

Experience for Management of Surgical Treatment in Patients with Carcinomas of the Pancreatic Head or Periapillary Region

LUO Tao¹, LI Xing², GONG Jianping², LI Qujin^{2,*}

¹Department of General Surgery Hospital of traditional Chinese medicine of Yubei, Chongqing, 401120, China

²Department of Hepatobiliary Surgery, the Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China

*Corresponding author: 312436339@qq.com

Abstract Objective: Pancreaticoduodenectomy was considered as the standard choice of surgery treatment to carcinomas in the pancreatic head or periapillary region. This study will focus on the experience summary to manage the patients with carcinomas in the pancreatic head or periapillary region who underwent surgery treatment in west area of China to investigate the different surgical methods, prognosis and long term survival. Method: We consecutively reviewed 73 patients underwent surgery treatment in our hospital between January 2007 and December 2011. Surgery treatment described as radical operation of PD treatment and palliative operation of choledochojejunostomy plus drainage. We assessed different variables to summarize the management of patients and to evaluate the long term survival. Result: 32 patients received PD treatment and 41 patients received palliative surgery treatment. Histologic diagnosis indicated that all patients had malignant disease. PD procedures spent more time to complete the operation. 3 patients in PD group developed pancreatic fistula and 1 of them died on the seventh days postoperative. 2 patients developed wound infection and 1 patient developed malnutrition which finally reversed by medical intervention. The postoperative mortality in PD group was observed in 2 of 32 patients. The postoperative mortality in PD group was 6.25% (n=2). Long term survival of PD and palliative surgery group was described as 15.4 months and 5.6 months respectively. Conclusion: The treatment of patients with carcinomas in the pancreatic head or periapillary region continues to be associated with high incidence of postoperative complications. Early diagnosis and pancreaticoduodenectomy represents the only possibility of cure.

Keywords: carcinomas in the pancreatic head or periapillary region, pancreaticoduodenectomy, choledochojejunostomy plus drainage, palliative operation

Cite This Article: LUO Tao, LI Xing, GONG Jianping, and LI Qujin, "Experience for Management of Surgical Treatment in Patients with Carcinomas of the Pancreatic Head or Periapillary Region." *American Journal of Cancer Prevention*, vol. 5, no. 1 (2017): 1-9. doi: 10.12691/ajcp-5-1-1.

1. Introduction

The term "carcinomas in the pancreatic head or periapillary region" refers primarily to cancers that develop in the pancreatic head as well as distal cholangiocarcinoma, ampullary carcinoma and duodenal carcinoma. They are considered to cause the same symptom: obstructive jaundice. Pancreatic cancer accounts for only 2% of new cancers in the United States and it is the fourth leading cause of cancer deaths [1]. The over-all 5-year survival rate was reported as 4%. About 15% to 20% of patients have resectable disease at the time of presentation [2]. Surgical resection is the only chance of cure, but the surgical resection offers the only chance for cure with reported 5-year survival rates of 8% to 21%. In 1898, Halsted performed the local excision of carcinoma of ampulla of Vater. In 1909, Kausch performed the first successful regional resection of a periapillary tumor. Finally, in 1940, Whipple completed the whole pancreaticoduodenectomy (PD) with a reconstruction of the alimentary tract including gastroenterostomy, cholecystogastrostomy and

pancreaticojejunostomy. Within the technique and surgery equipment developed, the postoperative mortality decreased dramatically, but the postoperative morbidity has remained between 30%-50% [3], which result in prolonged hospitalization and effect in the postoperative living quality. In our study, we assess the preoperative general state of health, laboratory values, operative details, the histologic diagnosis, the length of staying ICU, the length of staying hospital, the main postoperative complications which including delayed gastric empty, pancreatic fistula, biliary fistula, gastrointestinal fistula, intro-abdominal abscess, early or delayed intro-abdominal hemorrhage and wound infection and long term survival in order to summarize and investigate the experience of management to patients performed pancreatico- duodenectomy or palliative surgery in west area of China.

2. Patients and Methods

Between January 2009 and December 2013, 73 consecutive patients underwent surgery treatment at the Department of Hepatobiliary Surgery, the Second

Affiliated Hospital, Chongqing Medical University, China. All operations were performed by experienced surgeons in our institution. All patients were received ultrasonographic (US), computer tomography (CT) or magnetic resonance image (MRI) examination in order to evaluate the lesion of the pancreatic head or periampullary region before surgery intervention. CT/MRI is also recommended for the detection of distant metastases. 32 patients were performed pancreaticoduodenectomy and 41 patients were performed palliative operation. Data on preoperative, intraoperative, and postoperative was collected carefully. Preoperative parameters including patient demographics as age and gender, presenting symptom as obstructive jaundice, abdominal pain and weight loss, laboratory values as hemoglobin, concentrations of serum albumin, total bilirubin level, prothrombin time (PT), diabetes mellitus, CA19-9 and preoperative biliary drainage; intraoperative parameters include total operative time, type of resection, blood loss, and blood transfusion. Mortality was defined as death occurring within 30 days of the operation or during postoperative hospitalization [4]. Postoperative complications were recorded according to the following definition. Postoperative hemorrhage refers to a significant drop in hemoglobin level or hemodynamic in stability which necessitates blood transfusion. Postoperative hemorrhage can be recognized to early phase and delayed phase according to the period of the complication occurring. Early postoperative hemorrhage defined as the hemorrhage within the first 24 hours after surgery which is caused by technical failure and generally requires immediate laparotomy whereas delayed postoperative hemorrhage defined as the break point on the fifth postoperative day or later which carries a high mortality. Pancreatic fistula defined as any measurable drainage from an operative place drain on or after postoperative day 3, with an amylase content greater than 3 times the upper limit of normal serum amylase level [5]. Delayed gastric empty defined as patients were failure to resume oral liquid intake by postoperative day 10, and/or emesis > 500 ml on or continued nasogastric drainage > 500 ml on or after postoperative day 5. Biliary leakage defined as bilious drainage from intraoperative placed drainage tube. Wound infection was defined as presence of pus requiring wound opening and draining. Treatment of the postoperative complications was also recorded. Histologic diagnosis was showed in Table 1 and confirmed by the pathologists. All tumors should be classified according to the TNM staging system in order to guide the treatment. R0 resection defined as no microscopic evidence of tumor at any of edges of the resection specimen even there are lymph node metastases. No prophylactic somatostatin or octreotide was given before the operation. VitK was supplied to all patients to correct the preoperative coagulopathy caused by obstructive jaundice. All patients had been received intravenous broad-spectrum antibiotic treatment, H2 blocker fluid and electrolyte supplement and omeprazole routinely during the entire postoperative hospital course. The nasogastric tube was removed when the bowel sounds returned, usually on the postoperative day 1 or 2 in palliative surgery group versus on the postoperative day 7 or 9 in PD group. Parental nutrition supplement had been performed for 7 days since the surgery in both groups. Patients underwent PD had

