

Original Article

A prospective, randomized trial of pancreatectomy combined with isolated hepatic perfusion via a dual route or conventional postoperative adjuvant therapy in patients with advanced pancreatic head carcinoma

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Abstract: Prognosis of locally advanced pancreatic head carcinoma after Whipple remains poor. This study is to investigate the efficacy and safety of regional lymphadenectomy and chemotherapy of isolated hypoxic perfusion (IHP) via dual-route, and to analyze the effect for survival period. Consecutive patients subjected to our department from January 1, 2006 to December 31 2011 for locally advanced pancreatic head carcinoma were prospectively divided into two groups according to therapeutic modality, and clinical and follow-up data was recorded. In study group, operation duration and postoperative stay time were shorter, blood loss and blood transfusion were less, and incidence of complications was lower. The mean and median survival time was 17.4 ± 0.76 months and 18.0 months in study group, longer than control group of 14.1 ± 0.85 months and 17.6 months. Regional lymphadenectomy can be performed with low mortality and morbidity, and combined postoperative IHP via dual-route can improve survival time.

Keywords: Pancreatic carcinoma, lymphadenectomy, Whipple, isolated hypoxic perfusion, chemotherapy

Introduction

Over the past twenty years, the incidence of pancreatic carcinoma in China has increased 2.5 times, and there were an estimated 60000 new cases and 54000 deaths in 2010 [1]. The median overall survival of pancreatic carcinoma is only 6-8 months, and less than 20% patients can live 12 months after diagnosis. Prolonged survival mainly relies on complete resection and a median of 12 months in large series can be reached with additional therapy [2].

For pancreatic carcinoma, more than 70% of them arise from the pancreatic head, and Whipple procedure, also known as pancreaticoduodenectomy (PD) is the standard surgical modus. With improvement in surgical skill and postoperative care, the resection rate and security of pancreatic carcinoma for Whipple have been greatly increased. However, for all pathological staging combined, 5-year survival

rate following Whipple is only 5% [3]. The primary reason for such a poor prognosis is that, in a substantial number of patients, most pancreatic head carcinoma is considered locally advanced at the time of diagnosis [4]. Early postoperative recurrence and metastasis of the carcinoma constrained severely the prognosis. In order to suppress the postoperative recurrence and metastasis of pancreatic carcinoma in early stage, focus was put on radical lymph node dissection, and extended retroperitoneal lymph nodes dissection during Whipple connected with postoperative systemic chemotherapy has been the mainstream therapeutic option for locally advanced pancreatic head carcinoma. Although survival period is definitely prolonged by this method, controversy remains on it because of high incidence of complications and impaired life quality. Furthermore, carcinoma recurrence and metastasis seems inevitable and improvement in prognosis is very limited.

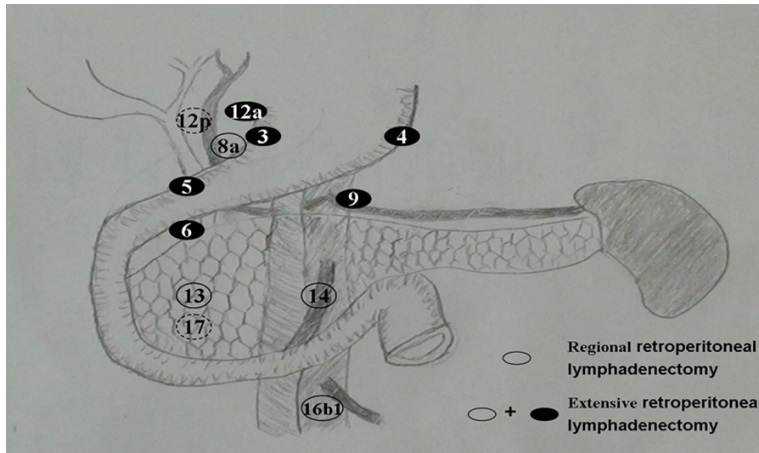


Figure 1. Lymph nodes to be dissected for locally advanced pancreatic head carcinoma.

In these years, based on the characteristic of retroperitoneal lymph node metastasis of locally advanced pancreatic head carcinoma, we intentionally designed and performed a series of regional retroperitoneal lymphadenectomy during Whipple to clean the micro metastasis of carcinoma lesion. At the same time, we put special effort on postoperative local chemotherapy and performed isolated hypoxic perfusion (IHP) via hepatic artery and superior mesenteric artery (dual-route) to suppress the recurrence and metastasis of carcinoma. In the current study, we investigated the efficacy and safety of this combined therapy for locally advanced pancreatic head carcinoma, and analyzed the effect of this therapy to prolong survival period by comparing with conventional methods.

