

## Radical resection for pancreatic cancer

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### Abstract

Ductal adenocarcinoma of the pancreas is still characterized by (1) poor prognosis after surgery and (2) extreme difficulty in early diagnosis, and we need a breakthrough. For the first problem, we have performed a wide range of lymphatic and connective tissue clearance (extended pancreatectomy) which has succeeded in improving the 5-year survival rate from 8% to 24% via decreasing the incidence of locoregional recurrence. When liver perfusion chemotherapy via the hepatic artery and the portal vein was added to the patients who had received extended pancreatectomy, the 5-year survival rate was further elevated to 40% via decreasing the incidence of hepatic metastasis. We conclude that pancreatic cancer should be treated by the better-balanced treatments between locoregional control and prevention of hepatic metastasis. For the second problem, we have more actively collected pancreatic juice to perform cytodiagnosis even though no obvious tumor was delineated by the conventional imaging diagnoses. When cancer cells were detected in the pancreatic juice, our method of intraoperative cytology was very useful in precisely locating the occult lesion indicating an appropriate range of pancreatectomy. The resected pancreas was proven to have included borderline malignancy and in situ or minimally-invasive carcinoma by the postoperative histology, and disease-free 5-year survival rate was 100%. In the future, we need to detect patients with a high risk of pancreatic cancer and develop a less-painful method to collect the pancreatic juice. (*Acta gastroenterol. belg.*, 2002, 65, 166-170).

**Key words:** pancreatic cancer, extended pancreatectomy, liver perfusion chemotherapy, and cytology of pancreatic juice.

### The locoregional recurrence — the first barrier in resecting pancreatic cancer

The incidence of adenocarcinoma of the pancreas has risen in many countries during the last three decades. Surgical resection has long offered the only curative strategy for this cancer to date, and recent advances in the operative procedures and postoperative care have succeeded in decreasing the postoperative mortality rate. However, the long-term outcome after resection of this cancer is still pessimistic because the fact remains that more than half of the patients die within 2-postoperative years (1).

In 1976, Tepper (2) reported a 16% operative mortality rate, a 15% 5-year survival rate and a 50% local recurrence rate in patients treated with radical surgery. At our institution before 1981, the 5-year survival rate was as low as 8% after resection of pancreatic head cancer and locoregional recurrence was the leading cause of surgical failure (Figs. 1 and 2). Likewise, we failed to obtain 5-year survivors from the patients with nodal

involvement (3). Thus, most surgeons realized the limited role of conventional pancreatectomy alone, and some surgeons in western countries began chemo-radiation therapy in combination with pancreatectomy. As a result, the GITSG (4) performed a prospective randomized study to clarify that the 2-year survival rate was improved from 18% to 43% by adding postoperative chemoradiation to the conventional pancreatoduodenectomy. Even at present, a combination of chemoradiation with conventional pancreatectomy still stands as one of the standard strategies for this cancer (5).

On the other hand, some Japanese surgeons including us, began to add a wide range of lymphatic and connective tissue clearance to the conventional pancreatectomy. This technique was based on the clinicopathologic evidence that cancer extension (invasion and metastasis at a microscopic level) beyond the confines of the pancreas was common even in small pancreatic tumors measuring 2 cm or less in diameter (6,7). A high incidence of perineural cancer invasion especially warned us that cancer

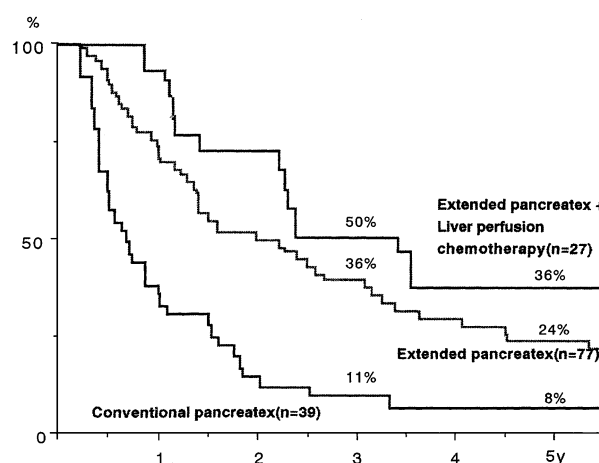


Fig. 1. — Cumulative survival rates compared among the three groups.

The 5-year survival rate is 8% in conventional pancreatectomy, 24% in extended pancreatectomy and 36% in liver perfusion chemotherapy plus extended pancreatectomy. A statistically significant difference is seen between each of the two groups.