received total enteral nutritional supplement since the 14th day. The peribiliary drains were removed in the fifth days postoperative. If there was evidence of anastomotic leakage or any sign of an infective complication, the drains were left in place until the problem resolved. If draining tube was left longer, the infection risk would be increased [3]. Patients with histology-proven malignancy were in poor conditions which were not permitted to receive adjuvant therapy. None of the 32 patients in PD group received adjuvant chemotherapy. 41 patients performed palliative surgery were received gemcitabine and oxaliplatin loaded a dose of 1000 mg/m² and 85 mg/m² respectively on days 1 and 7 of 14-days cycle as chemotherapeutic adjuvant treatment. Long term survival status (alive vs. dead) was determined by the following-up telephone interview as well as the record of re-examination in hospital. All data in this study were collected and reported in strict compliance with patient confidentiality guidelines and approved by Chongqing Medical University Committee Board.

2.1. Operational Techniques

Pancreaticoduodenectomy: Patients underwent pancreaticoduodenectomy in our department with a radical lymphadenectomy of portal and/or superior mesenteric artery region, in order to achieve R0 resection. Pancreaticoduodenectomy was performed via midline incision. Abdominal exploration performed routinely followed by generous Kocher maneuver which were performed first to determine whether the Superior Mesenteric Vein (SMV) or portal vein (PV) was invaded by tumors. If no invasion to the periampullary region, the gallbladder was removed first and the transected the common bile duct.

The anterior aspect of the portal vein was then dissected free of the pancreatic neck. The regional lymph node clearance was including the soft tissue and nodes around the pancreatic head and along the superior mesenteric vein-splenic vein confluence. Subsequently, the stomach was transected by endoscopic linear cutter, followed by transection of the pancreatic neck, uncinate process, and jejunum distal to the ligament of the Treitz. Truncal vagotomy was performed in most patients undergoing hemigastrectomy. Reconstruction was undertaken with a limb of jejunum in retrocolic fashion and anastomosed with an end-to-side pancreaticojejunostomy, followed by an end-to-side choledochojejunostomy and an end-to-side gastrojejunostomy. The pancreaticojejunostomy was performed using a duct-to-mucosa anastomosis. The pancreaticojejunostomy and choledochojejunostomy were drained out of the abdominal wall routinely. Finally, for necessary, some patients in the series according to the condition underwent prophylactic gastrostomy placement or not for postoperative stomach decompression and alimentation.

Palliative surgery treatment: Choledochojejunostomy plus drainage was performed in our hospital in order to decrease the serum bilirubin level. The procedures were performed via midline incision. Laparotomy and a generous Kocher maneuver were performed routinely in order to determine whether the SMV or PV and inferior caval vein or abdominal aorta was invaded by tumor. If

invasion was involved the periampullary region which mans radical resection of the tumors could not be performed and there is no metastasis to liver or gastric duct, choledochojejunostomy should be performed as the palliative operational treatment. Adhesions between the duodenum and hilus of the liver should be divided carefully then needed blunt dissection. Great care must be exercised to avoid unnecessary bleeding and possible injury to the underlying structures. We exposed tissue directly toward identifying the foramen of Winslow. Cut the jejunum 15-20 cm away from the Treitz ligament. Then separate, cut, ligate the mesentery, which ends being wrapped in gauze. The distal

Jejunum would be pulled in front of the transverse colon in order to anastomosis with the distal common bile duct. Enclose the posterior and anterior wall by stitches, finally sutured the proximal and distal jejunum and suture mesenteric fissures. A T-tube may be used for selected patients with difficult anastomoses. Intra-abdominal drainage out of the abdominal wall should also be performed routinely.

2.2. Statistics

Data were expressed as means \pm standard error of the mean. Median values of continuous data were computed by using independent T test. A p-value less than 0.05 were considered statistically significant. All confidence levels were at the 95% level. Long term survival was estimated using the non parametric product limit method (Kaplan-Meier) and plot the graph. All statistic analyses were performed by using SPSS 17.0.

3. Results

Preoperative variables

A total 73 patients were enrolled to receive surgery treatment in this study. The mean age of the subject was 62.35 years old (ranges, 28-90). Preoperative imaging was performed in all patients with CT scan or MRI. 32 patients received PD treatment and 41 patients received palliative surgery treatment. Different variables according to characteristics, preoperative factors and preoperative laboratory findings of these patients were recorded in [Table 1](#). Obstructive jaundice was the most common presenting symptom in both 2 groups (n=56). The mean level of hemoglobin was 113.50 ± 20.20 mg/L in PD group and 112.10 ± 18.0 mg/L in palliative surgery group. The mean concentration of serum albumin in PD group was 36.90 ± 5.70 mg/L compared to 36.80 ± 5.20 mg/L in palliative surgery group. The serum total bilirubin level was indifferent in both groups, described as 182.80 ± 142.90 μ mol/L and 215.30 ± 171.50 μ mol/L respectively. 4 patients with the high serum total bilirubin more than 342 μ mol/L received preoperative biliary drainage in PD group compared 6 patients in palliative surgery group. 14 patients with the histologic diagnosis of pancreatic ductal adenocarcinoma had been got a high level of CA19-9 than those with other histologic type in both PD group and palliative surgery group. 38 patients diagnosed of pancreatic ductal adenocarcinoma had been got a high level of CA19-9. 22 patients with the histologic diagnosis of pancreatic ductal adenocarcinoma had been got

preoperative diabetes mellitus in both groups (8 patients in PD group and 14 patients in palliative surgery group).

