ORIGINAL ARTICLE

Selective radical resection for unresectable pancreatic cancer

Resección radical selectiva para el cáncer de páncreas irresecable

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Abstract

Objective: *The objective of the study was to evaluate safety and value of radical resection for unresectable pancreatic cancer (UPC).* **Materials and methods:** *Clinical data were analyzed retrospectively. In unresectable group, 360° resection of the involved artery sheath, resection and reconstruction of the involved artery, resection and reconstruction of the involved vein as well as resection and reconstruction of combined organs were, respectively, performed. Operation time, intraoperative blood loss, intensive care unit (ICU) transitional treatment, pancreatic fistula, bleeding, reoperation, and survival time were analyzed for two groups.* **Results:** *Operation time and intraoperative blood loss were greatly increased in the unresectable group. The incidence of intractable diarrhea and abdominal hemorrhage in the unresectable group was higher. However, the rate of ICU transitional therapy, delayed gastric emptying, and reoperation was lower. Grade C pancreatic fistula occurred in neither group.* **Conclusions:** *Surgical treatment through strict selection for patient with UPC is safe and their median survival time is similar to patient with resectable pancreatic cancer.*

Keywords: *Pancreatic cancer. Radical resection. Complications. Survival time. Prognosis.*

Resumen

Objetivo: *evaluar la seguridad y el valor de la resección radical para el cáncer de páncreas irresecable (CPU).* **Material y métodos***: Los datos clínicos se analizaron de forma retrospectiva. En el grupo irresecable, se realizó resección de 360° de la vaina de la arteria afectada, resección y reconstrucción de la arteria afectada, resección y reconstrucción de la vena afectada, así como resección y reconstrucción de órganos combinados, respectivamente. Se analizaron el tiempo operatorio, la pérdida de sangre intraoperatoria, el tratamiento transitorio en la UCI, la fístula pancreática, el sangrado, la reintervención y el tiempo de supervivencia para dos grupos.* **Resultados:** *El tiempo de operación y la pérdida de sangre intraoperatoria aumentaron considerablemente en el grupo irresecable. La incidencia de diarrea intratable y hemorragia abdominal en el grupo irresecable fue mayor. Sin embargo, la tasa de terapia de transición en la UCI, el retraso del vaciamiento gástrico y la reintervención fueron menores. La fístula pancreática de grado C ocurrió en ninguno de los grupos.* **Conclusiones:** *el tratamiento quirúrgico mediante selección estricta del paciente con CP irresecable es seguro y su mediana de supervivencia es similar a la del paciente con CPR.*

Palabras clave: *Pancreatic cancer. Radical resection. Complications. Survival time. Prognosis.*

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Introduction

Patients with pancreatic cancer have poor prognoses[1,2]. Because pancreas is closely related to blood vessel and pancreatic cancer infiltratively grows, it is prone to invade portal vein, superior mesenteric vein (SMV) and superior mesenteric artery (SMA) to make its operation more difficult. In domestic and foreign guidelines for diagnosis and treatment of pancreatic cancer, based on the relationship between tumor and blood vessel, pancreatic cancer is divided into three types: resectable, borderline resectable and unresectable. For pancreatic head carcinoma, if (1) SMA is encapsulated by the tumor more than 180° and the tumor is close to celiac artery trunk; or if (2) SMV or portal vein is involved to make resection or reconstruction impossible; for pancreatic carcinoma of body and tail, if (1) SMA or celiac artery trunk is encapsulated more than 180°; or if (2) SMV and portal vein is involved to make resection or reconstruction impossible, the tumor is considered to be unresectable[3,4]. However, in addition to pre-operative imaging evaluation, the resectability of pancreatic cancer is closely related to experience and ability of surgeons[5,6]. There is no identical standard for clinical application in unresectable pancreatic cancer (UPC)[7,8]. We selectively carried out radical surgery on some patients with UPC and explored its safety and significance compared with the surgery for resectable pancreatic cancer (RPC).