Patients and methods

Patients

From January 1, 2006 to December 31, 2011, all consecutive patients subjected to our department for locally advanced pancreatic head carcinoma were enrolled in this study. The preoperational evaluation included history and physical examination, blood analysis, chest X-ray, dynamic pancreas and pelvic CT scan, gadolinium-enhanced MRI with cholangiopancreatography (ERCP) and angiography, and ¹⁸F-FDG whole-body fusion positron emission tomography/computed tomography (PET/CT) or endoscopic retrograde.

ERCP as needed. The resectability for locally advanced pancreatic head carcinoma was

determined by the multidisciplinary management team and the inclusion criteria were as follows: (1) tumor was confined to the pancreatic head and its surrounding retroperitoneal space; (2) simple invasion with short portion of the superior mesenteric vein (SMV) or portal vein (PV); (3) tumor was adjacent to the superior mesenteric artery or inferior vena cava, or encased the gastroduodenal artery; (4) the superior mesenteric vein was occluded, but proximal and distal segment were both unobstructed; (5) no invasion of the celiac trunk; (6) adequate function of vital organs.

According to the report from M. D. Anderson cancer center, simple invasion was defined as vessel involvement of less than half of the perimeter, and encasement was defined as more than half of the perimeter [5]. All included patients were randomly divided into two groups prospectively. One was study group with regional lymphadenectomy and dual-route IHP, and the other was control group with extended lymphadenectomy and systemic chemotherapy.

Surgical procedure

Whipple was performed as standard procedures. The resected organs included pancreatic neck, gastroduodenum, proximal jejunum, gallbladder and common bile duct. The margin of the pancreatic body was 3 cm far away from the tumor and was just in front of the superior mesenteric vein (SMV), where the uncinate process of pancreas was perfectly resected. In cases of SMV/PV invasion, segmental resection and reconstruction by end-to-end anastomosis or by an artificial vascular graft were performed. The following regional retroperitoneal lymphadenectomy was carried out according to the Japan Pancreas Society Classification made in 1996 (**Figure 1**). Regional lymphadenectomy included posterior and anterior pancreaticoduodenal lymph nodes (station 13 and 17), lymph nodes in the posterior-inner side of hepatoduodenal ligament (station 12p), and lymph nodes anterior to hepatic artery and

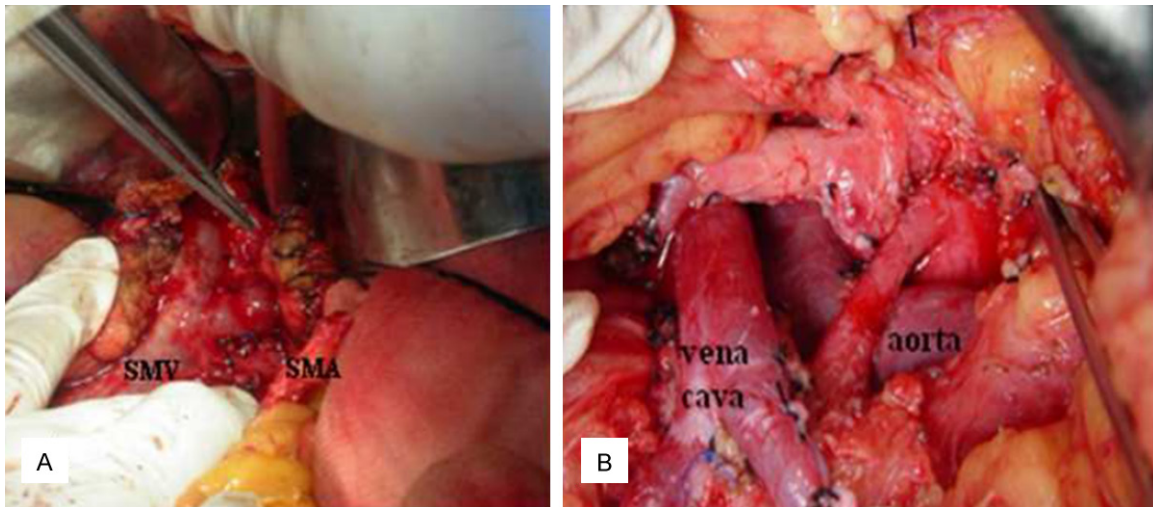


Figure 2. Peripancreatic vascular skeletonization during Whipple. A shows removal of the lymph nodes and soft tissue along the anterior aspect of the superior mesenteric artery and the superior mesenteric vein. B shows lymphadenectomy along the vena cava and aorta. SMV, superior mesenteric vein; SMA, superior mesenteric artery.