3.1. Pathological Findings

Histologic diagnosis confirmed all patients with malignant disease (pancreatic ductal adenocarcinoma in 53 patients, ampullary carcinoma in 2 patients, distal cholangiocarcinoma in 3 patients and duodenal carcinoma in 15 patients of PD group versus 39 pancreatic ductal adenocarcinoma patients and 2 ampullary carcinoma patients of palliative surgery group). Histologic diagnosis showed that the patients in palliative surgery group with pancreatic ductal adenocarcinoma were more than the patients in PD group whereas the patients in palliative surgery group with ampullary carcinoma were less than the patients in PD group. Definitive pathological reports showed lymph nodes metastases in 16 patients and PV/SMV or retroperitoneal tissue involvement in 10 patients of PD group. In palliative surgery group, all patients had lymph node metastases or PV/SMV or retroperitoneal tissue involvement. All patients were reported that the pancreatic, gastric and bile duct resection margins were free from tumor involvement and received an R0 resection in PD group.

3.2. Operative Information

There were significant differences between the 2 groups in the variables of operation time, blood loss, blood transfusion, the length of staying ICU, the length of staying hospital and the main postoperative complications. ([Table 1](#)). PD procedures were much more complicated than palliative surgery procedures which spent more time to complete the operation. The mean operation time was 548.28 ± 111.78 min in PD group and 217.29 ± 65.96 min in palliative surgery group. The mean blood loss was 942.18 ± 287.12 ml in PD group which was significantly higher than in palliative surgery group. Patients required an average transfusion of 618.75 ± 192.50 ml of packed red blood cells in PD group. Patients in palliative surgery group require the average transfusion of 51.22 ± 116.45 ml of packed red blood cells in palliative surgery group. Limited blood loss (mean blood loss: 51.22 ml) and the homeostatic assessment can explain the difference in two groups. The mean size of lesion in pancreatic head or periampullary region was recorded as the diameter of 4.5cm and the mean diameter of common bile duct was 1.5 cm in PD group. Data including size of lesion and diameter of common bile duct were not available in palliative surgery group because of limited material recording.

3.3. Postoperative Complications

The overall postoperative morbidity across all the study groups was 38.3%, and PD group developed more possibilities (59.3%) to occur postoperative complications which caused the longer ICU staying and hospital staying. No patients stay in ICU after palliative operation. The mean length of staying ICU was 1.06 ± 0.25 days and the mean length of staying in hospital was 33.88 ± 14.59 days in PD group. The most common complication was delayed gastric empty (37.5%). 3 patients in PD group developed

pancreatic fistula and 1 of them died of pancreatic leakage in the seventh day postoperative according to the serum trypsinogen more than 5 times the upper limit of normal level. The average postoperative total bilirubin level were $75.93 \pm 74.05 \mu\text{mol/L}$ in PD group compared $109.39 \pm 94.97 \mu\text{mol/L}$ in palliative surgery group. PD and palliative surgery both could provide an efficient way to decrease the total bilirubin level (Table 2). 2 patients developed wound infection and one patient developed malnutrition which finally reversed by medical intervention.

The postoperative mortality in PD group was 6.2% (n=2). One patient described as before. Another patient underwent pancreaticoduodenectomy following by mass bleeding and died in ICU staying. In palliative surgery group, no patient died after operation. Comparisons of preoperative and postoperative varied in patients of 2 groups have identified the laboratory values and presenting symptom smoothed quickly which mean the radical lesion excision and alimentary tract reconstruction provide more effective surgery treatment.

Table 1. Different variable according to patient characteristics, preoperative factors and preoperative laboratory findings

Variables	Standard PD	Palliative Surgery
Patients characteristics:		
Age (mean)	59,(22-77)	67,(29-90)
Gender:		
Male	21	22
Female	11	19
Tumor histologic diagnosis:		
Pancreatic ductal adenocarcinoma	14	39
Duodenal carcinoma	13	0
Ampullary carcinoma	2	0
Distal extrahepatic cholangiocarcinomas	3	2
Major Symptom:		
Jaundice	32	24
Upper abdominal pain or vague uncomfortable	7	15
Weight loss	2	0
Preoperative laboratory test:		
Hemoglobin (mg/L)	113.53±20.24	112.12±18.02*
Serum albumin (mg/L)	36.93±5.74	36.81±5.21*
Total bilirubin level ($\mu\text{mol/L}$)	182.87±142.93	215.30±171.49*
PT (second)	13.12±1.69	12.81±1.20*
Preoperative biliary drainage		
Total operative time	548.28±111.78	217.29±65.96#
Blood loss	942.19±287.12	209.76±124.11#
Blood transfusion	618.75±192.50	51.22±116.45#
Postoperative complication:		
DGE (delayed gastric empty)	12	3
Pancreatic fistula	3	0
Wound infection	2	1
Mulnutrition	1	0
Postoperative hemorrhage	1	1
Lung infection	0	1
Acite	0	3
Chemotherapy	0	48
Death	2	0

*p>0.05, #p<0.05.

