Surgical Treatment and Oncological Problems in Pancreatic Cancer

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Despite the development of more sophisticated diagnostic techniques, it remains difficult to detect pancreatic carcinoma in the early stage compared with distal bile duct carcinoma or duodenal papilla carcinoma. The resection rate of the pancreatic carcinoma has been increasing due to recent advances in surgical techniques and the application of extensive surgery. However, the postroperative 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 surgical experience and oncological problems in pancreatic cancer.

Introduction

Pancreatic cancer is the fifth most common cause of death by malignant neoplasm in Japan [1]. The number of deaths in Japan due to pancreatic cancer has steadily increased, reaching 17000 in 1996 [1]. After the first successful pancreatoduodenectomy by Whipple *et al*. [2], many kinds of reconstruction of the alimentary tract after pancreatoduodenectomy have been reported [3–5]. However, the resection rate and prognosis in cases of pancreatic cancer have been very low and poor. The regional pancreatectomy introduced by Fortner [6] impressed many Japanese pancreatic surgeons. Consequently, the resection rate has gradually improved, but the postoperative prognosis is still poor. This paper introduces our surgical experience and recent advances in molecular-biological studies in pancreatic cancer.

Patients and Methods

Isolated Pancreatectomy Using Catheter-Bypass Method of the Portal Vein

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 (Fig. 1) [7, 8]. Since then, we have been aggressively performing extensive surgical resections, including portal vein resection by the non-touch isolation technique [9, 10] using this bypass method accompanied by extensive lymph node dissection and extrapancreatic nerve plexus dissection (Fig. 2, 3).

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 Japan Pancreas Society conclusive stage [11] are shown in Figure 4. Postoperative prognosis of stage I and II is relatively good, but that of 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.

Results

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 [12, 13]. Intraoperative quick immunostaining [14, 15] 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 [10].

The cumulative survival rates according to lymph node metastasis are shown in Figure 5. The survival

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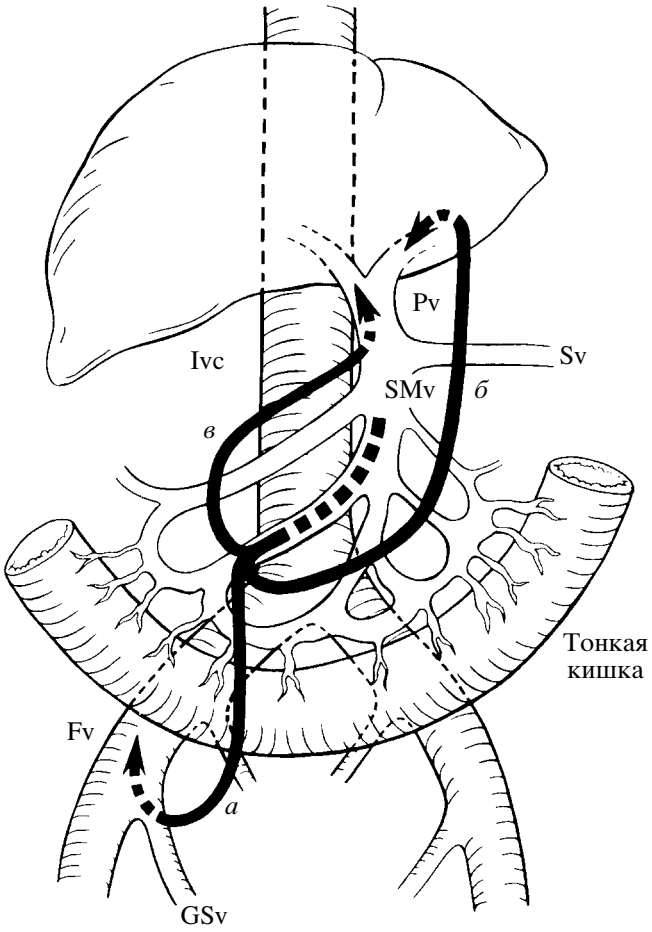

Fig. 1. Scheme of catheter placing for portal vein bypass

а) Mesenteric vein – Femoral vein

б) Mesenteric vein – Left portal vein though Umbilical vein

в) Mesenteric vein – Intrahepatic branch of portal vein

Fv – Femoral vein; GSv – Great saphenous vein; Ivc – Inferior vena cava; Pv – Portal vein; Sv – Splenic vein; SMv – Superior mesenteric vein.