Material and Methods

Patients

Patients with pancreatic cancer who underwent radical resection from August 2010 to January 2018 in Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine and had complete follow-up data were selected. Inclusion criteria were the patients being diagnosed as pancreatic cancer before operation through enhanced CT and/or enhanced MRI, together with tumor markers; no distant metastasis; with resectable tumor according to pre-operative imaging and intraoperative judgment, vascular invasion and possible arterial sheath resection or vascular segmental resection and reconstruction. There were 77 patients with pancreatic cancer undergoing radical surgery during the above period, including 43 males and 34 females, aged 47-79 years, with a median age of 63.5 years. There was no significant difference in gender and age between the two groups ($p > 0.05$), which was comparable. According to the guideline[3], 69 cases were resectable (to form a resectable group) and eight cases were unresectable (to form an unresectable group) for more than 180° of arterial encapsulation or vein invasion for neither resection nor reconstruction. There were 56 cases and six cases of pancreatic head carcinoma, respectively, in the resectable group and in the unresectable group, and 13 cases and two cases of pancreatic carcinoma of body and tail in the two groups. There were seven cases of tumor invading artery and one case of tumor invading vein for carrying out neither resection nor reconstruction in the unresectable group (Table 1).

Treatment and surgical procedures

Radical resection with no pre-operative chemotherapy was performed on the patients in the resectable group. While pancreaticoduodenectomy (PD) with standard or extended lymphatic dissection was performed upon the patients with pancreatic head carcinoma, pancreatic splenectomy with standard or extended lymphatic dissection was performed on the patients with pancreatic carcinoma of body and tail. Chemotherapy was performed for three cases in the unresectable group before operation, of which, two cases were treated with gemcitabine and one case was treated with modified Folfirinox. The other five cases refused preoperative chemotherapy, so they were not treated with it. PD was performed on the patients with pancreatic head carcinoma in the unresectable group. According to preoperative imaging and intraoperative vascular exploration, we performed 360° arterial sheath resection or resection and reconstruction of the involved artery and the involved vein. Pancreatic splenectomy was performed on the patients with pancreatic carcinoma of body and tail in the unresectable group. According to pre-operative imaging examination, intraoperative vascular exploration and adjacent organ involvement, 360° arterial sheath resection or resection and reconstruction of the involved artery and combined organs were performed. 360° arterial sheath resection was performed (Figure 1) while SMA or celiac trunk artery sheath was encapsulated more than 180° but arterial sheath was not involved. Arterial resection and reconstruction were performed on the patients with arterial adventitia and intimal infiltration (Figure 2). Respective anastomosis of Y-type iliac

Table 1. The data of the unresectable group

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (years)	68	54	63	64	61	64	64	55
Gender	male	male	male	female	Male	male	male	female
Position	head of pancreas	head of pancreas	pancreatic body and tail	pancreatic body and tail	head of pancreas	head of pancreas	head of pancreas	head of pancreas
Tumor vascular invasion	more than 180° of SMA encapsulation	SMV was all involved with jejunal vein, ileum vein, and portal vein	more than 180° of celiac trunk encapsulation	more than 180° of celiac trunk, hepatic artery and splenic artery encapsulation	more than 180° of SMA encapsulation and splenic vein involvement	more than 180° of SMA encapsulation and SMV invasion	more than 180° of SMA encapsulation	more than 180° of SMA encapsulation
Pre-operative chemotherapy	No	No	Yes	Yes	No	Yes	No	No
Operation	PD+360° SMA sheath resection	PD+resection of affected segment vein+ reconstruction of Y-type iliac artery and portal vein and jejunal ileovenous anastomosis	360° celiac trunk artery sheath resection+ pancreas body tail splenectomy resection+total gastrectomy resection+left lateral lobe resection	resection of celiac trunk and common hepatic artery with end-to-end anastomosis+ pancreas body tail splenectomy resection	PD+SMA root resection, left gastric artery anastomosis with SMA end-to-end and reconstruction, splenic vein resection in the invaded segment and other splenic vein exclusion	PD+360° SMA sheath resection+ affected SMV resection and end-to-end anastomosis reconstruction	PD+360° SMA sheath resection	PD+360° SMA sheath resection
Operation time（min）	340	450	300	360	630	600	330	350
Intraoperative blood loss（ml）	700	800	900	700	900	1000	500	600
ICU transitional treatment	No	No	No	No	No	No	No	No
Pancreatic fistula	No	No	No	Grade B	No	No	No	Grade A
Diarrhea	Yes	No	No	No	Yes	Yes	No	Yes
Delayed gastric emptying	No	No	No	No	No	No	No	No
Postoperative bleeding	No	No	No	Yes	No	No	No	No
Reoperation	No	No	No	No	No	No	No	No
Post-operative chemotherapy	No	Yes	No	Yes	Yes	No	No	Yes
Survival time（months）	8.1	12.5	26.3	13.1	13.2	10.3	16.6	15.4