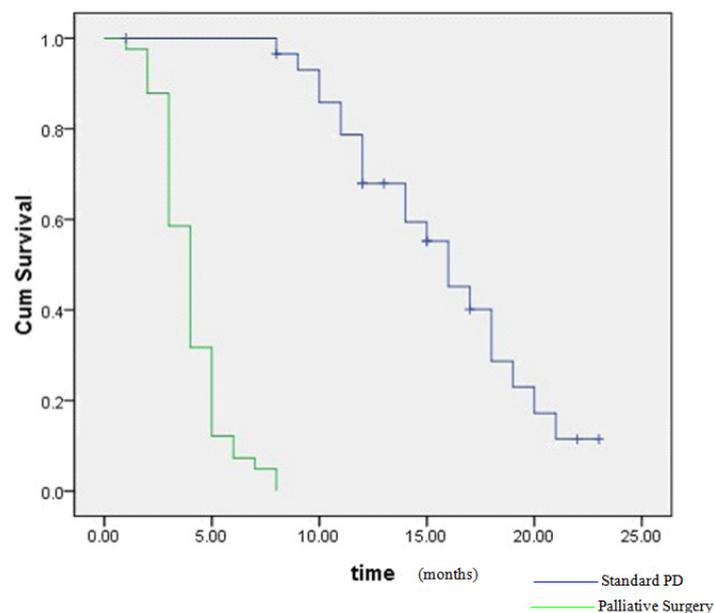


Figure 1. Survival curve of PD group and palliative surgery group

Table 2. Total Bilirubin levels for each group.

Group	PD	Palliative Surgery
Pre-operation (μmol/L)	177.77 ± 144.01	215.30 ± 171.49
Post-operation (μmol/L)	75.93 ± 74.05*	109.39 ± 94.97*

*p<0.05.

3.4. Long Term Survival

The median survival time of patients underwent PD treatment was 20 months (95% CI, 15.71-24.29 months) compared to 4 months (95% CI, 3.47-4.53 months) of patients underwent palliative surgery. 68 patients totally died from the disease related recurrence or metastasis. 3 patients with the histological diagnosis of ampullary carcinomas were alive in PD group during the follow-up period. Figure 1 shows the Kaplan-Meier survival curves for 2 groups of patients with two different surgery treatments. In patients underwent palliative surgery, mortality was 100% and there was no patient who lived for 1 year after operational treatment.

4. Discussion

Carcinoma which developed at periampullary region is still an incurable disease. Surgery remains the gold standard for the treatment of carcinomas in the pancreatic head or periampullary region. Even in patients who are surgical candidates, the 5-year overall survival remains dismal, with a median overall survival of approximately 12 months after pancreaticoduodenectomy (PD) and The post-operative 5-year survival rate is only around 20% in pancreatic cancer patients. With advances in pathological technology, it has been found that actually 20-86% of pancreatic head cancer patients do not actually reach the R0 resection after the surgical treatment and the R1 resection in many pancreatic head cancer patients has been believed to be caused by the incomplete resection of the mesopancreas [6,7]. But some researchers insisted extended lymphadenectomy has been proved to increase postoperative morbidity with no benefit to prolong the survival. Despite the advance in diagnosis and the improvement in survival recent years, postoperative morbidity of these patients are common. In this study, we found that PD did have beneficial effect on the prognosis of carcinomas in the pancreatic head or periampullary region compared to palliative operation. We support the viewpoint that patients who underwent a radical operation with adequate lymph nodes dissection will lead to a longer survival and also a high—quality living standard. In this study, we cite our experience during the past 4 years with 73 cases underwent surgery treatment. Evaluation of patients with carcinomas in the pancreatic head or periampullary region received PD procedures was focused on the four directions including pre-operative, intra-operative, post-operative evaluation and long-term survival.

The patients of carcinomas in the pancreatic head or periampullary region usually present the painless jaundice as the first symptom to seek treatment. Weight loss was another common symptom. Every patient should received physical examination after staying hospital. The signs would help surgeons to diagnose the disease. But the

result of most patients revealed no more abnormalities. Only a few patients feel vague discomfortable or slight upper abdominal pain when hands pressed on the upper abdomen. The laboratory tests were routinely performed to every patient. Preoperative laboratory values were important factors associated with survival.

There are many factories associated with the survival of carcinomas in the pancreatic head or periampullary region [8]. Elevation of serum total bilirubin, glucose and CA19-9 levels could predict poor survival. A report shows that CA19-9 and CEA are associated with the prognosis of carcinomas in the pancreatic head or periampullary region [9]. Serum total bilirubin level was an important factor because patients with elevation of serum total bilirubin would be likely to have MOF leading to death. The level of serum total bilirubin was all above the upper limitation. If patient with jaundice for a long period, preoperative biliary drainage should be considered to be conducted. Van der Gaag [10] and Eshuis [11] reported that the preoperative biliary drainage could not improve survival to patients whereas increase the postoperative morbidity and prolong the hospital staying which was consistent to our experience. Only 4 patients in PD group and 6 patients in palliative group received the intervention, 4 patients in PD group receive the intervention because they all got a high level of serum total bilirubin more than 342 umol/L for 2 months which were deemed as urgent to resolve the high serum bilirubin level. The date of operation delayed one week and no more relative complication occurred. Other 6 patients in palliative surgery group received the intervention because of high level of serum total bilirubin, low level of total protein and albumin which may make patients not hold the operative shock.