Рис. 1. Схемы установки катетера для шунтирования воротной вены.

а – брыжеечная вена – бедренная вена;

б – брыжеечная вена – левая ветвь воротной вены (через пупочную вену);

в – брыжеечная вена – внутрипеченочно расположенная ветвь воротной вены.

Fv – бедренная вена; GSv – большая подкожная вена; Ivc – нижняя полая вена; Pv – воротная вена; Sv – селезеночная вена; SMv – верхняя брыжеечная вена.

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% (16) in pancreatic head carcinoma and 13% (17) in pancreatic body and tail carcinoma. Perigastric lymph node metastasis in pancreatic head carcinoma was observed only in infrapyloric lymph nodes, and the incidence was 14% (16). 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 6. 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 [18, 19]. Recently, a more accurate diagnosis of portal vein invasion using intraportal ultrasonography has been developed [20, 21].

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 [22]. In pancreatic head carcinoma, complete dissection of the extrapancreatic nerve plexus, especially the nerve plexus around the superior mesenteric artery, causes

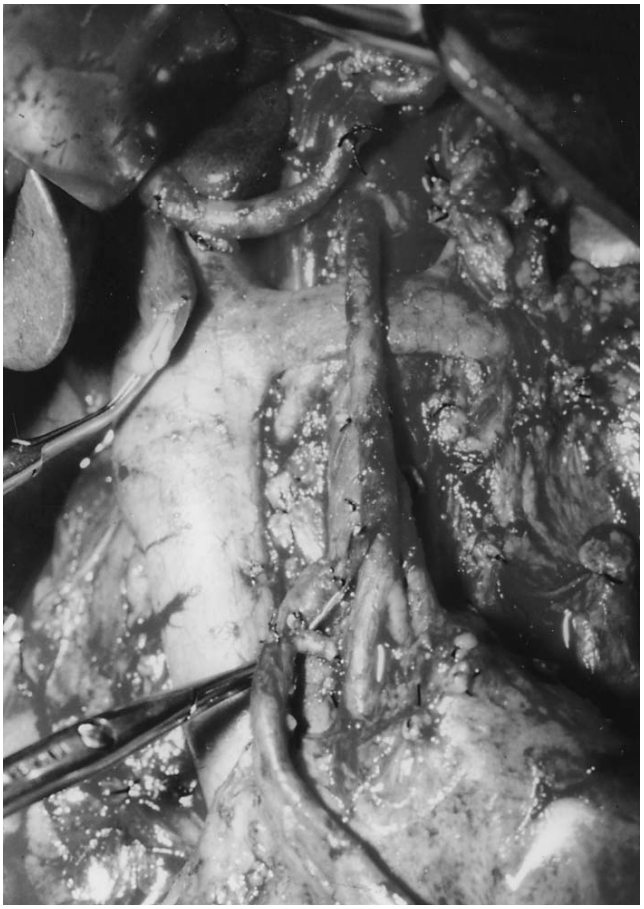

Fig. 2. View of abdominal cavity after pancreatoduodenectomy in combination with portal vein resection.

Рис. 2. Вид брюшной полости после панкреатодуоденальной резекции, дополненной резекцией воротной вены.

