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ORIGINAL ARTICLE

Central pancreatectomy for early-stage pancreatic ductal adenocarcinoma: a single-center case–control study

Hao Gao[1,2] · Tongtai Liu[1,2] · Guangfu Wang[1,2] · Yong Gao[1,2] · Lingdi Yin[1,2] · Yunpeng Peng[1,2] · Nan Lyu[1,2] · Kai Zhang[1,2] · Wentao Gao[1,2] · Junli Wu[1,2] · Kuirong Jiang[1,2] · Jishu Wei[1,2] · Yi Miao[1,2]

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Abstract

Purpose Central pancreatectomy (CP) has been applied for treating benign and low-grade malignant tumors in pancreatic neck, but studies regarding CP for pancreatic ductal adenocarcinoma (PDAC) are quite limited. We aimed to investigate the role of central pancreatectomy in the treatment of PDAC in the neck of the pancreas.

Methods Patients who underwent CP at our hospital between 2009 and 2016 were identified. Patients treated by distal pancreatectomy (DP) were matched according to the tumor size, location, and staging. The surgical and survival outcomes were compared between the CP and DP groups.

Results Nine patients had CP. Five (56%) had postoperative complications and three (33%) had clinically significant (grade B + C) fistula. No significant difference was found between the CP and DP groups for the rate of overall morbidity, pancreatic fistula, reoperation, and readmission. Tumor size was smaller in the CP group compared to the DP group. The mortality of both groups was zero. The median postoperative survival was similar between the two groups (20.4 months for CP vs 19.4 months for DP, $P = 0.842$).

Conclusions CP is safe for patients with small PDAC at the neck of the pancreas. Considering the good preservation of pancreatic endocrine and exocrine functions, CP could be considered as an alternative procedure for single small PDAC in pancreatic neck.

Keywords Central pancreatectomy · Morbidity · Pancreatic ductal adenocarcinoma · Pancreatic fistula · Postoperative survival

Introduction

Neoplasms located in the neck of pancreas pose a challenge to pancreatic surgeons. In general, tumors in this location are resected by distal pancreatectomy (DP) [1]. However, DP removes a significant amount of normal pancreatic parenchyma and may cause endocrine and exocrine insufficiency [2–4]. Central pancreatectomy (CP) has been proposed as an alternative to DP for benign or low-grade malignant tumors in the neck of the pancreas because it spares normal pancreatic tissue and potentially preserves the function [5]. In addition, CP was also applied to treat metastatic lesions to the pancreas [6, 7]. Central pancreatectomy, also known as middle pancreatectomy or medial pancreatectomy, was first performed by Dagradi and Serio [8] in patients with oncological indication in 1982. Since then, an increasing number of cases have been reported. Some systematic reviews and meta-analyses [9–11] showed that CP could decrease the risk of exocrine failure and impairment of endocrine function than DP, although it was associated with a slightly higher postoperative morbidity.

In recent years, data in favor of limited resections for pancreatic tumors have been accumulating. Enucleation has been reported to be alternative procedure to radical pancreatectomy [12–14] and patients treated by pylorus-preserving pancreaticoduodenectomy (PPPD) could achieve similar long-term survival as patients undergoing pancreaticoduodenectomy (PD) [15]. However, there is concern that CP is not an adequate oncological procedure

Hao Gao and Tongtai Liu contributed equally to this work. Jishu Wei and Yi Miao contributed equally to this article and are considered as joint corresponding authors.

✉ Jishu Wei
weijishu@njmu.edu.cn

✉ Yi Miao
miaoyi@njmu.edu.cn

[1] Pancreas Center, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Nanjing 210029, China

[2] Pancreas Institute of Nanjing Medical University, Nanjing, China

for pancreatic ductal adenocarcinoma (PDAC) [16, 17]. Studies regarding CP for PDAC are quite limited. With the advancement of radiology, more early-stage PDAC are detected. In this context, there is a need to study the role of CP in the treatment of small PDAC.

Therefore, this case–control study was performed to analyze operative morbidity, mortality, and, more importantly, survival outcomes to evaluate the real effect, safety, and feasibility of CP in PDAC.

Material and methods

Patient database

A prospectively maintained pancreatectomy database was reviewed retrospectively to identify all eligible patients between November 2009 and December 2016. The study was approved by the Institutional Review Board of the First Affiliated Hospital of Nanjing Medical University. Preoperative imaging workup included computed tomography, magnetic resonance imaging, and/or endoscopic ultrasonography with fine-needle aspiration. The following criteria were used to select patients: (1) patients with PDAC undergoing CP or DP; (2) solitary PDAC localized in the pancreatic neck. The exclusion criteria included (1) incomplete medical record or follow-up data and (2) the operation involved resection of adjacent organs or vessels. Patient records were reviewed to obtain the demographic features, clinical characteristics, intraoperative and postoperative data, and pathological findings. Follow-up was based on radiologic, clinical, and laboratory assessments every 6–12 months.