Other factors were less significant associated with survival or long term survival, but also could reflect the whole condition of the patient. Despite the preoperative laboratory values mentioned above, diabetes mellitus should be deemed as an independent factor. Diabetes in patients of pancreatic cancer was general conditions, which have been widely reported being associated with the BMI and family history. Diabetes was more prevalent (4%-64%) in patients with new-onset tumor lesion, which might become a powerful diabetogenic state [12]. Some researchers advocated that the duration of diabetes less than 4 years may predict increasing risk of pancreatic cancer, and very few studies have directly define the new-onset diabetes. In 2009, Pannala defined the new-onset diabetes as diabetes reported to be < 2 years duration. Strategy of using hyperglycemia as a screening tool to predict the probability of having asymptomatic pancreatic cancer must be differentiated from the type 2 diabetes. The exact pathogenesis of new-onset pancreatic cancer associated diabetes remains unknown. The tumor grade and endocrine secreted function of the gland may have been involved in pancreatic cancer associated diabetes. Patients with resected tumor in the head of the pancreas always got a high blood glucose level for a moment. Tumor resection may resolve the pancreatic cancer associated diabetes. In this study, 22 patients with the histologic diagnosis of pancreatic ductal adenocarcinoma were deemed as preoperative diabetes mellitus. Specific histologic diagnosis may be associated with the abnormality of blood glucose level. Further investigation should be

conducted. CA19-9 was an important biomarker which has been demonstrated useful for disease diagnosis and therapeutic monitoring of pancreatic cancer. In our study, the level of CA 19-9 in the blood of all patients diagnosed as pancreatic duct adenocarcinoma were all greater than three times upper to the limitation (37U/ml). But the same result was not observed in other patients with different pathologic diagnosis. CA19-9 was not a specific biomarker. In patients with pancreatitis the level of CA19-9 may increased. The replaced biomarker should be further investigated. Imaging examination was considered widely to be used to diagnose and evaluate the patients. In our study, we use helical computed tomography (HCT), multi-detector computed tomography (MDCT), magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) as the imaging technique to improve the accuracy of the diagnosis and tumor stage division. But only about 15-20% patients with carcinomas in the pancreatic head or periampullary region have resectable disease at the time of presenting. Imaging examination has a very high positive predictive value for unresectability, but it is less accurate for predicting respectability. The preoperative imaging may not accurate to imply vascular invasion of the pancreatic tumor into the critical vessels. Bipat had reported the sensitivity and specificity of HCT for tumor resection of 81% and 82%. Other research had reported the MDCT yielded a negative predictive value of 100 percent, with no false negative finding, and an accuracy of 99% for detection of vascular invasion [13]. MDCT technique allows to figure out the relation between the tumor, superior mesenteric celiac axis, superior mesenteric vein, portal vein and also the distant organs. The imaging showed a mass located in the head of the pancreas, with or without the dilation of the pancreatic duct and encompassed the blood vessels. Further diagnostic methods were also recommended, such as endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography (ERCP). The former technique did not perform routinely in our institution because the MDCT was much more convenient to collect datas of tumor involvement. The later technique was also a useful treatment to relieve jaundice caused by bile duct obstruction. We prefer percutaneous transhepatic biliary drainage (PTCD) to perform the preoperative bile duct drainage rather than ERCP according to the experience. The complications of ERCP included bile duct perforation and hemorrhage at sphincterotomy could delay surgery which may affect the resection rate and survival. In our study, the patients in PD group did not received chemotherapy, because it may prolong recovery period before or after operation and provide no benefit on the survival rates when compared with historical trials. But 41 patients in palliative surgery group were received gemcitabine plus oxaliplatin as chemotherapeutic adjuvant treatment. These treatments were performed in order to downstage the local tumor advance and improve the survival rate after palliative operation. But the results were still dismal. A series studies have proved chemoradiation therapy was superior to radiation therapy, but the effect was too toxic. The exact effect of chemoradiation was disputable. No evidence could get a firm conclusion [14]. Most studies supported the treatment would not show any benefit in survival rate, so in our institution, we did not

perform the chemoradiation as the routine adjuvant treatment.

The effect on prophylactic use of perioperative somatostatin and its analogues to prevent the postoperative complication remains controversial [2]. The effect of suppressing the exocrine pancreatic secretion may prevent postoperative complication. But no definite evidence has proved the benefit of the interventional procedure. In our institution, somatostatin loaded a dose of 100 µg per day were received by patients routinely for 3 days after PD. The type of operation was strongly associated with survival. Blood loss during the operation was a significant factor associated with poor survival. But blood transfusion may help to weak the association between blood loss and survival. Despite of these factors, we deemed PD continues to be a challenging and substantially morbid procedure but an effective surgery way to be conducted.

4.1. Postoperative Complications

The postoperative morbidity remains high and approaches 50% even in large series. The complications of pancreatoduodenectomy contain two parts, one is general complications and other is Specific complications. Pancreatoduodenectomy is a major surgery, patients suffered long time anesthesia and huge surgical trauma, so it has general complications frequently. The common general complications are incision infection, pulmonary infection, urinary tract infection, etc. For these general complications, we should strict to the principle of asepsis, use antibiotics in the perioperative period to prevent the infection, establish the unobstructed drainage, strength the sputum and autonomous urination early.

The special complications included pancreatic fistula, Bile leakage, postoperative hemorrhage, delayed gastric empty, diabetes mellitus and so on.

The key determinant of outcome after pancreatoduodenectomy remains the pancreaticoenteric anastomosis. Sepsis and hemorrhage, caused by pancreatic fistula, are associated with mortality of 20% to 40% and result in prolonged hospitalization and increased hospital expenses.