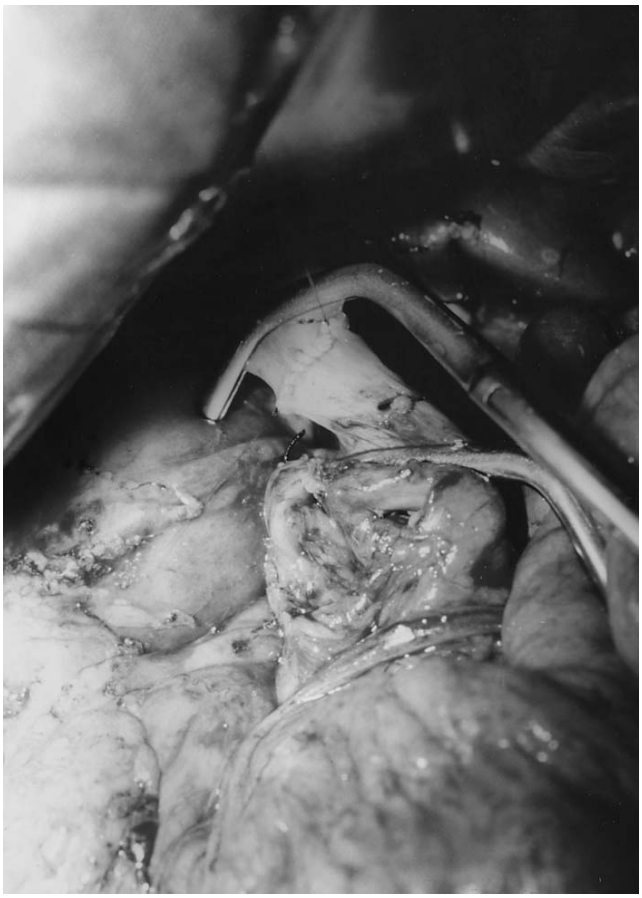

Fig. 3. Portal vein and superior mesenteric vein anastomosis.

Рис. 3. Анастомоз между воротной и верхней брыжеечной венами.

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 [23]. 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 severe diarrhea, which causes malnutrition.

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 postopertaive prognosis (Table 1) [24–27]. The first cause of a poor postoperative prognosis in pancreatic cancer is liver metastasis. Although occult liver metastasis may be suspected on the

Table 1. Incidence of postoperative recurrence in pancreatic cancer

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

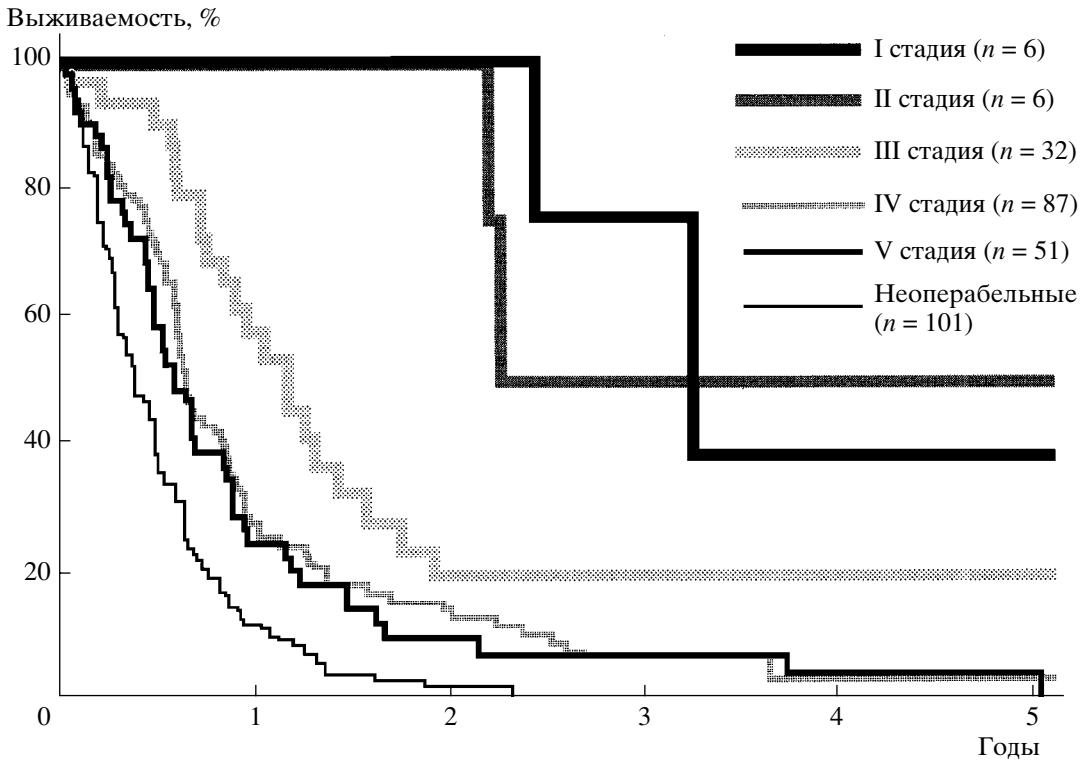

Fig. 4. Survival after radical surgery depending on pancreatic cancer stage (classification of Japanese Pancreatologic Association).