Survival time has been followed up until August 1, 2018.

artery allografts with portal vein and venae jejunales et ilei was performed on the patients whose SMV was all involved, with portal vein involvement at the top and jejunal ileal vein below (Figure 3). Extended lymphatic dissection was performed on the patients in the unresectable group.

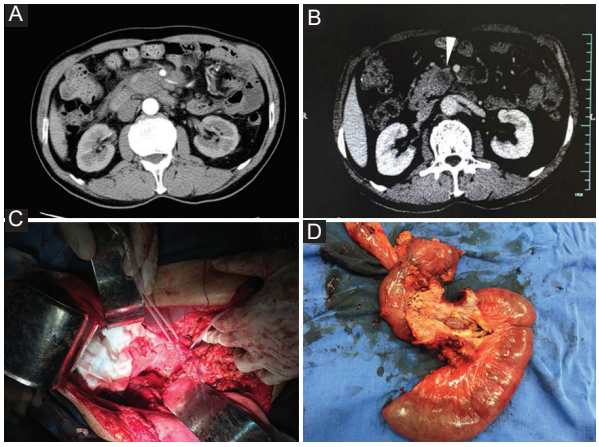

Figure 1. *Case 6 in the unresectable group.* **A:** *pancreatic CT showed that superior mesenteric artery was encapsulated more than 270°.* **B:** *CT showed that the tumor completely invaded superior mesenteric vein and occluded it to about 1.5 cm long. The arrow points to the occluded superior mesenteric vein.* **C:** *SMA sheath has been removed by 360°.* **D:** *in the isolated specimen, superior mesenteric artery, and vein appeared to be encapsulated by the tumor more than 270°.*

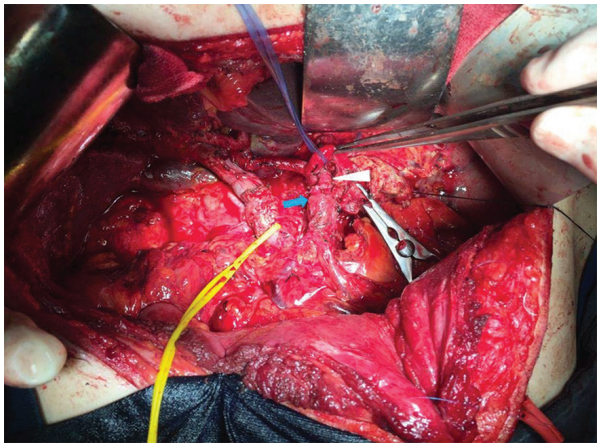

Figure 2. *Case 5 in the unresectable group. Left gastric artery and superior mesenteric artery were anastomosed and reconstructed. Left gastric artery was obliquely cutoff to enlarge its lumen diameter. Distal left gastric artery was ligated and proximal left gastric artery was pulled down from splenic artery to anastomose with superior mesenteric artery. Triangular arrow points to left gastric artery and the arrow points to superior mesenteric artery.*

Intraoperative and post-operative observation indicators

Operation time, intraoperative blood loss, post-operative intensive care unit (ICU) transitional treatment, post-operative pancreatic fistula, bleeding, reoperation, and survival time were recorded.