Postoperative morbidity, including postoperative pancreatic fistula (POPF) [18], delayed gastric emptying (DGE) [19], chyle leak [20], and hemorrhage [21], was assessed according to the definitions of International Study Group of Pancreatic Surgery. Postoperative mortality was defined as death before hospital discharge or within 30 days after the operation. Readmission was defined as another admission within 30 days after the last hospital discharge. Reoperation was defined as operation again before hospital discharge or within 30 days after the last operation. Tumor, node, and metastasis (TNM) staging was classified by the *American Joint Committee on Cancer staging manual, 8th edition* [22].

Surgical procedure

The decision to perform a CP or DP was finally based on tumor location and size during operation at the surgeons' discretion. A CP was performed according to previously described techniques [5]. The proximal pancreatic remnant was oversewn after ligating the main pancreatic duct. For distal pancreatic remnant, an end-to-side one-layer interrupted pancreaticojejunostomy was performed for reconstruction. In the DP group, splenectomy and lymph node dissection were routinely performed. Besides, the pancreas end was sutured interruptedly after separate ligation of the main pancreatic duct. All surgeries were done using open laparotomy. Two closed suction drains were routinely placed in the end of surgery.

Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) whenever appropriate. Categorical variables were compared using the Pearson χ^2 test and Fisher exact test when the cell count was < 5. Normally distributed continuous variables were compared using the Student *t* test, and the Mann–Whitney *U* test was used for nonnormally distributed variables. Survival analyses were conducted using the Kaplan–Meier method with the log-rank test. A *P* value less than 0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS software version 13.0 (SPSS Inc., IL, USA).

Results

Patient and tumor characteristics

Patient and tumor characteristics are shown in Table 1. A total of 64 patients were enrolled in the present study with 9 patients undergoing CP and 55 with DP. In the CP group, patients had a mean age of 65 ± 8.0 years, and four (44%) of nine patients were men. The most frequent symptom was abdominal pain or discomfort (78%). Of the 55 patients undergoing DP, 30 (55%) were men and 25 (45%) were women with a mean age of 63 ± 9.2 years. Similarly, the most common symptom was abdominal pain or discomfort (53%), followed by an incidental finding (40%).The two groups were well matched in demographics. No significant difference was found between the two groups in CA19-9 ($P = 0.170$), TNM staging ($P = 0.501$), N staging ($P = 0.809$), and differentiation ($P = 0.151$). The patients undergoing DP had larger tumor diameter ($P = 0.010$) and higher T staging ($P = 0.016$) than patients undergoing CP. The CP group had fewer but not significant ($P = 0.063$) lymph nodes resected than the DP group.

Surgical outcomes

Surgical outcomes, including intraoperative and postoperative data, are detailed in Table 2. The mean operative time of the CP group was 214 ± 53 min, which was similar to that of the DP group (177 ± 69 min, $P = 0.130$). No significant difference

Table 1 Patient and tumor characteristics

	CP ($n = 9$)	DP ($n = 55$)	P
Gender			0.839
Male	4 (44%)	30 (55%)	
Female	5 (56%)	25 (45%)	
Age (year)	65 ± 8.0	63 ± 9.2	0.649
Symptom			–
Abdominal pain or discomfort	7 (78%)	29 (52%)	
Back pain	0	2 (4%)	
Weight loss	0	2 (4%)	
Incidental finding	2 (22%)	22 (40%)	
CA19-9 (U/mL)	14.4 (1.7–300.2)	86.4 (27.6–204.2)	0.170
Greatest tumor diameter (cm)	1.9 ± 0.6	3.3 ± 1.5	0.010
TNM staging			0.466
IA	3 (33%)	11 (20%)	
IB	3 (33%)	20 (36%)	
IIA	0	4 (7%)	
IIB	3 (34%)	18 (33%)	
III	0	2 (4%)	
T staging			0.016
T1	6 (67%)	15 (27%)	
T2	3 (33%)	29 (53%)	
T3	0	11 (20%)	
N staging			0.809
N0	6 (67%)	35 (64%)	
N1	3 (33%)	18 (33%)	
N2	0	2 (3%)	
Lymph nodes resected	1 (0–6)	5 (2–9)	0.063
Differentiation			0.151
High	1 (11%)	0	
High–medium	0	4 (7%)	
Medium	5 (56%)	19 (35%)	
Medium–low	3 (33%)	29 (53%)	
Low	0	3 (5%)	

CP, central pancreatectomy; *DP*, distal pancreatectomy

was observed in blood loss ($P = 0.477$) and blood transfusion ($P = 0.364$) between the CP and DP groups. Mortality of both groups was zero. We saw no statistical difference of the rates of overall morbidity, overall POPF, biochemical leak, clinically significant (grade B + C) pancreatic fistula, DGE, abdominal collections, and readmission between the CP and DP groups. No difference was found in chyle leak, hemorrhage, and pulmonary complications between the two groups. The median postoperative hospital stay was similar between the CP and DP groups [13 (10.5–18.5) vs 12 (10.0–16.0), $P = 0.628$]. No patient underwent reoperation in the CP group, while one patient in the DP group underwent reoperation due to bleeding caused by grade C pancreatic fistula. The DP group had a higher trend of R0 rate compared with the CP group (93% vs 67%, $P = 0.052$).