Рис. 4. Выживаемость больных после радикальных вмешательств в зависимости от стадии рака ПЖ (классификация японской панкреатологической ассоциации).

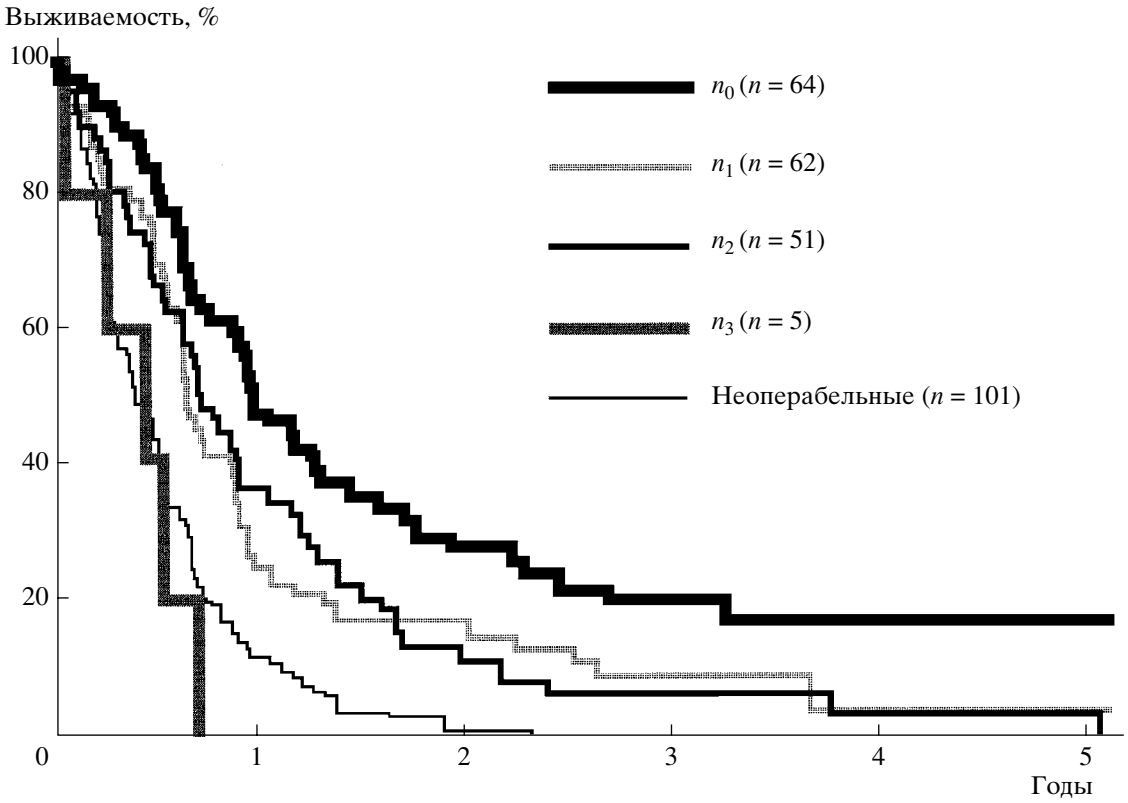

Fig. 5. Survival after radical surgery considering metastatic lymph nodes.

Рис. 5. Выживаемость больных после радикальных операций с учетом поражения метастазами лимфоузлов.