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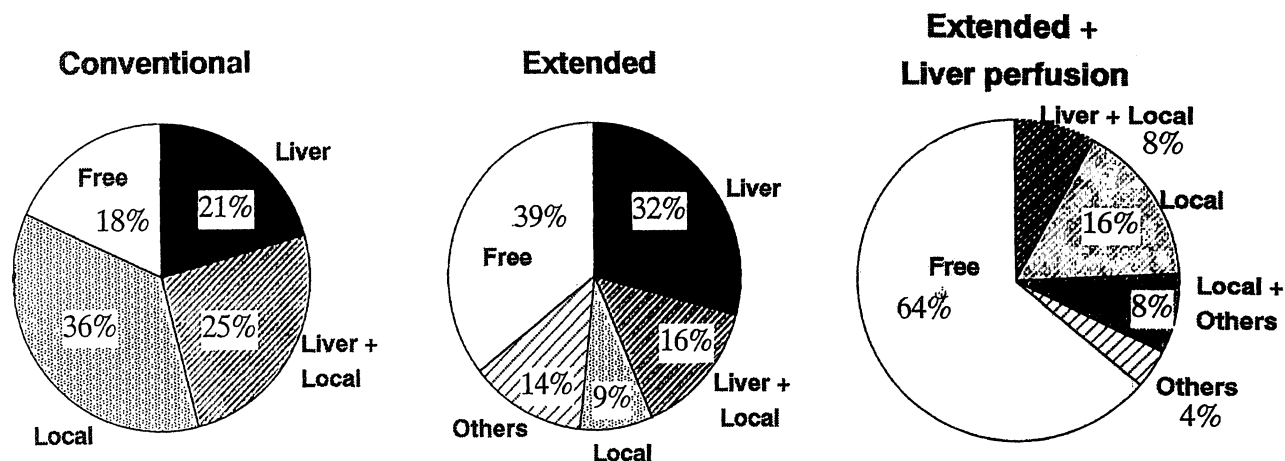


Fig. 2. — The cause of cancer death compared among the three groups.

The extended pancreatotomy was superior to the conventional pancreatotomy in locoregional control. The incidence of liver metastasis was decreased when liver perfusion chemotherapy was added to an extended pancreatotomy.

cells were likely to be left behind in the nerve plexi which surrounded the major vessels such as the superior mesenteric artery, the celiac artery and so on (8). After converting from the conventional pancreatotomy to an extended pancreatotomy (3), we have succeeded in improving the 5-year survival rate to 24% via decreasing the incidence of locoregional recurrence (Fig. 1 and 2). In addition, our extended pancreatotomy was superior to the conventional pancreatotomy in the 5-year survival rates for the patients with nodal involvement (9) and portal vein invasion (10).

On the other hand, it became clear that these 5-year survivors had scarcely revealed many (4 or more) positive nodes (9) or severe degrees (bilateral or 2-cm or more in length (10); and the depth of cancer invasion exceeded the tunica adventitia (11,12)) of the portal vein involvement. This knowledge leads us to remember that Fortner (13), a pioneer of extended pancreatotomy, failed to improve the long-term outcome when his patients had larger tumors either measuring 5 cm or more in diameter or involving the neighbouring arteries. Thus, our extended pancreatotomy should not be indicated to remove the macroscopically-obvious invasion or metastases but to eradicate the microscopic level of cancer foci. For instance, Demeure (14) performed a genetic examination (point mutation in K-ras gene) of the surgically removed lymph nodes which had been once diagnosed as negative in cancer involvement by routine histology, and 70% of the patients were newly diagnosed as positive in K-ras mutation in their lymph nodes. Yamada (15) also reported that the status of nodal involvement diagnosed by K-ras mutation was more associated with the patient's prognosis rather than histopathologic diagnosis, but we should confirm whether resection of the micrometastasis by an extended lymphadenectomy contributed to the survival benefit. With regard to the microinvasion to the surrounding tissues, we obtained touch smear of the superior mesen-

teric vein and/or the portal vein (SMPV) which had been once preserved (left behind) during pancreatoduodenectomy because of a macroscopically intact appearance (16). As a result, 30% of the patients showed a positive result in intraoperative cytology and their SMPVs were then resected. Postoperative histology showed that all but one patient revealed cancer invasion into the SMPVs.

It is of no doubt that our extended pancreatotomy have removed higher quantities of cancer foci by sacrificing the excessive non-cancerous tissues in comparison with the conventional pancreatotomy. Since there is a wide variety of cancer extension among the patients, we should select more efficient (made-to-order) procedures which can preserve as much non-cancerous tissues as possible without any fear of cancer residual. For this purpose, we should develop the new diagnostic tool which can detect cancer foci at a microscopic or genetic level during laparotomy. For instance, nerve plexi around the superior mesenteric artery are vulnerable to cancer invasion, but the presence of cancer cells was occasionally overlooked by the routine histologic examination using a light microscopy (17). If the entire circle of nerve plexi around the superior mesenteric artery is removed with a prophylactic intent, diarrhea continues at least one or two postoperative years. However, postoperative diarrhea is easily controllable if the hemicircle of them are correctly judged as negative in cancer invasion and thereby preserved.

