 mRNA, along with immunocytochemical staining (Table 2).

Occult lymph node metastasis in pancreatic cancer has been also detected by the studies of *K-ras*.<sup>39)</sup>

## DISCUSSION

Surgical techniques for pancreatic cancer have been developed, and the resection rate has increased in Japan over the past 20 years. These developments have contributed to an improved prognosis for pancreatic cancer. However, the prognosis of stage IV patients with pancreatic cancer is still poor even with aggressive surgery. The reason for such a poor prognosis after surgical resection is the high incidence of recurrence. Occult and micrometastasis have been more precisely diagnosed by immunocytochemical and molecular biological studies. On the basis of such data, adjuvant multimodal therapies targeting occult and micrometastasis with radical surgery are recommended. Perioperative liver perfusion chemotherapy<sup>40)</sup> or intraoperative radiation therapy<sup>41)</sup> may decrease postoperative liver metastasis or local recurrence. Nevertheless, the effectiveness of these adjuvant multimodal therapies must be clarified and more effective adjuvant therapies must be developed.

## REFERENCES

- 1) Statistics and Information Department, Minister's Secretariat, Ministry of Health and Welfare. *Vital Statistics of Japan* (1998).
- 2) Whipple, A.O., Parsons, W.B., Mullins, C.R.: Treatment of carcinoma of the ampulla of Vater. *Ann. Surg.*, 102, 763–779 (1935).
- 3) Catell, R.B.: Resection of the pancreas. Discussion of special problems. *Surg. Clin. North Am.*, 23, 753–766 (1943).
- 4) Child, C.G.: Pancreaticojejunostomy and other problems associated with the pancreas. *Ann. Surg.*, 119, 845–855 (1944).
- 5) Imanaga, H.: A new method of pancreaticoduodenectomy designed to preserve liver and pancreatic function. *Surgery*, 47, 577–586 (1960).
- 6) Fortner, J.G.: Regional resection of cancer of the pancreas; A new surgical approach. *Surgery*, 73, 307–320 (1973).
- 7) Nakao, A., Horisawa, M., Suenaga, M., Yamamoto, T., Kondo, T., Kawase, S., Nagaoka, S., Mori, Y.: Temporal portosystemic bypass with the use of the heparinized hydrophilic catheter. *Jpn. J. Artif. Organs*, 11, 962–965 (1982).
- 8) Nakao, A., Nonami, T., Harada, A., Kasuga, T., Takagi, H.: Portal vein resection with a new anti-thrombogenic catheter. *Surgery*, 108, 913–918 (1990).
- 9) Nakao, A., Horisawa, M., Kondo, T., Ando, H., Kishimoto, W., Ichihara, T., Sakou, T., Takimoto, H., Ito, S.: Total pancreatectomy accompanied by portal vein resection using catheter-bypass of the portal vein. *Shujutsu (Operation)*, 37, 1–6 (1983) (in Japanese).
- 10) Nakao, A., Takagi, H.: Isolated pancreatectomy for pancreatic head carcinoma using catheter bypass of the portal vein. *Hepato-Gastroenterol.*, 40: 426–429 (1993).