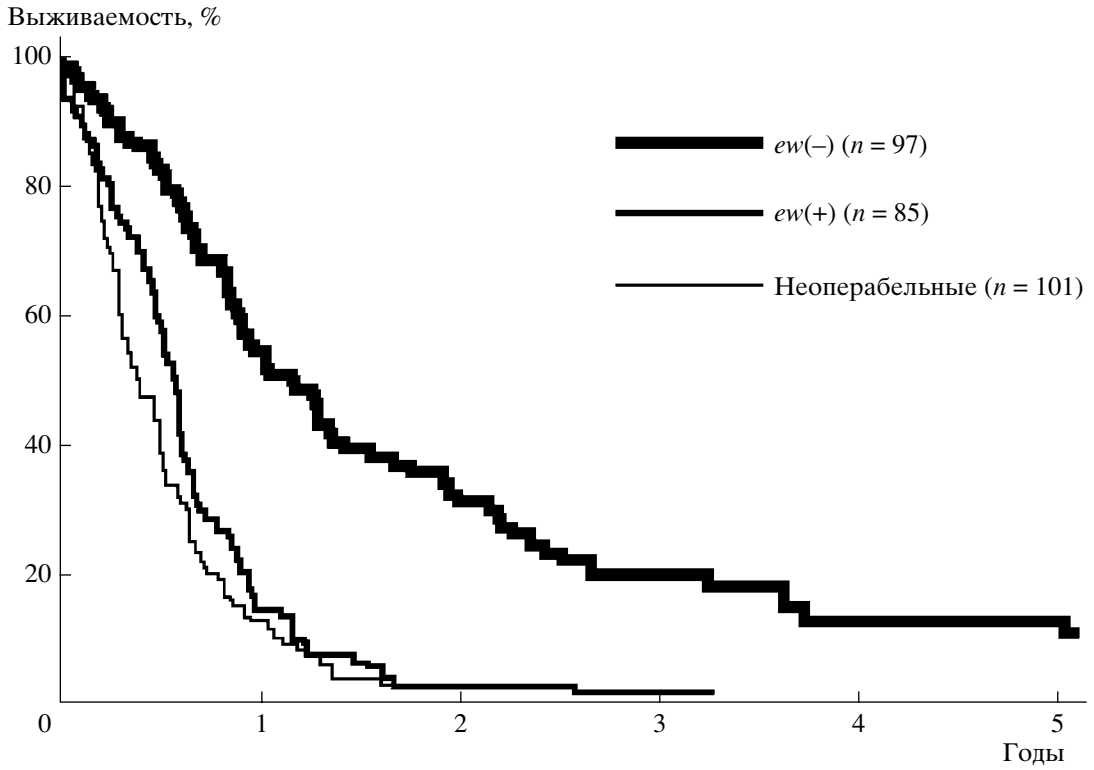

Fig. 6. Survival depending on radical surgery, *ew* – cancer invasion.
Рис. 6. Выживаемость больных раком ПЖ после операций в зависимости от радикальности вмешательства: *ew* – раковая инвазия.

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.

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% (28–32). However, an incidence as high as 57% by immunocytochemical staining using monoclonal antibodies against tumor-associated antigens and cytokeratins was reported [33]. The high incidence of K-*ras* point mutation of codon 12 in pancreatic cancer has also been observed. Occult pancreatic cancer cells have been de-

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

Author	Year	Incidence
Tada *et al*. [34]	1993	peripheral blood, K-*ras*: 2/6 (33%)
Juhl *et al*. [33]	1994	bone marrow, immunostaining: 15/26 (58%)
Inoue *et al*. [39]	1995	liver tissue, K-*ras*: 13/17 (76%)
Nomoto *et al*. [31]	1996	peripheral blood, K-*ras*: postoperative period 10/10 (100%)
Funaki *et al*. [36]	1996	peripheral blood, CEAmRNA: 3/9 (33%)
Aihara *et al*. [37]	1997	peripheral blood, Keratin 19mRNA: 2/38 (5%)
Miyazono *et al*. [38]	1999	peripheral blood, CEAmRNA: 13/21 (61.9%)

tected in peripheral blood [34–38], bone marrow [33], and liver [39] by studies of K-*ras*, CEAmRNA, Keratin 19mRNA, along with immunocytochemical staining (Table 2).

Occult lymph node metastasis in pancreatic cancer has been also detected by the studies of K-*ras* [40].

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 extended 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 combined with radical surgery are recommended. Perioperative liver perfusion chemotherapy [41] or intraoperative radiation therapy [42, 43] 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.

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