Statistical method

SPSS 16 software was used for statistical analysis. Its measurement data were expressed by $x \pm s$ and unpaired Student t-test or Welch's t test was adopted on the comparison between two groups, while counting data were expressed by rate and Pearson X^2 or Fisher's exact test was adopted on the comparison between groups. Survival analysis was performed by Log rank test. The difference with $p < 0.05$ was considered to be statistically significant.

Results

In this research, no deaths occurred during perioperative period in any group. Compared with the resectable group, operation time and intraoperative blood loss in the unresectable group were greatly increased ($p < 0.01$). For post-operative complications, the incidence of intractable diarrhea and abdominal hemorrhage in the unresectable group was obviously higher than those in the resectable group ($p < 0.01$). The rate of ICU transitional therapy, delayed gastric emptying, and reoperation in the unresectable group was significantly lower than the resectable group ($p < 0.01$). The patients in the unresectable group have a higher incidence of pancreatic fistula than the patients in the resectable group ($p < 0.01$), but Grade C pancreatic fistula occurred in neither group. There were three cases (4.4%) in the resectable group of post-operative abdominal hemorrhage, of which, two cases received interventional embolization to stop bleeding and one case received reoperation to stop bleeding. In the unresectable group, one case (12.5%) of abdominal hemorrhage received interventional embolization to stop bleeding and no reoperation occurred. In

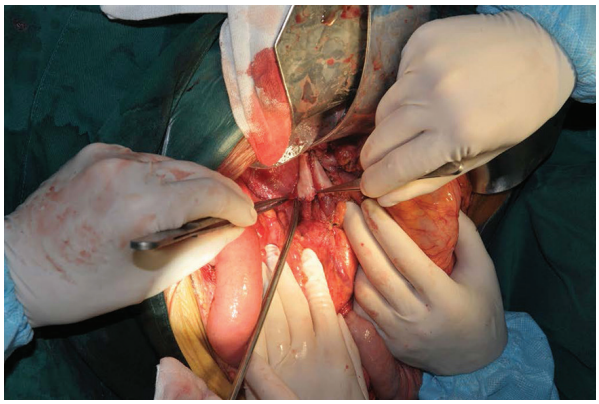

Figure 3. *Case 2 in the unresectable group. SMV was all involved, with portal vein involvement at the top and jejunal ileal vein below, respective anastomosis of Y-type iliac artery with portal vein, and jejunal ileum vein.*

the unresectable group, reoperation rate was significantly lower than that in the resectable group. Post-operative survival time of 69 patients with RPC was 8.2-72.4 months and median survival time was 15.8 months. In the unresectable group, post-operative survival of 8 patients was 8.1-26.3 months and median survival time was 14.3 months. With the same median survival time of the two groups ($p > 0.01$), there were three cases (4.4%) in the resectable group with survival time of longer than 5 years, but in the unresectable group, survival time of all the cases was < 3 years. Long-term survivors in the resectable group were significantly more than the unresectable group ($p > 0.01$) (Table 2).

Discussion

In domestic and foreign guidelines, surgical treatment is not recommended for the patients with UPC, but some scholars performed radical surgery on the patients with UPC after strict selection[8,9] and achieved a similar survival time with the patients with RPC[7,10]. Research shows that even if radical R0 resection is not achieved, the prognosis of locally advanced pancreatic cancer could be improved[11,12].