- 11) Japan Pancreas Society. Classification of Pancreatic Carcinoma, 1<sup>st</sup> English ed. Tokyo: Kayahara Publishing (1996).
- 12) Ichihara, T., Nagura, H., Nakao, A., Sakamoto, J., Watanabe, T., Takagi, H.: Immunohistochemical localization of CA19-9 and CEA in pancreatic carcinoma and associated diseases. *Cancer*, 61, 324–333 (1988).
- 13) Nakao, A., Ichihara, T., Nonami, T., Harada, A., Koshikawa, T., Nakashima, N., Nagura, H., Takagi, H.: Clinicohistopathologic and immunohistochemical studies of intrapancreatic development of carcinoma of the head of the pancreas. *Ann. Surg.*, 209, 181–187 (1989).
- 14) Ichihara, T., Nakao, A., Sakamoto, J., Nonami, T., Harada, A., Watanabe, T., Nagura, H.: Application of immunoperoxidase method of rapid intraoperative pathological diagnosis of pancreatic cancer. *J. Surg. Oncol.*, 40, 8–16 (1989).
- 15) Ichihara, T., Nakao, A., Suzuki, Y., Sakamoto, J., Nonami, T., Harada, A., Nagura, H., Takagi, H.: Improvement of the rapid immunoperoxidase staining method for intraoperative pathological diagnosis of pancreatic cancer using microwave irradiation. *J. Surg. Oncol.*, 42, 209–214 (1989).
- 16) Nakao, A., Harada, A., Nonami, T., Kaneko, T., Murakami, H., Inoue, S., Takeuchi, Y., Takagi, H.: Lymph node metastasis in carcinoma of the head of the pancreas region. *Br. J. Surg.*, 82, 399–402 (1995).
- 17) Nakao, A., Harada, A., Nonami, T., Kaneko, T., Nomoto, S., Koyama, H., Kanazumi, N., Nakashima, N., Takagi, H.: Lymph node metastasis in carcinoma of the body and tail of the pancreas. *Br. J. Surg.*, 84, 1090–1092 (1997).
- 18) Nakao, A., Harada, A., Nonami, T., Kaneko, T., Inoue, S., Takagi, H.: Clinical significance of portal invasion of carcinoma of the head of the pancreas. *Surgery*, 117, 50–55 (1995).
- 19) Nakao, A., Harada, A., Nonami, T., Kaneko, T., Takagi, H.: Regional vascular resection using catheter by-pass procedure for pancreatic cancer. *Hepato-Gastroenterol.*, 42, 734–739 (1995).
- 20) Kaneko, T., Nakao, A., Inoue, S., Harada, A., Nonami, T., Ito, S., Endo, T., Takagi, H.: Intraportal endovascular ultrasonography in the diagnosis of portal vein invasion by pancreatobiliary carcinoma. *Ann. Surg.*, 222, 711–718 (1995).
- 21) Nakao, A., Kaneko, T.: Intravascular ultrasonography for assessment of portal vein invasion by pancreatic cancer. *World J. Surg.*, 23, 892–895 (1999).
- 22) Nakao, A., Harada, A., Nonami, T., Kaneko, T., Takagi, H.: Clinical significance of carcinoma invasion of the extrapancreatic nerve plexus in pancreatic cancer. *Pancreas*, 12, 357–361 (1996).
- 23) Kaneko, T., Nakao, A., Inoue, S., Nomoto, S., Nagasaka, T., Nakashima, N., Harada, A., Nonami, T., Takagi, H.: Extrapaneatic nerve plexus invasion by carcinoma of the head of the pancreas. *Int. J. Pancreatol.*, 19, 1–7 (1996).
- 24) Kayahara, M., Nagakawa, T., Ueno, K., Ohta, T., Takeda, T., Miyazaki, I.: An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined antopsy and diagnostic imaging. *Cancer*, 72, 2118–2123 (1993).
- 25) Takahashi, S., Ogata, Y., Miyazaki, H., Maeda, D., Murai, S., Yamataka, K., Tsuzuki, T.: Aggressive surgery for pancreatic duct cell cancer: feasibility, validity, limitations. *World J. Surg.*, 19, 653–660 (1995).
- 26) Sperti, C., Pasquali, C., Piccoli, A., Pedrazzoli, S.: Recurrence after resection for ductal adenocarcinoma of the pancreas. *World J. Surg.*, 21, 195–200 (1997).
- 27) Nakao A, Inoue S, Nomoto S, Kasai Y, Kaneko T, Harada A, Nonami T, Takagi H.: Extended radical surgery for pancreatic carcinoma: indications and oncological problems. *Asian J. Surg.*, 20, 192–197 (1997).
- 28) Lei, S., Kini, J., Kim, K., Howard, J.M.: Pancreatic cancer. Cytologic study of peritoneal washings. *Arch. Surg.*, 129, 639–642 (1994).
- 29) Fernandez-del Castillo, C., Rattner, D.W., Warshaw, A.L.: Further experience with laparoscopy and peritoneal cytology in the staging of pancreatic cancer. *Br. J. Surg.*, 82, 1127–1129 (1995).
- 30) Leach, S.D., Rose, J.A., Lowy, A.M., Lee, J.F., Charnsangavej, C., Abbruzee, J.L., Katz, R.L., Evans, D.B.: Significance of peritoneal cytology in patients with potentially resectable adenocarcinoma of the pancreatic head. *Surgery*, 1018, 472–478 (1995).
- 31) Nomoto, S., Nakao, A., Kasai, Y., Inoue, S., Harada, A., Nonami, T., Takagi, H.: Peritoneal washing cytology combined with immunocytochemical staining and detecting mutant K-ras in pancreatic cancer. *Pancreas*, 14, 126–132 (1997).
- 32) Juhl, H., Stritzel, M., Wroblewski, A., Henne-Bruns, D., Kremer, B., Sohmiegl, W., Neumaier, M., Wagner, C., Schreiber, H.-W., Kalthoff, H.: Immunocytological detection of micrometastatic cells: comparative evaluation of findings in the peritoneal cavity and the bone marrow of gastric, colorectal and pancreatic cancer patients. *Int. J. Cancer*, 57, 330–335 (1994).
- 33) Tada, M., Omata, M., Kawai, S., Saisho, H., Ohto, M., Saiki, R.K., Shinsky, J.J.: Detection of ras gene mutations in pancreatic juice and peripheral blood of patients with pancreatic adenocarcinoma. *Cancer Res.*, 53, 2472–2474 (1993).