Operation time, operation skill and reasonable surgical anastomosis were closely related to pancreatic fistula. The most important treatment for pancreatic fistula is unobstructed drainage, fasting and somatostatin are promoting the treatment of pancreatic fistula. Pancreatic fistula as a major complication was considered to take significant suffering to patients received PD procedures. Experienced surgeon as an important factor to reduce the morbidity was necessary to perform the operation. Researchers reported the risk factor associated to postoperative pancreatic fistula could be evaluated by the time-signal intensity curve of pancreas (TIC) analysis which evaluated based on dynamic contrast enhanced MRI. The texture of remnant pancreas based on the pancreatic TIC analysis confirmed that a hard texture of pancreatic gland and dilated pancreatic duct allow a more robust anastomosis and a lower output of pancreatic enzymes which reduce the risk of postoperative pancreatic fistula after PD procedure by experienced surgeon whereas the rate of pancreatic fistula was higher in patients with small pancreatic duct and minimal fibrosis of

the pancreatic remnant [2,5]. There is no difference of influence between different anastomotic methods which caused pancreatic fistula. Only the fetal pancreatic fistula caused abdominal sepsis (described above) or hemorrhage needs relaparotomy. Pancreatectomy plus splenectomy were considered as the only effective way to solve the complication and avoid death of patient, but this procedure is rarely performed now. Only when extensive necrosis occurred, the aggressive procedures were the way to save patient's life, and the mortality remains high. Yoshio reported the prediction scoring system as "Estimation of Physiologic Ability and Surgical Stress" (E-PASS) to predict postoperative morbidity and mortality [16]. The Total Risk Point designed of 9 different scores was significant correlated to the occurrence of the complication. Although the two method of predicting postoperative morbidity were standard, the obvious risk factors were not observed in the patient of PD group who died in the 7th day after operation. The patient received antibiotic, somatostatin and blood transfusion to the fatal pancreatic fistula caused erosive hemorrhage, then he refused to performed exploratory laparotomy, finally died of MOF. The pancreatic fistula remains a continuous issue for the surgeon.

Bile leakage is another common complication. The reasons for bile leakage are free bile duct too long and anastomosis not tight. Usually the bile drainage, anti-infection treatment and good nutrition support could promote the healing of bile leakage effectively.

Postoperative hemorrhage as another common and serious complication occurs to be 3.9% of patients after PD procedures. Postoperative hemorrhage mainly includes abdominal bleeding and gastrointestinal bleeding. There are three factors associated with the prognosis which described as time of bleeding, localization and severity of bleeding. Suddenly deteriorated signs of patients, peritoneal bloody drainage and spontaneous drop in hemoglobin levels were caused by postoperative hemorrhage as the three ingredients which could help surgeons to detect the postoperative hemorrhage as early as possible. However, despite the high mortality, the complicated procedures largely depend on equipment of hospital, enough blood transfusion for hemostasis and experienced expertise availability. Hemostasis during operation, especially for pancreas wound and intestinal anastomosis, could control postoperative hemorrhage effectively. During the operative period, interventional angiography may provide the precise localization of the bleeding during the relaparotomy. Postoperative stress ulcer bleeding should be considered as an independent postoperative hemorrhage, which may not need surgical intervention. Hemostatics plus Omeprazole or cimetidine were effective treatment. If necessary, blood transfusion should also be applied.

Diabetes mellitus as an independent factor of postoperative complication was always turn to normal level automatically or by insulin contral. A research suggested when 80% or more of the pancreas was removed, hyperglycemia occurred immediately, and diabetes did not occur when less than 70% was removed. But in our study, recording of postoperative blood glucose level between the 2 groups were not sufficient to be analyzed. Further investigation should be conducted.

Some researchers advocated that liver abscess was another ominous complication which increased risk of sepsis and death. The risk factors contributed to liver abscess was associated with malignance liver metastasis and the type of liver-directed therapy [15]. But in our study, no patients had been developed liver abscess during the in-hospital procession. Perhaps there was no liver metastasis aggressed of the patients in our study.

Delayed gastric empty (DGE) was reported with the incidence ranging from 7% to 37% in most studies. DGE was not life-threatening compared to other post operative complication [17]. But in our study, DGE was the most common postoperative complication. The true pathogenesis of DGE remains unclear. Most reports advocated the rate of patients underwent pylorus-preserving pancreatectomy developed DGE was more frequent than patients underwent standard pancreatectomy. The rate of DGE was also considered to be associated to the anastomotic method. The anastomotic type of pancreaticojejunostomy may decrease the occurrence of DGE. Yeo reported that giving erythromycin after PD reduced the incidence of DGE from 30% to 19% [17]. The treatment for delayed gastric empty is mainly to control infection, continuous gastrointestinal decompression, balance of water and electrolytes, the proper using of drugs to promote gastrointestinal peristalsis and gastric lavage with warm saline and so on. Patients in our institution were received nutrition and enzyme supplementation before the normal diet was returned. All patients with DGE finally were recovered.

4.2. Operational Technique

The prognosis may be associated with the stage of the carcinomas and the clearance of the positive lymph nodes as well as the option of surgery. Total resected rate (100%) and long-term survival can prove this viewpoint. The preoperative assessment is the one of the most significant steps, and the resectable assessment for carcinomas in the pancreatic head, orperiampullary region is the most important part. It is associated with the prognosis and complications [18]. Tumors are considered unresectable when metastatic disease or local vascular invasion is present. The vessels often involved are the celiac trunk, the hepatic artery, the superior mesenteric artery, as well as, the superior mesenteric vein and the portal vein. According to the biology of the tumor cell and the specific anatomical position, tissue of peripancreatic head are more inclined to be invaded, especially SMV and PV. Patients with SMV and PV involved of tumors have to abandon surgery treatment. Some researchers advocated the venous reconstruction by using of polytetrafluoroethylene (PTFE) in PD to remove the tumors metastasized in SMV or PV, but the prognosis were controversial. Traditional segmental vascular resection was typically performed using autologous vein, but prosthetic grafts were generally avoided due to concerns of increased infection and decreased patency. Performing the venous reconstruction may lead the mass intra-operative bleeding [19]. The survival of patients received extended pancreatoduodenectomy with vascular resection was similar when compared to patients after standard pancreatoduodenectomy. The regional lymph node dissection was performed including clearance

of the soft tissue and nodes around the head of the pancreas and along the confluence of superior mesenteric vein and splenic vein. Lymphadenectomy was still considered to play an important role in the management of patients with lymph nodal disease [20].

In our institution, the major venous resection is not routinely performed during Whipple procedure. The Kocher maneuver [21] is able to expose the aorto-caval area and perform lymphadenectomy. The method first was a better choice enable surgeon to identify the presence of the early SMA involvement. The procedure could also help surgeon to identify the most common aberration of hepatic artery which was replaced by right hepatic artery arising from the SMA and avoid to impairing or ligating the SMA.