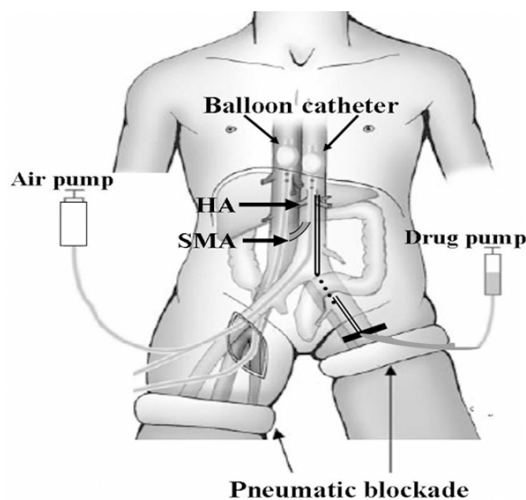


Figure 3. Schematic depiction of the isolated hypoxic perfusion (IHP) technique.

along the superior mesenteric artery (SMA, station 8a and 14). The lymph nodes before the aorta from the left renal vein to the inferior mesenteric artery (IMA, station 16b1) were also included in the regional retroperitoneal lymphadenectomy. For extended retroperitoneal lymphadenectomy, except for the lymph nodes mentioned above, resection of the gastric lesser curve and greater curve lymph nodes (station 3 and 4), superior and inferior pyloric lymph nodes (station 5 and 6), celiac lymph node (station 9), and lymph nodes in the inner side of hepatoduodenal ligament along hepatic artery (station 12a) were also included. All

resected lymph nodes were sent for frozen pathological examination during operation. The anterior and right lateral aspects of the SMA were all skeletonized, which meant dissection of lymph nodes and soft tissues along the anterior aspect of the SMA and the SMV, and clearance along the vena cava and aorta (**Figure 2**). This step was performed after removal of the specimen, and the retroperitoneal soft tissues and lymph nodes were dissected separately.

Digestive tract reconstruction was performed according to the modified Child's technique [5]. Pancreaticojejunal anastomosis was performed by means of end to side anastomosis. Tube gastrostomy or tube jejunostomy were not routinely performed. Internal duct tube stents were used in the anastomotic stoma of pancreatico-jejunal and cholangio jejunum. Two drainage tubes, one placed posterior to the pancreatic anastomosis and the other near to the omental bursa, were retracted 7 days post operation if no abnormality had been found.

H₂ receptor antagonists and octreotide were routinely used for 5 to 7 days post operation.

IHP techniques via dual-route regional chemotherapy and systemic chemotherapy schedule

IHP via dual-route regional chemotherapy was executed under anesthesia with intubation and extended cardiopulmonary monitoring. Two balloon catheters (arterial stop-flow catheter F12-

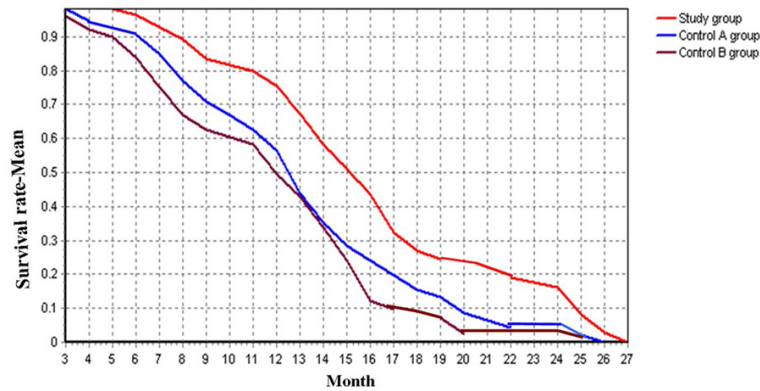


Figure 4. Survival curves of the study group and the control group. Red curve shows the survival curve of the control group; Green curve shows the survival curve of the study Group.