#### Liver metastasis — the second barrier after locoregional control

In reviewing the previous reports where radiation therapy was added to the pancreatotomy, some authors (18-20) indicated that the incidence of hepatic metastasis was increased despite the decreased incidence of locoregional recurrence. This was the main reason why

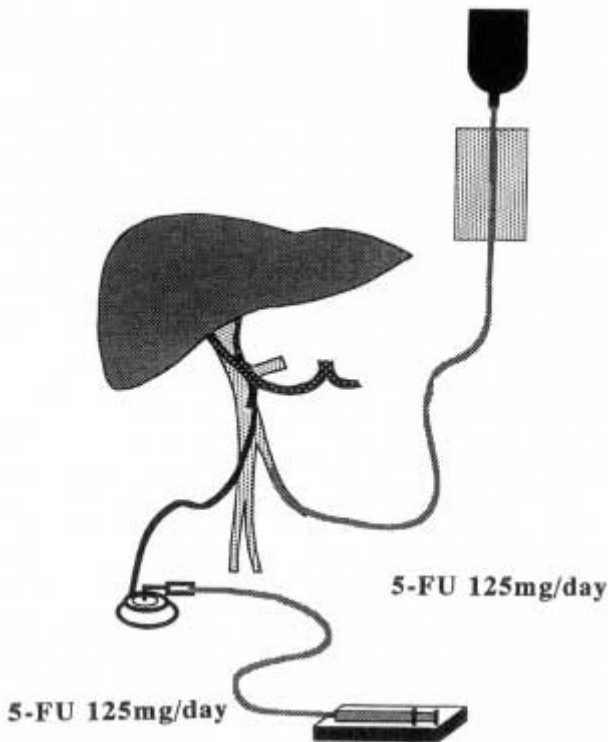


Fig. 3. — Liver perfusion chemotherapy.

One catheter is placed in the gastroduodenal artery and another one in one of the branches of the superior mesenteric vein. Immediately after surgery, 5-fluorouracil (125 mg/day) is continuously infused from each of the two routes for 28 days or more.

the long-term survival rate was not improved significantly by adjuvant chemoradiation (locoregional treatment). There has been no report of systemic chemotherapy which was effective in preventing hepatic metastasis, while Taylor (21) reported that the 5-Fu-infusion from the portal vein was effective in preventing hepatic metastasis after colon cancer resection. In addition, cancer cells at the initial stage of hepatic metastasis (before or immediately after lodging in the vessels lumen) would be supplied by the portal blood flow while the arterial blood supply may become dominant as they invade the vessel walls and the hepatic parenchyma (22). Thus, we began to infuse 5-fluorouracil (5-Fu) via both the portal vein and the hepatic artery continuously for at least 28 postoperative days (125 mg/day  $\times$  2 routes) immediately after an extended pancreatectomy (23,24) (Fig. 3). Usually, before closing the abdominal wall, one catheter was placed in the gastroduodenal artery and another one catheter in one of the branching veins of the superior mesenteric vein. During the chemotherapy, the concentration of 5-Fu in the systemic circulation was continuously 0.02 microgr/ml or less and no patients experienced such adverse effects as nausea, anorexia, liver dysfunction etc. The incidence of hepatic metastasis was thereby decreased significantly, and the 5-year survival rate was elevated to 36% (Figs. 1 and 2).

However, if we had performed this regional chemotherapy for the patients who had received conventional pancreatectomy, such a prognostic improvement might have been canceled out by its higher incidence of locoregional recurrence. Beger (25) repeated the placement of a catheter in the celiac artery using Seldinger's method after pancreatectomy, and thereby infused the chemotherapeutic agents into the hepatic artery and the splenic artery. The drug, once delivered into the splenic artery, reached the spleen and the remnant pancreas and then returned to the liver via the portal vein. He succeeded in improving the 3-year survival rates from 5% to 30% for the stage-III (UICC-classification; positive in nodal involvement) cancers via decreasing the incidence of liver metastasis. Since Komaki (26) reported that prophylactic hepatic irradiation was effective in the locally-advanced and non-resectable cancers of the pancreas, this treatment is being tried also for the resectable cases by some surgeons (5,27).

In conclusion, the pancreatic cancer should be treated by the better-balanced treatments which are focused on both locoregional control and prevention of hepatic metastasis. If such type of combination therapy is effective, we will be able to gradually widen the operative indication again for such advanced cases that had not been cured by the traditional treatments. Neoadjuvant therapy would be also promising in order to strictly select the surgical candidates, and it is more desirable to predict either chemo-sensitivity or radiosensitivity for each patient beforehand.

