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Standard *Versus* Extended Pancreaticoduodenectomy in Treating Adenocarcinoma of the Head of the Pancreas

Jun Gong^{1,2}, Gang Mai², Zhen-jiang Zheng², Guang-ming Xiang², Wei-ming Hu²,
Bo-le Tian², Zhao-da Zhang², and Xu-bao Liu^{2*}

¹Department of Hepatobiliary and Pancreatic Surgery, Sichuan Academy of Medical
Science and Sichuan Provincial People's Hospital, Chengdu 610072, China

²Department of Hepatobiliary and Pancreatic Surgery, West China Hospital,
Sichuan University, Chengdu 610041, China

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Objectives To compare the postoperative complications and survival of standard pancreatoduodenectomy (SPD) and extended pancreatoduodenectomy (EPD) in patients with resectable adenocarcinoma of the head of the pancreas.

Methods Between January 1994 and December 2011, 165 patients with biopsy-proven adenocarcinoma of the pancreatic head were treated in West China Hospital, among whom 93 underwent SPD and 72 had EPD. Complications and survival after the surgery were analyzed retrospectively.

Results The median operation time of the EPD group was longer compared with the SPD group (375 minutes *vs.* 310 minutes, $P < 0.01$), the volume of blood transfusion was larger (700 mL *vs.* 400 mL, $P < 0.05$), while the median hospital stay (13.5 days *vs.* 12 days, $P = 0.79$) and the total complication rates were comparable (34.7% *vs.* 32.4%, $P = 0.93$). The total recurrence rates of the SPD and EPD groups were not significantly different (52.7% *vs.* 43.1%, $P = 0.83$). No significant differences were found between the SPD and EPD groups in 1-year (81.7% *vs.* 86.1%), 3-year (38.7% *vs.* 43.1%), 5-year (16.7% *vs.* 19.4%), and median survivals (19.8 months *vs.* 23.2 months, $P = 0.52$).

Conclusion The postoperative complications and survival do not differ significantly between SPD and EPD.

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PANCREATIC cancer now represents the fourth leading cause of cancer-related mortality in both sexes according to recent statistics.¹ Approximately 200 000 people are diagnosed with pancreatic cancer worldwide each year.² Surgical resection is the only potentially curative treatment for patients with pancreatic cancer. In the past two decades, advances in surgical techniques have brought the operative mortality of pancreatic head resection down to <5% in specialty centers.³ The overall improvement in surgical outcomes over the last 30-40 years has been remarkable, most of which is the result of technology progress benefiting the care of surgical patients both in and outside the operating room.⁴

Different factors can influence survival and be used in screening patients for resection and adjuvant therapy. The predictive value for survival has been shown for age, gender, duration of symptoms, perioperative blood transfusions, lymph node metastases, perineural invasion, and tumor size.^{5,6} It is not known whether better patient selection and lower operative mortality improve survival, and what prognostic factors are relevant with improved patient selection. For the past few years, extended resection for pancreatic cancer has been performed successfully around the world. Based on the outcomes of surgical patients, this study retrospectively evaluated

whether extended pancreatoduodenectomy (EPD) for adenocarcinoma of the head of the pancreas could prolong long-term survival and reduce postoperative complication rate compared with standard pancreatoduodenectomy (SPD).

PATIENTS AND METHODS

Patient selection

From January 1994 to December 2011, there were 165 patients received pancreaticoduodenectomy for pancreatic head cancer in the Department of Hepatobiliary and Pancreatic Surgery in West China Hospital. Patients were excluded from this study if any of the following conditions existed: having received palliative resection, resection of part of the portal vein and superior mesenteric vein and/or superior mesenteric artery for cancer invasion; and having residual carcinoma indicated by postoperative histopathology. SPD was performed in 93 patients and EPD in 72. Tumor differentiation was defined based on World Health Organization criteria.⁷ Tumor stage was determined according to the criteria by the American Joint Committee on Cancer.⁸ The tumor stage of the 165 patients is described in Table 1.