600 mm and venous stop-flow catheter F12-600 mm; PFM Produkte für die Medizin GmbH, 49133 Deetershofen, Germany) were introduced at the inguinal region into the common femoral artery and vein. The tip of the catheter was placed proximal to the branching of the celiac trunk (aorta) and hepatic veins (vena cava inferior). Cessation of blood flow in the periphery was achieved by using pneumatic blockades for perfusion at both thighs. Digital subtraction angiography (DSA) was used to image blood perfusion, to check correct and tight placement of the balloon catheters and to exclude leakage. Then 5-Fr Rosch hepatic catheters were placed using Seldinger's technique via the femoral artery of another side, and the position was confirmed by digital subtraction angiography (DSA) with the tip into the hepatic artery and the SMA (**Figure 3**). Chemotherapy regimen included gemcitabine (1000 mg/m²) and 5-fluorouracil (600 mg/m²). One-third of these drugs were given via hepatic artery and two-thirds via SMV. For initiation of chemotherapy, balloons and pneumatic blockades were completely shut after application of 5000 international units of heparin intravenously to prevent embolism and thrombosis. Using the technique, an isolated compartment was created including the whole abdominal cavity below the diaphragm, the retroperitoneal space and the pelvis. Patients in the study group undertook this therapy 4 weeks after the surgical procedure for first time, and repeated the cycle every 4-6 weeks for 6 cycles. Systemic chemotherapy was performed in the control group 4 weeks after operation and also used the regimen of gemcitabine combined with 5-FU. Gemcitabine (1000 mg/m²) and 5-fluorouracil (600 mg/m²)

through intravenous infusion way was given on 1st, 8th, and 15th day of each cycle with every 28 days forming a cycle. Each patient in the control group also repeated the cycle every 4-6 weeks for 3 cycles.

For all patients included in this study, demographic information, surgical management, pathological result, hospital course and follow-up data were recorded. Survival time was calculated from the day when radical operation was performed (**Figure 4**).

Statistical analysis

Data are presented as mean \pm standard error (SE). Numerical variables of the three groups were analyzed by U test ($n > 100$) and categorical variables were analyzed by Fisher's exact test and χ^2 test. Kaplan-Meier analysis and Log-Rank test were used to show and compare the survival rates. A value of $P < 0.05$ was considered statistically significant.

Results

137 patients with locally advanced pancreatic head carcinoma identified from January 1, 2006, to December 31, 2011 were performed laparotomy. 9 patients didn't undertake Whipple because of severe vital vascular invasion in 5 patients, metastasis to liver in 2 patients, and extensive adhesion with severe chronic pancreatitis in 2 patients, and only palliative operations were performed in them. 5 patients died in one week after Whipple because of arterial hemorrhage due to pancreatic fistula. 11 patients didn't undertake postoperative chemotherapy because of various reasons. They were all excluded from further analysis. The remaining 112 patients, including 57 patients of the study group (regional lymphadenectomy + dual-route IHP) and 55 patients of the control group (extended lymphadenectomy + systemic chemotherapy) underwent the whole radical operation and chemotherapy as planned.

The demographic and pathological findings showed that no difference existed in the gender composition, age and pathological types between these two groups. Comparing of the

Table 1. Demographic, clinical, and pathological variables of study group vs. control groups