### How to detect an early and potentially curable cancer

It is our goal to detect pancreatic cancer at such an early stage that would be potentially curable by less-invasive surgery alone without performing an extended pancreatectomy or any adjuvant therapies. It is of no doubt that the smaller the size of the tumor, the better the expected prognosis would be after resection. However, the 5-year survival rate was reported to be only 40% for carcinomas measuring 2 cm or less in diameter (1), and 57% for those measuring 1 cm or less in diameter (28). Thus, we should detect far smaller and less-invasive cancers such as carcinoma in situ or those invading the basement membrane of the pancreatic duct alone. Since pancreatic juice is the most direct specimen to detect ductal adenocarcinoma of the pancreas, we began to both collect pure pancreatic juice during ERP and perform cytologic examination among patients in whom no obvious pancreatic tumor had been delineated by any imaging techniques (ultrasonography, computed tomography, magnetic resonance imaging, endoscopic retrograde pancreatography and so on) (29,30). When cancer cells are detected in the pancreatic juice, it is difficult to identify the location of cancer and determine the appropriate range of pancreatectomy. During laparotomy for cytology-positive cases, the pancreatic neck in front of

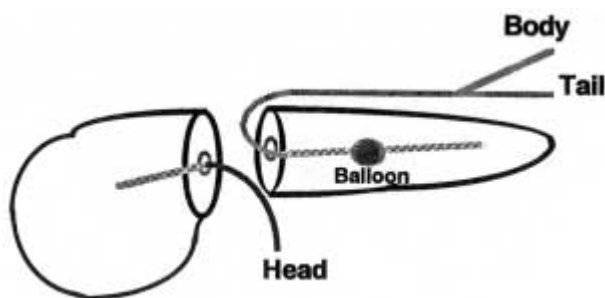


Fig. 4. — Cytology-guided pancreatectomy (3-segmental cytology).

After the pancreatic neck is cut at a right angle to the main pancreatic duct, one catheter is placed in the main duct of the cranial segment, and a balloon-catheter with triple lumens is placed in the main duct of the caudal pancreas. The balloon is inflated to block the main pancreatic duct at the borderline between pancreatic body and tail. The pancreatic juice can be collected separately from the pancreatic head, body and tail, respectively. The resection is done for the segment in which cancer cells are detected by the intraoperative cytology.

Table 1. — Operative procedures determined by intraoperative cytology and postoperative development of diabetes

Intraoperative Cytology	No. of Cases	Operative procedures				
		PD	CP	TP	PH+PB	PB
2-Segmental	8 (4)	3	3 (2)	2 (2)	0	0
3-Segmental	10 (1)	4	1 (1)	0	1	4

PD : pancreatoduodenectomy ; CP : caudal pancreatectomy ; TP : total.

Pancreatectomy ; PB : pancreatic body resection ; ( ) : number of patients, who developed diabetes newly after surgery (four by insulin injection and one by oral mediation).

The 3-segmental cytology was superior to the 2-segmental cytology in providing us with a chance of preserving both higher volume of intact pancreas and higher glucose-tolerating function.

the superior mesenteric vein was divided at a right angle to the main pancreatic duct (MPD). One catheter was placed in the MPD of the pancreatic head and another one catheter in the MPD of the caudal pancreas (2-segmental cytology) (29). More recently, we used a balloon catheter with triple lumens. One lumen is connected with the balloon, other two lumens were used for collecting pancreatic juice from the pancreatic tail and pancreatic body (3-segmental cytology, Fig. 4) (31). According to the result of intraoperative cytology, we determined the range of pancreatectomy (operative procedures), i.e. pancreatoduodenectomy when cancer cells were detected from the pancreatic head alone. We have performed this procedure without lymphatic or connective tissue clearance for 18 patients and postoperative histology proved carcinoma in situ or minimally invasive cancer for 14 patients and borderline lesions for 4 patients. No patients died of cancer and one patient died of dia-

betic complication. With regard to the postoperative quality of life, the 3-segmental cytology provided us with a chance of preserving a higher volume of intact pancreas and higher glucose-tolerating function compared with the 2-segmental cytology (Table 1).

The ERP is an invasive and painful examination, but the previous studies have shown that pancreas with a slight dilation of MPD and/or small cysts was at a high risk of occult pancreatic cancer, although these lesions did not always represent (correspond to) the neoplastic foci. Either MPD-dilation or small cysts can be easily delineated by ultrasonography. When they are detected, we should more actively perform ERP and collect the pancreatic juice. At the same time, concomitant determination of telomerase activity and K-ras mutation is useful for the follow-up (32). Even if no cancer cells are detected in the pancreatic juice, a positive result in telomerase activity or K-ras mutation may predict the patient as a high risk of eventual development of pancreatic cancer.

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