Table 1. Demographic features, operative details, and tumor characteristics of patients with adenocarcinoma of the pancreatic head who underwent either standard pancreatoduodenectomy (SPD, $n=93$) or extended pancreatoduodenectomy (EPD, $n=72$)

Groups	Gender [n (%)]		Age [years, median (range)]	Operation time [min, median (range)]	Intraoperative blood transfusion [mL, median (range)]	Hospital stay [d, median (range)]	Survival [months, median (range)]	Tumor type [n (%)]		
	Male	Female						Duct epithelial adenocarcinoma	Mucinous cystadenocarcinoma	Acinar cell carcinoma
SPD	61 (65.6)	32 (34.4)	56 (22-76)	310 (260-350)	400 (0-1000)	12 (9-51)	19.8 (8-138)	85 (91.4)	6 (6.5)	2 (2.2)
EPD	47 (65.3)	25 (34.7)	59 (23-79)	375 (320-650)	700 (0-1800)	13.5 (8-76)	23.2 (6-144)	70 (97.2)	2 (2.8)	0
<i>P</i>	0.87		0.70	<0.01	<0.05	0.79	0.52	0.91		

Groups	Union Internationale Contre le Cancer stage (n)					Histological differentiation (n)					Total number of lymph nodes involved [median (range)]	Tumor size [cm, median (range)]
	1A	1B	2A	2B	3	Well	Moderately	Poorly	Positive N1, nodes	Positive N2, nodes		
SPD	3	8	31	35	16	18	43	31	41	7	19 (4-32)	3.4 (1.9-4.2)
EPD	1	2	19	20	20	10	34	28	40	21	26 (8-56)	3.8 (2.1-4.6)
<i>P</i>	0.35					0.55					<0.05	0.39

Surgical procedure

SPD was carried out according to the classical description, including a regional lymphadenectomy with *en bloc* resection of the lymph nodes around the duodenum and pancreas. EPD includes the removal of all the lymph nodes of group 16 with clearance of all the connective and lymphatic tissues, beginning at 3 cm to the right of the duodenum and extending to the mid-portion of the left kidney, and from the inferior margin of the liver across the diaphragmatic hiatus, well above the origin of the celiac trunk to the origin of the common iliac arteries. The anterior aorta was cleared of all the lymphatic and neurovascular tissues, including the tissue around the celiac axis. A left adrenalectomy is optional.⁹

In both the EPD and SPD groups, the pancreaticojejunostomy was performed in an intussusceptive end-to-side fashion; the common hepatic duct was anastomosed end-to-side with the jejunum, with interrupted absorbable sutures in a sero-muscular layer. The operation was completed with a gastrojejunostomy or an end-to-side duodenojejunostomy. All anastomoses were performed on the same loop according to the modified Child's technique and were not stented. A H-2 receptor antagonist and antibiotics were administered preoperatively. Somatostatin and proton pump inhibitor analogues were used prophylactically.

Postoperative follow-up

All the patients were examined with laboratory tests and abdominal ultrasound scan every 3 months, and abdominal computed tomography scan every 6 months, or when recurrence was suspected based on the result of ultrasound scan. No postoperative adjuvant therapy was performed in this series of patients. Survival was defined as the time from surgery to death and was censored at the last follow-up date if no events had occurred. The follow-up was completed in all patients on 31 December 2011, or until death.

Statistical analysis

The statistical analysis was performed using SPSS version 13.0. Data are presented as the median or mean±standard error. Differences between the SPD group and the EPD group were analyzed with the Chi-square test. Log-rank test and the Kaplan-Meier method were used to assess differences in survival between the 2 groups. Associations were considered significant if the *P* value was < 0.05.

RESULTS

The 165 patients participated in this study consisted of 107 men and 58 women. The mean age of the SPD group

was 56 years (range, 22-76 years) and that of the EPD group was 59 years (range, 23-79 years). The main demographic, clinical, and pathologic characteristics of the patients are listed in Table 1.

Both the operation time and the volume of blood transfusion were greater in the EPD group than in the SPD group (both *P*<0.05, Table 1). The final pathology indicated that the 93 patients in the SPD group and the 72 patients in the EPD group had pancreatic head duct epithelial adenocarcinoma, mucinous cystadenocarcinoma, or acinar cell carcinoma. There were more cases of grade 3 neoplasms in the EPD group than in the SPD group. The total number of lymph nodes involved in the EPD group (median, 26; range, 8-56) was larger than that in the SPD group (median, 19; range, 4-32; *P*<0.05; Table 1). Of the 93 patients in the SPD group, 41 (44.1%) had positive first-echelon N1 nodes and 7 (7.5%) had positive second-echelon N2 nodes. The mapping and number of patients (in parentheses) with positive second-echelon nodes N2 were as follows: superior mesenteric (6), hepatic (4), and hepatoduodenal arteries (4). Of the 72 patients in the EPD group, 40 (55.6%) had positive N1 nodes, and 21 (29.2%) had positive second-echelon N2 nodes. The mapping and number of patients with positive second-echelon nodes N2 were as follows: para-aortic (16), celiac (4), superior mesenteric artery (18), hepatic artery (9), and hepatoduodenal artery (6).