Some surgeons put forward radical nerve dissection in the carcinoma of head of pancreas [22]. And radical nerve dissection could get potential advantages in the fields of surgery-associated risk and prognosis compared with the Whipple, but this view need further well-designed research of large sample size to confirmed. Another viewpoint shows a surgical technique using an isolating tape, then oriented extrapancreatic nerve plexus for first dissection in PD [23]. Recent studies reported the prognosis of patients with vein resection and vascular reconstruction was similar to the prognosis of patients without vein involvement. Poor prognostic factors included lymph node metastasis, a high tumor grade and positive margins of resection. Despite the absence of the gold standard of pancreaticoenteric reconstruction, the methods have been described more than 80 different types. But anastomose pancreatic remnant with jejunum or stomach is the common practices. In our institution, we choose the former one as the routine program of the procedure. The type of pancreatic anastomosis mainly described as in invagination anastomosis and in “duct-to-mucosa” anastomosis. The former method makes the cross section of the pancreatic remnant completely insert into the jejunal loop, and the later method primarily makes the pancreatic duct sutured to the mucosa of the jejunal loop. The pancreatic secretion needs to be drained by the purse-string suture line of the jejunal wall to cover the pancreatic draining duct. The draining duct was placed by stitches through the abdominal wall. “Duct-to-mucosa” with end-to-side pancreaticojejunostomy was the routine procedures in our institution, even if the prognosis of the invagination anastomotic technique was not significantly different. The operational procedure of pancreaticojejunostomy was performed by 4-5 transpancreatic U-suture to close the pancreatic remnant but avoid impairing the main pancreatic duct first. Then anastomosed the posterior part of jejunal wall with pancreatic remnant. The main duct should be stitched by 6-0 prolene to adaptable jejunal loop. The duct of pancreatic secretion should be inserted into the main pancreatic duct and guided into the jejunum without lateral aperture. Purse-string suture should be conducted beneath the anastomosis more than 10 cm to stable the draining duct which should be left out through the abdominal wall. Finally finished the anterior parts of jejunal wall with pancreatic remnant. The procedures were performed by experienced surgeon in our institution. Other reports have suggested mostly the surgeon’s experience with different operational technique was the

most important factor to minimal the postoperational complication.

4.3. Pathologic Diagnosis

The pathological type and stage are associated with the prognosis and complications postoperative closely for patients with carcinomas in the pancreatic head or periampullary region [24]. Pathologic diagnosis with TMN classification was a significant guideline in helping to manage patients. The TNM classification was described as reference mentioned. T4 plus N0 or N1 represented the tumor involved the celiac axis or superior mesenteric artery which could not be removed totally. The common contraindication of radical surgical treatment was deemed as local advanced tumors (T3/T4 tumor) with vascular involvement of the critical adjacent vessels [25]. This viewpoint was consistent to our experience. Despite the distant metastasis, the resection of vessels or arteries improved the rate of intraoperative bleeding which may lead to increase the risk of postoperative morbidity and mortality. Different tumor tissue with TNM classification may predict the prognosis of the patients. Pancreatic duct adenocarcinoma with more than stage 3 of TNM classification had lower survival than any other type. Some researchers concluded that tumor grade was not only the factor to predict the prognosis of cancer developed in the pancreatic head. Lymph nodes status maybe another factor contributed to the long term survival. The positive margin status was significantly correlated with lymph nodes status. Katz reported the rate of microscopically positive margins of PD specimens ranged between 16% and 85% [25]. R1 pancreatic tumor may represent a biologically more aggressive cancer [26]. The existence of positive lymph nodes, margin—positive status, poor differentiation and not receiving PD predicted a lower survival.

In contrast to the survival curves of PD and palliative surgery groups, PD can supply a better long term survival, but more postoperative morbidity even leading to death. The clinical benefit of extended PD procedures must be balanced with the postoperative risk. The long term survival of the patients with tumor stage II or stage III who underwent PD, is significantly higher than those after palliative operation. If patients with tumor stage more than III (including III), the tumor could not resected completely palliative operation may provide a sufficient method to ameliorate obstructive jaundice, duodenal obstruction, nausea, impairment of liver biologic function, ascites, gastric hemorrhage and losing weight. The median survival of unresectable pancreatic cancer was 4–6 months, which meant living after operation for no more than 1 year which was consistent to our research data. In our study, statistic suggested the morbid state of patients postoperative 30-day after palliative operation is better. But this result could not replace PD as the golden standard treatment to carcinomas in pancreatic head or periampullary region. Statistic also indicated that operational treatment was important to patients with higher stage tumor.

This study is important because it summarizes the experience of surgery and postoperative management of patients in the southwest area of china who underwent radical pancreaticoduodenectomy. We found that the

overall morbidity following PD procedure was 59.3% which represented more postoperative complication, but prolonged the long term survival when compared to palliative surgery treatment. The curable treatment is still need to be explored and the guideline should be provided in helping to clinically manage this group of patients with the aggressive disease.

5. The Way Forward

Carcinomas in the pancreatic head or periampullary region will remain a challenging problem to surgeons. Improvements of the treating technique will be expected to facilitate the progression of the management to the patients. Understanding the molecular mechanism of the cancer may be helpful to develop a series treatment of inhibiting specific signal transduction pathways that mediate the aggressive biology of cancer. Operational treatment with adjuvant treatment plus molecular interventional treatment may become a novel direction for carcinomas in the pancreatic head or periampullary region.

Acknowledgments

Shan-mao Nie and Xing Li contributed equally to this work. The Second Affiliated Hospital of Chongqing Medical University is thanked for providing the data of this study. The heading of the Acknowledgment section and the References section must not be numbered.