In this research, after rigorous and systematic selection, 360° arterial sheath resection was performed on the patients with pancreatic cancer while arterial sheath was encapsulated more than 180° without arterial adventitia involved. Arterial resection and reconstruction with radical operations were performed on the patients with arterial adventitia and intimal infiltration. Reconstruction of Y-type iliac artery allografts to make portal vein and jejunal ileovenous anastomosis was performed on the patients whose SMV was all involved, with portal vein involvement at the top and jejunal ileal vein below. These radical operations have all achieved good efficacy. In this study, death occurred during perioperative period in neither group. Although operation time and intraoperative blood loss in the unresectable group were significantly greater than those in the resectable group, the rate of post-operative ICU transitional therapy, delayed gastric emptying, and reoperation was significantly lower than the resectable group ($p < 0.01$), and there was no Grade C pancreatic fistula. These indicate that it is safe to undergo surgical treatment for the patients with UPC by strict selection. In this research, median survival time was 15.8 months in the resectable group and 14.3 months in the unresectable group. There was no significant difference in median survival time between the two groups ($p > 0.01$). The patients in the unresectable group had the same median survival time of 11-18 months reported in the previous literatures[1,2]

Table 2. Intraoperative and post-operative comparison between the two groups (cases [%])

Group	Cases	In the operation		After the operation						
		operation time (min, x ± s)	intraoperative blood loss (ml, x ± s)	ICU transitional treatment	pancreatic fistula	intractable diarrhea	delayed gastric emptying	intraperitoneal hemorrhage	reoperation	death during perioperative period	median survival time (months)
Resectable	69	329.4 ± 45.0	478.3 ± 190.0	3/69（4.4）	9/69（13.0）	1/69（1.4）	5/69（7.2）	3/69（4.4）	1/69（1.4）	0	15.8
Unresectable	8	432.5 ± 124.0[a]	762.5 ± 168.5[a]	0/8(0)[a]	2/8 (25.0)[a]	4/8 (50.0)[a]	0/8 (0)[a]	1/8 (12.5)[a]	0/8 (0)[a]	0	14.3

[a]$p < 0.01$.

for the patients with RPC. This proofs that surgical resection for UPC patients who are strictly selected is effective. However, long-term survival rate in the resectable group was significantly higher than that in the unresectable group ($p > 0.01$). Three cases (4.4%) in the resectable group had a survival time of more than 5 years and no patients (0%) in the unresectable group had a survival time of more than 3 years. Even there were two patients in the unresectable group in this research with all negative lymph nodes (case 4, 0/16 and case 5, 0/27), their survival time was only 13 months. One died of Budd-Chiari syndrome with liver metastasis and the other died of consumption and malnutrition caused by refractory diarrhea. This indicated that even if arteriovenous invasion of pancreatic cancer was caused only by specific site of the tumor, it was also prone to early local recurrence and metastasis to result in poor long-term prognosis. Neoadjuvant chemotherapy is still the first choice for UPC. Operation should be performed after conversion therapy. Intractable diarrhea is the most common complication after extended radical resection of pancreatic cancer, especially SMA sheath resection and SMA reconstruction. About 50% of cases in the unresectable group presented with intractable diarrhea and one of them died of intractable diarrhea. Retaining artery sheath at the root of SMA as far as possible may reduce its incidence and severity.

At present, resectability assessment of pancreatic cancer is based on preoperative imaging, so there is the possibility of over-diagnosis and under-diagnosis[6]. Many guidelines consider > 180° of main artery encapsulation as a criterion of UPC, but for many these patients, the tumor has been proven in surgery technically resectable and biological benefits have been achieved[6].

The present study also has some limitations. First, the sample size is listed,

Conclusions

In this research, radical operations including 360° arterial sheath resection and arterial resection and reconstruction were performed on the patients with main artery were encapsulated more than 180° or even 270° based on pre-operative assessment. There was no death during perioperative period and the patients even achieved the same survival time as the resectable group to suggest that radical resection for some patients with UPC is technically feasible. Therefore, the author believes that it could be regarded as an option to give active surgical treatment to UPC cases with rejection of neoadjuvant chemotherapy, unsatisfactory response or intolerance to chemotherapy, good general condition and no distant metastasis, which can alleviate the symptoms and provide a good basis for follow-up combined treatment. Of course, both arterial resection and reconstruction and 360° arterial sheath resection are technically difficult, which require sophisticated surgical planning, elaborate surgical operation and experienced surgical, and anesthetic teams as the guarantee.

Conflict of Interest

There are no any competing interests

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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