Variable	Study Group (n = 57)	Control A Group (n = 55)	Control B Group (n = 51)	P
Sexuality				
Male	34 (59.6%)	36 (65.4%)	31 (60.8%)	0.80
Female	23 (40.4%)	19 (34.6%)	20 (39.2%)	
Age	47.5 ± 6.8	49.3 ± 7.2	47.2 ± 6.5	0.23
Operation duration	4.8 ± 0.6 h	6.8 ± 1.2 h	4.7 ± 0.7 h	< 0.01* 0.43# < 0.01&
Blood loss	320 ± 60 ml	550 ± 130 ml	340 ± 70 ml	< 0.01* 0.11# < 0.01&
Blood transfusion	550 ± 100 ml	850 ± 150 ml	580 ± 110 ml	< 0.01* 0.14# < 0.01&
Postoperative stay in hospital	15.8 ± 4.3 d	23.6 ± 7.7 d	16.1 ± 4.4 d	< 0.01* 0.72# < 0.01&
Resected lymph nodes	13.2 ± 3.6	22.4 ± 6.4	13.3 ± 3.5	< 0.01* 0.88# < 0.01&
Complication	16 (28.1%)	29 (52.7%)	14 (27.5%)	0.01* 0.94# 0.01&
Pancreatic fistula	9 (15.8%)	20 (36.4%)	7 (13.7%)	0.03* 0.76# 0.01&
Bile leakage	4 (7.0%)	13 (23.6%)	3 (5.9%)	0.01* 0.81# 0.01&
Infection	5 (8.8%)	9 (16.4%)	4 (7.8%)	0.30
Gastroplegia	2 (3.5%)	9 (16.4%)	2 (3.9%)	0.02* 0.69# 0.04&
Hemorrhage	3 (5.3%)	8 (14.5%)	5 (9.8%)	0.26
Stress ulceration	2 (3.5%)	3 (5.5%)	2 (3.9%)	0.87
R status				
R0 resection	53 (93.0%)	52 (94.5%)	48 (94.1%)	0.94
R1 resection	4 (7.0%)	3 (5.5%)	3 (5.9%)	
Pathological type				
Ductal adenocarcinoma	45 (78.9%)	43 (78.2%)	40 (78.4%)	0.98
Mucinous adenocarcinoma	8 (14.0%)	7 (12.7%)	6 (11.8%)	
Neuroendocrine carcinoma	4 (7.0%)	5 (9.1%)	5 (9.8%)	
Differentiation				
Middle differentiation	20 (35.1%)	17 (30.9%)	16 (31.4%)	0.88
Poor differentiation	37 (64.9%)	38 (69.1%)	35 (68.6%)	

*Study group vs. Control A group, #Study group vs. Control B group, &Control A group vs. Control B group.

operation-related variables showed that the average operation duration and postoperative stay time were much longer in the control group ($P < 0.01$), the average blood loss and blood transfusion in peri-operative period were also significant more in the control group ($P < 0.01$). The number of resected lymph nodes in the study group was 13 ± 3.6 (ranging from 11 to 16), while the number in the study group was 22 ± 6.4 (ranging from 20 to 31), and the difference was statistically significant ($P < 0.01$). Comparing of the incidence of postoperative complications, including pancreatic fistula, bile leakage and gastroplegia, showed that the study group was lower than the control group ($P < 0.05$), but no difference was found in the incidence of intra-abdominal infection and hemorrhage, and in the incidence of stress ulceration between the two groups (Table 1).

In the study group, SMV invasion was found in 17 patients. 11 of them undertook segmental resection and reconstruction by end-to-end anastomosis, and the other 6 undertook vascular lateral resection. PV invasion was found in 5 patients, with segmental resection and man-made vascular grafts were performed for them. In the control group, SMV invasion was found in 16 patients. 12 of them undertook segmental resection and reconstruction by end-to-end anastomosis, and the other 4 undertook vascular lateral resection. PV invasion was found in 4 cases, and segmental resection and man-made vascular grafts were also performed for them. Vascular invasion rate of PV/SMV in these two groups did not differ (38.6% of the study group vs. 36.4% of the control group, $P > 0.05$). Lymph nodes metastasis was confirmed by immunohistochemical tests in 43 patients

Table 2. Metastasis of carcinoma to lymph nodes of study group vs. control group

Lymph node group	Positive cases			P
	Study group (%)	Control A group (%)	Control B group (%)	
8a (anterior to hepatic artery)	11 (19.3%)	9 (16.4%)	8 (15.7%)	0.87
12p (posterior-inner side of hepatoduodenal ligament)	13 (22.8%)	10 (18.2%)	11 (21.6%)	0.82
13 (posterior pancreaticoduodenal)	25 (43.9%)	22 (40.0%)	21 (41.2%)	0.91
14 (around the superior mesenteric artery)	30 (52.6%)	29 (52.7%)	24 (47.1%)	0.80
16b1 (aorta from left renal to inferior mesenteric artery)	10 (17.5%)	9 (16.4%)	6 (11.8%)	0.67
17 (anterior pancreaticoduodenal)	12 (21.1%)	10 (18.2%)	9 (17.6%)	0.89
3 (lesser curvature)	—	3 (5.5%)	—	—
4 (greater curvature)	—	2 (3.6%)	—	—
5 (superior pyloric)	—	3 (5.5%)	—	—
6 (inferior pyloric)	—	5 (9.1%)	—	—
9 (around the celiac trunk)	—	6 (10.9%)	—	—
12a (inner side of hepatoduodenal ligament along hepatic artery)	—	4 (7.3%)	—	—
Total	43 (75.4%)	40 (72.7%)	36 (70.6%)	0.85