References

- [1] Schmidt C Max, Powell Emilie S, Yiannoutsos Constantin T, et al. Pancreaticoduodenectomy a 20-year experience in 516 patients. *Arch Surg*. 2004; 139: 718-725.
- [2] Lai EC, H, Lau SH, Y, Lau WY. Measures to prevent pancreatic fistula after Pancreatoduodenectomy. *Arch Surg*. 2009, 144: 1074-1080.
- [3] Kong Justin, Ganadha Sivakumar, Hugh TJ, et al. pancreaticoduodenectomy: role of drain fluid analysis in the management of pancreatic fistula. *Anz J. Surg*, 2008; 78: 240-244.
- [4] Fuks David, Piessen Guillaume, Huet Emmanuel, et al. Life-threatening postoperative pancreatic fistula (grade C) after pancreaticoduodenectomy: incidence, prognosis, and risk factors. *Am J Surg*, 2009; 197: 702-709.
- [5] PatrikPessaux, Alain Sauvanet, Christophe Mariette, et al. External pancreatic duct stent decreases pancreatic fistula rate after pancreaticoduodenectomy: prospective multicenter randomized trial. *Ann Surg*, 2011; 253: 879-855.
- [6] Weitz J, Rahbari N, Koch M, et al. The "artery first" approach for resection of pancreatic head cancer. *J Am Coll Surg*. 2010; 210:e1-4.
- [7] Gaedcke J, Gunawan B, Grade M, et al. The meso-pancreas is the primary site for R1 resection in pancreatic head cancer: relevance for clinical trials. *Langenbecks Arch Surg*. 2010, 395: 451-8.
- [8] Petrou A1, Soonawalla Z, Silva MA, at al. Prognostic indicators following curative pancreatoduodenectomy for pancreatic carcinoma: A retrospective multivariate analysis of a single centre experience. *J BUON*. 2016 Jul-Aug; 21(4):874-882.
- [9] Xu HX, Liu L, Xiang JF, et al. Postoperative serum CEA and CA125 levels are supplementary to perioperative CA19-9 levels in predicting operative outcomes of pancreatic ductal adenocarcinoma. *Surgery*. 2016 Nov 9. [Epub ahead of print].
- [10] Van der Gaag, Rauws Erik A.J, Van Eijck Casper H, et al. Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 2010; 362: 129-137.
- [11] Eshuis Wietse J, Van Der Gaag N A, Rauws Erik A, et al. Therapeutic delay and survival after surgery for cancer of the pancreatic head with or without preoperative biliary drainage. *Annals of Surg* 2010; 252: 840-849.
- [12] Pannala Rahul, Leirness Jeffery, Bamlet William R, et al. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. *Gastroenterology* 2008; 134: 981-987.
- [13] Olivie Damien, Lepanto Luigi, Billiard Jean Sébastien, et al. Predicting resectability of pancreatic head cancer with multi-detector CT. Surgical and pathologic correlation. *JOP* 2007; 8: 753-758.
- [14] Hidalgo Manuel. Pancreatic cancer. *N Eng J Med* 2010; 362: 1605-1617.
- [15] De Jong Mechteld C, Farnell Michael B, Sclabas Guido, et al. Liver-directed therapy for hepatic metastases in patients undergoing pancreaticoduodenectomy. *Ann Surg* 2010; 252: 142-148.
- [16] Haga Yoshio, Wada Yasuo, Takeuchi Hitoshi, et al. Prediction of anastomotic leak and its prognosis in digestive surgery. *World J Surg* 2011; 35: 716-722.
- [17] Kawai Manabu, Yamaue Hiroki. Analysis of clinical trials evaluating complications after pancreaticoduodenectomy: a new era of pancreatic surgery. *Surg Today*, 2010; 40: 1011-1017.
- [18] Wu W, Wang X, Wu X, et al. Total mesopancreas excision for pancreatic head cancer: analysis of 120 cases. *Chin J Cancer Res*. 2016 Aug; 28(4):423-8.
- [19] Chu Carrie K, Farnell Michael B, Nguyen Justin H, et al. Prosthetic graft reconstruction after portal vein resection in pancreaticoduodenectomy: a multicenter analysis. *J Am CollSurg* 2010; 211: 316-324.
- [20] Chua Terence C, Saxena Akshat. Extended pancreaticoduodenectomy with vascular resection for pancreatic cancer: a systematic review. *J Gastrointest Surg*, 2010; 14: 1442-1452.
- [21] Xu Yufei, Liu Zuojin, Gong Jianping. Pancreaticoduodenectomy with early superior mesenteric artery dissection. *Hepatobiliary Pancreat Dis Int*. 2010, 9: 579-583.
- [22] Lin Q, Tan L, Zhou Y, et al. Radical nerve dissection for the carcinoma of head of pancreas: report of 30 cases. *Chin J Cancer Res*. 2016 Aug; 28(4):429-34.
- [23] Fujioka S, Misawa T, Yanaga K. Isolating tape method is useful for an early judgment of curability during pancreaticoduodenectomy forpancreatic cancer. *J Hepatobiliary Pancreat Sci*. 2016 Oct; 23(10): 20-24.
- [24] Yan L, Siddiqui AA, Laique S, et al. A large multicenter study of recurrence after surgical resection of branch-duct intraductal papillary mucinous neoplasm of the pancreas. *Minerva Gastroenterol Dietol*. 2016 Nov 8. [Epub ahead of print]
- [25] Werner Hartwig, Thilo Hackert, Ulf Hinz, et al. Pancreatic cancer surgery in the new millennium better prediction of outcome. *Ann Surg* 2011; 254: 311-319.
- [26] Katz Matthew H G, Merchant Nipun B, Brower Steven, et al. Standardization of surgical and pathologic variables is needed in multicenter trials of adjuvant therapy for pancreatic cancer: results from the ACOSOG Z5031 trial. *Ann Surg Oncol*, 2011; 18: 337-344.