Postoperative survival

The median survival of the EPD group was 23.2 months. Follow-up ranged from 12-144 months (mean, 43.8 months). At the last follow-up, 46 patients (63.9%) were still alive, 21 patients (29.2%) had died, and 5 (6.9%) were lost in follow-up. The median postoperative hospital stay was 13.5 days (range, 8-76 days). The 1-, 3-, and 5-year survival rates were 86.1%, 43.1%, and 19.4%, respectively. Three patients (4.2%) survived for > 10 years, and 14 (19.4%) for > 5 years.

The median survival of the SPD group was 19.8 months. Follow-up ranged from 12 to 144 months (mean, 43.8 months). At the last follow-up, 64 patients (68.8%) were alive, 23 (24.7%) had died, and 6 (6.5%) were lost in follow-up. The median postoperative hospital stay was 12 days (range, 9-51 days). Overall, the 1-, 3-, and 5-year survival rates were 81.7%, 38.7%, and 16.7%, respectively. Three patients (3.2%) survived for >10 years, and 11 (11.8%) for > 5 years.

Postoperative recurrence and complications

In the SPD group, 34 patients (36.6%) had no postoperative

recurrences. Recurrence at a single site occurred in 47 patients (50.5%) and that at ≥ 2 sites in 12 patients (12.9%). The leading recurrence site was local (36/93, 38.7%); other recurrence sites were liver (16/93, 17.2%), peritoneum (10/93, 10.8%), and lymph nodes (3/93, 3.2%). In the EPD group, 30 patients (41.7%) had no recurrences. Seven of the 72 patients had diabetes mellitus before resection. Recurrence at a single site occurred in 27 patients (37.5%) and that at ≥ 2 sites in 11 patients (15.3%). The most common recurrence sites were local (13/72, 18.1%), liver (10/72, 13.9%), peritoneum (8/72, 11.1%), lung (4/72, 5.6%), and lymph nodes (2/72, 2.8%). The recurrence rates of the 2 groups showed no significant difference (52.7% vs. 43.1%, $P=0.83$).

Forty-five patients (62.5%) in the EPD group and 63 (67.7%) in the SPD group were discharged without nosocomial complications. Thirty patients (32.3%) in the SPD group had complications and 25 (34.7%) in the EPD group had complications ($P=0.93$). The presence of complications could not be determined in 4 patients of the EPD group because of inadequate clinical information. The most common complications were wound infections, pancreatic fistulas, and delayed gastric emptying (Table 2).

DISCUSSION

Hitherto, surgical resection is the only curative treatment for patients with pancreatic cancer. However, only 10%-20% of the diagnosed pancreatic cancer patients will proceed to surgical resection.¹⁰ During the past decade, there have been improvements in the management of patients with pancreatic cancer. The diagnostic technology has been refined and the resectability rate has increased.¹¹ Improvements and centralization of surgical techniques have elevated the safety of surgery for pancreatic cancer lowered operative mortality.^{12,13}

In spite of these improvements, the prognosis for patients with pancreatic cancer remains poor. This malignancy is highly fatal, with an overall 5-year survival rate lower than 4%. The poor prognosis is related to a lack

of specific symptoms, and the lack of effective non-operative treatment modalities.

Surgical resection of pancreatic cancer was complicated by high perioperative morbidity and mortality. Long-term survival results were equally dismal, with some studies reporting no 5-year survivors.¹⁴ With advances in surgical techniques, improvements in perioperative care, and centralization of expertise, perioperative mortality rates <5% are now commonly reported in large surgical centers.¹⁵ However, long-term survival has not seen clear improvement in spite of recent reports of increases in actuarial survival.¹⁶ Actual survival results are not as optimistic as actuarial estimates.