(75.4%) from the study group and in 40 patients (72.7%) from the control group respectively, and no difference existed ($P > 0.05$). The metastasis to lymph nodes of station 13 and 14 were most frequently observed in the both groups, and the categorized comparison according to metastatic lymph station showed no difference existed between the study group and the control group ($P > 0.05$). Extended lymphatic metastasis was confirmed in 7 patients (12.7%) of the control group, and the detailed data were shown in **Table 2**.

Regular follow-up was given to all of the 112 patients and nobody was lost. In the study group, 19 patients died in first year, 10 patients died in second years, and 7 patients died in third year. 21 patients were still alive until termination of the study, with 15 of them survived more than 1 year. The mean and median survival time was 17.4 ± 0.76 months and 18.0 months respectively. In the control group, 27 patients died in first year, 9 patients died in second year, and no patients survived more than 2 years. 19 patients were still alive until termination of the study, with only 6 patients survived more than 1 year. The mean and median survival time was 14.1 ± 0.85 months and 17.6 months respectively. Difference between the study group and control group was significant ($P < 0.05$). **Figure 4** shows the Kaplan Meier survival curve of these two groups.

Discussion

To prolong the survival period of patients suffering from carcinoma of pancreatic head, radi-

cal resection such as Whipple was proposed to increase the radical resection rate and to improve the prognosis. American Joint Committee on Cancer (AJCC) classifies pancreatic carcinoma into stage 0~IV, with stage 0~II were regarded as resectable and III~IV unresectable [6]. However, carcinoma in a stage between II and III, also known as locally advanced carcinoma, occupies a great proportion in clinics, and adds much uncertainty to the performance of radical operation [7]. Clinical practice guidelines in pancreatic adenocarcinoma of National Comprehensive Cancer Network (NCCN) 2008 pointed out that [8], microscopically positive margins (R1) and residual lymph micro-metastasis were the main indications of poor prognosis for locally advanced pancreatic carcinoma after radical operation. Just in order to improve the long-term survival of pancreatic head carcinoma at locally advanced stage, some surgeons put emphasis on the improvement of operation modus and proposed extended retroperitoneal lymph nodes dissection so that microscopically negative margins (R0) could be acquired. In this operation, except for N1 nodes dissection, including nodes of anterior and posterior pancreaticoduodenal, nodes in the lower hepatoduodenal ligament, and nodes along the right lateral aspect of the SMA and SMV. N2 nodes dissection was also added, including sequential retroperitoneal lymphadenectomy from the right renal hilum to the left lateral border of the aorta in the horizontal axis and from the PV to the IMA in the vertical axis, as well as celiac node dissection, was undertaken [9]. But because the positive rate of second-order nodes (N2) was only 15%, while operation-relat-

ed mortality could reach 20%, an extended retroperitoneal lymphadenectomy after standardization has been widely used. This operation includes N1 node dissection of station 6, 8a, 12a, 12p, 13, 14, and 17, N2 node dissection of station 9 and 16b1, and N3 node dissection of station 3 and 5 [10]. Whipple and extended retroperitoneal lymphadenectomy of standard, combined with systemically adjuvant chemotherapy has been the most widely used surgical method for pancreatic head carcinoma at locally advanced stage in China since beginning of this century [11]. In this study, we used this method as control, and acquired a median survival time of 14.1 months, longer than the median survival time of 8-10 months reported in Surgery Branch of Chinese Medical Association [12].