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- 34) Nomoto, S., Nakao, A., Kasai, Y., Harada, A., Nonami, T., Takagi, H.: Detection of *ras* gene mutations in peripheral blood with pancreatic adenocarcinoma. *Cancer Res.*, 87, 793–797 (1996).
- 35) Funaki, N., Tanaka, J., Kasamatsu, T., Ohshio, G., Hosotani, K., Okino, T., Imamura, M.: Identification of carcinoembryonic antigen mRNA in circulating peripheral blood of pancreatic carcinoma and gastric carcinoma patients. *Life Science*, 59, 2187–2199 (1996).
- 36) Aihara, T., Noguchi, S., Ishikawa, O., Furukawa, H., Hiratsuka, M., Ohigashi, H., Nakamori, S., Monden, M., Imaoka, S.: Detection of pancreatic and gastric cancer cells in peripheral and portal blood by amplification of keratin 19mRNA with reverse transcriptase-polymerase chain reaction. *Int. J. Cancer*, 72, 408–411 (1997).
- 37) Miyazono, F., Takao, S., Natsugoe, S., Uchikura, K., Kijima, F., Aridome, K., Shintchi, H., Aikou, T.: Molecular detection of circulating cancer cells during surgery in patients with biliary-pancreatic cancer. *Am. J. Surg.*, 177, 475–479 (1999).
- 38) Inoue, S., Nakao, A., Kasai, Y., Harada, A., Nonami, T., Takagi, H.: Detection of hepatic micrometastasis in pancreatic adenocarcinoma patients by two-stage polymerase chain reaction/restriction fragment length polymorphism (PCR/RFLP) analysis. *Jpn. J. Cancer Res.*, 86, 626–630 (1995).
- 39) Ando, N., Nakao, A., Nomoto, S., Takeda, S., Kaneko, T., Kurokawa, T., Nonami, T., Takagi, H.: Detection of mutant *K-ras* in dissected para-aortic lymph nodes of patients with pancreatic adenocarcinoma. *Pancreas*, 15, 374–378 (1997).
- 40) Ishikawa, O., Ohigashi, H., Sasaki, Y., Furukawa, H., Kabuto, T., Kameyama, M., Nakamori, S., Hiratsuka, M., Imaoka, S.: Liver perfusion chemotherapy via both the hepatic artery and portal vein to prevent hepatic metastasis after extended pancreatectomy for adenocarcinoma of the pancreas. *Am. J. Surg.*, 168, 361–364 (1994).
- 41) Nakao, A., Harada, A., Nonami, T., Kaneko, T., Inoue, S., Takagi, H.: Intraoperative radiotherapy for resectable and unresectable pancreatic carcinoma. *Hep. Bil. Pancr. Surg.*, 1, 252–256 (1994).