Pancreatic cancer is characterized by a high frequency of intrapancreatic neural invasion (75%-100%).¹⁷ Detailed knowledge of lymphatic drainage is essential for radical pancreatic cancer surgery. Interlobular lymphatics emerge on the surface of the pancreas, and travel with blood vessels toward a ring of lymph nodes that intimately surrounds the pancreas. Three-major lymphatic routes for the anterior surface of the pancreatic head have been identified.¹⁸ Detailed studies showed that lymph nodes near the primary tumor (posterior and anterior pancreaticoduodenal nodes) are generally involved first, and nodes further away from the primary tumor (superior mesenteric artery nodes, para-aortic nodes, common hepatic artery nodes, and hepatoduodenal ligament nodes) primarily show metastasis only after involvement of the first nodes.¹⁹⁻²¹

SPD includes a regional lymphadenectomy with *en bloc* resection of the lymph nodes around the duodenum and pancreas, including lymph nodes at the right side of the hepatoduodenal ligament (12b1, 12b2, and 12c), the posterior pancreaticoduodenal nodes (3a and 13b), the nodes to the right of the superior mesenteric artery from the origin of the superior mesenteric artery at the aorta to the inferior pancreaticoduodenal artery (14a and 14b), and the anterior pancreaticoduodenal nodes (17a and 17b). In addition, the lymph nodes in the anterior-superior region of the common hepatic artery (8a) are removed separately.

Table 2. Complications of patients with adenocarcinoma of the pancreatic head who underwent SPD or EPD [n (%)]

Groups	Pancreatic fistula	Wound infection	Biliary leak	Hepatic abscess*	Fascial dehiscence	Delayed gastric emptying	Venous catheter sepsis	Pleural effusion and pneumonia	Postoperative hemorrhage
SPD ($n=93$)	5 (5.38)	6 (6.45)	3	0	0	9 (9.68)	2 (2.15)	6 (6.45)	3 (3.23)
EPD ($n=72$)	4 (5.56)	6 (8.33)	2	1 (1.39)	1 (1.39)	12 (16.67)	0	3 (4.17)	2 (2.78)

*Caused by preoperative percutaneous biliary drainage for jaundice.

SPD neglects resection of the lymph nodes of the porta hepatis, abdominal aorta, celiac trunk, and soft tissues around the pancreas. Most patients have recurrence within 2 years after surgery, commonly in 9-12 months.²²⁻²⁴ The high rate of local recurrence after SPD gives rise to doubts on surgical radicality or pathologic specimen assessment. Once a standardized pathological examination protocol is implemented, R1 resections are found in up to 85% of specimens.²⁵ The margin most frequently involved is the dorsal resection margin, exactly where local recurrence is found in most cases. As in many other types of cancer, these results suggest that the current approach is not radical enough with regard to local tumor control.²⁶ Therefore, to surgically eradicate pancreatic cancer, a complete plexus dissection around the superior mesenteric artery, common hepatic artery, and celiac axis, including soft tissue removal, is entailed, which is not performed in SPD.

EPD includes removal of all the lymph nodes of group 16 with clearance of all connective and lymphatic tissues. All the lymphatic and neurovascular tissues of the anterior aorta, including the tissue around the celiac axis, are cleared. A left adrenalectomy is optional.⁹

This study retrospectively compared 2 groups (SPD and EPD) comparable in gender, age, the size of the neoplasms, and the rate of positive loco-regional lymph nodes, the results showed that there were no significant differences in the postoperative complication rates and perioperative mortality between the 2 groups, in agreement with the literature.^{27,28} In addition, the extended part of operation does not involve the digestive tract, therefore the rates of local complications are not increased, such as pancreatic leakage and biliary fistulas.

The intent of EPD was to improve survival, but the results of this study show no survival benefit. Although EPD can not prevent distant metastases, a previous study²⁹ has shown that it permits a more radical local resection, lowering the risk of local recurrence and prolonging long-term survival. The postoperative complications of EPD are similar with those of SPD.³⁰⁻³² In contrast, some researchers reported no difference in survival,^{33,34} similar with the findings of this study. Therefore, the long-term survival benefits of EPD in comparison with SPD are still controversial, whereas Pedrazzoli *et al*³⁵ reported a clear improvement after performing EPD rather than SPD. A systematic review reported a prolonged long-term survival after EPD as compared with SPD, and suggested that the recurrence after SPD is actually the residual of the primary tumor.²⁸ Hence, they concluded that EPD can be considered a valid technique for reducing loco-regional recurrence.

In conclusion, EPD does not improve long-term survival, decrease local recurrence after the radical resection. However, caution must be taken in interpreting the results of this study because of the small size of the studied groups. A more convincing conclusion can be drawn only with a large-scale, multicenter, randomised controlled study. It would be necessary to precisely standardize the EPD technique in order to ensure the comparability of the data collected in different centers.

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