However, some surgeons still doubt the actual benefit of extended retroperitoneal lymphadenectomy. In an attempt to calculate the number of patients who would benefit from an extended lymphadenectomy in association with Whipple for adenocarcinoma of the pancreas, Pawlik et al. [13] offered a mathematical equation based on three assumptions. The author postulated that an extended lymphadenectomy would be of benefit only to patients with N2 positive, in whom Whipple was performed with R0 resection in the absence of distant metastatic disease. By assigning percentages to these three categories, and he calculated that only 1 in 250 patients would benefit from an extended lymphadenectomy. Furthermore, although extended retroperitoneal lymphadenectomy increases the rate of complications such as delayed gastric emptying and pancreatic fistula, and prolongs the duration of surgery and length of stay, the recurrence and metastasis of pancreatic cancer still seemed to be inevitable and long-term survival wasn't obviously improved [14]. So some Japanese surgeons began to have a full review for the scale of lymphadenectomy and try to get a "balance" between the long-term survival and postoperative quality of life. In these years, regional lymphadenectomy based on the characteristic of retroperitoneal lymph node metastasis of locally advanced pancreatic carcinoma was getting more attention. Nakao [15] reported that pancreatic adenocarcinoma in the head tended to metastasize towards posterior pancreaticoduodenal and the superior mesenteric lymph node group (46% and 35% respectively). Ishikawa [16] also

reported that the positive rate of station 13 was 49%, station 17 was 37%, station 16b1 was 47%, and station 12p was 15%. Jin's study was accordance with Ishikawa. He found that the positive rates of station 14 and 8a were also comparatively high, and extended lymph dissection to station 3, 4, 5, 6, 9 and 12a contributed little to survival improvement [17]. All of these studies provide solid basis for the performance of regional lymphadenectomy. In this study, we performed regional lymphadenectomy in association with Whipple for carcinoma of the pancreatic head, with the scale of lymphadenectomy smaller than most literatures, and acquired a satisfactory surgical effect. Our series study proved that the positive rate of extended lymph nodes for resectable pancreatic head carcinoma was only 12.7%, consistent with the results mentioned above.

In addition to surgical method, some surgeons also put emphasis on postoperative chemotherapy as an effective adjunctive therapy to prevent carcinoma recurrence and metastasis. Systemic chemotherapy was generally considered the standard treatment for pancreatic carcinoma. However, the clinical outcome of most advanced pancreatic carcinoma is marginally affected by this therapeutic modality [18]. Furthermore, patient quality of life may be heavily impaired and death may occur during systemic chemotherapy treatments because of side-effects following it, and finally, systemic chemotherapy may be contraindicated in patients because of a poor general condition or advanced age [19]. In the pursuit of new therapeutic approaches, loco-regional treatments claim the advantage of providing high drug concentrations at the tumor site combined with a low systemic toxicity. The IHP technique has been introduced in these years as a semi-invasive loco-regional drug delivery system [20]. This therapeutic approach is based on the interruption of the blood supply to the anatomical region of the tumor by means of inflatable balloon catheters. As well as having the pharmacokinetic advantage of reaching high drug concentrations at the tumor site, the IHP technique exploits the pharmacodynamic synergism between some antitubercular drugs and hypoxia. The results of the initial experiences with IHP in locally advanced abdominal cancer have been promising, with more than 50% response rates and an increase in median survival reported [21]. Although encouraging

results have been reported in terms of both feasibility and therapeutic activity, only a small number of clinical trials in pancreatic carcinoma have been conducted. In this study, we used IHP regional chemotherapy via dual-route for patients after Whipple and regional lymphadenectomy to prevent recurrence and metastasis of the tumor. Compared with traditional regional chemotherapy, IHP can take effects by introducing the theoretical advantages of increased drug exposure time, reduced systemic exposure and regional induction of hypoxia [22]. In consideration of hepatic metastasis of pancreatic cancer were most likely to happen, we chose both hepatic artery and superior mesenteric artery as perfusion route, because the chemotherapeutic drugs in superior mesenteric artery can be collected by portal vein and perfuse the liver again. Although deep venous thrombosis is the most frequently reported procedure related complication, no obvious deep venous thrombosis happened in our study. Only some minor complications with wound infection and ecchymoma were met in the study, and the systemic toxicity was very low with only 20% of the 57 patients. Our study showed that the postoperative survival time of the study group was obviously longer than the control group, and we think that the dual-route IHP regional chemotherapeutic method has contributed a lot to it.

Conclusion

In summary, regional lymphadenectomy with PD for locally advanced pancreatic head carcinoma can be performed with low mortality and morbidity. Combined with dual-route IHP regional chemotherapy to prevent the early postoperative recurrence and metastasis of tumor, survival time can be obviously prolonged and perspective of this surgical method is worth expecting. At present, regional lymphadenectomy and IHP are still considered as investigational approaches and review of cases in large sample should be made to evaluate the concrete effect.

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Disclosure of conflict of interest

None.

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