Long-term results

The follow-up data were complete and updated in May 2018. A total of 64 patients were included in the survival analysis. The median follow-up period for the CP and DP groups was 39.5 (24.7–74.8) and 23.5 (17.8–36.2) months, respectively. The CP group had a median postoperative overall survival of 20.4 (12.6–41.5) months (detailed in Table 3), while the survival for the DP group was 19.4 (12.9–31.5) months. As shown in Fig. 1, no significant difference was observed regarding postoperative overall survival between the two groups (log-rank $P = 0.842$). The rate of adjuvant chemotherapy was 45% in the CP group and 67% in the DP group. Because the information on adjuvant chemotherapy of three patients in the

Table 2 Intraoperative and postoperative data

	CP ($n = 9$)	DP ($n = 55$)	P
Operative time (min)	214 ± 53	177 ± 69	0.130
Blood loss (mL)	200 (100–500)	200 (100–200)	0.477
Blood transfusion	3 (33%)	8 (15%)	0.364
Mortality	0	0	–
Overall morbidity	5 (56%)	20 (36%)	0.468
Overall POPF	5 (56%)	24 (44%)	0.761
Biochemical leak	3 (33%)	18 (33%)	1.000
Grade B + C POPF	3 (33%)	6 (11%)	0.202
Grade B	3	5	
Grade C	0	1	
DGE	2 (22%)	6 (11%)	0.683
Chyle leak	0	5 (9%)	1.000
Hemorrhage	0	1 (2%)	1.000
Abdominal collections	1 (11%)	5 (9%)	1.000
Pulmonary complications	0	5 (9%)	1.000
Postoperative hospital stay (day)	13 (10.5–18.5)	12 (10.0–16.0)	0.628
Readmission	2 (22%)	4 (7%)	0.196
Reoperation	0	1 (2%)	1.000
Margin			0.052
R0	6 (67%)	51 (93%)	
R1	3 (33%)	4 (7%)	
Chemotherapy			–
Yes	4 (45%)	37 (67%)	
No	2 (22%)	16 (29%)	
NA	3 (33%)	2 (4%)	

CP, central pancreatectomy; *DP*, distal pancreatectomy; *DGE*, delayed gastric emptying; *NA*, not available; *POPF*, postoperative pancreatic fistula

CP group and 2 patients in the DP group was not available, statistical analysis could not be performed.

Discussion

There is a trend of limited resections for pancreatic tumors without compromising the oncologic principles. For instance, solitary benign or low-grade malignant pancreatic tumors can be resected by enucleation [12–14]. A Cochrane meta-analysis [15] suggested no relevant difference in mortality, morbidity, and survival between PPPD and PD. In general, CP has the following potential advantages [23]: (1) parenchyma preserving to reduce endocrine and exocrine insufficiency even with a slightly higher morbidity rate; (2) spleen preserving.

One of the major concerns of CP is its high operative morbidity rate, particularly POPF. As Table 4 presents, we summarized recent studies on CP. The table indicated that the CP group had a slightly higher postoperative morbidity but better preservation of pancreatic function than the DP group. The overall morbidity of the CP group ranges from 28 to 72%. Overall POPF ranges from 7 to 63% with clinically significant (grade B + C) POPF ranging from 16 to 44%. Such a large range of POPF rate may be attributed to different assessments and definitions of POPF. Operative mortality is also low and many studies have reported zero mortality. In this study, the overall morbidity of the CP group was 56%. The overall POPF was 56%, yet the grade B + C POPF accounted for 33%, which was consistent with the reported findings. Fortunately, no postoperative deaths occurred in the series. From the viewpoint of short-term results, these data reflected that CP was a safe procedure with morbidity and mortality consistent with other reported findings.

In this case–control study, demographic features, CA19-9 and tumor TNM staging, N staging, lymph nodes resected, and differentiation were well matched in the two groups, except the greatest tumor diameter and T staging. Although the DP group had larger tumors, which could result in some bias, the two groups were generally

Table 3 Survival data of the CP group

ID	Gender	Age (year)	Date of operation	Postoperative hospital stay (day)	Postoperative survival (month)	Chemotherapy
Patient 1	Male	65	May 5, 2013	14	7.1	NA
Patient 2	Female	63	June 27, 2011	10	83.6	NA
Patient 3	Male	76	June 14, 2010	12	34.6	No
Patient 4	Male	55	November 12, 2009	14	5.9	NA
Patient 5	Male	70	May 22, 2014	8	48.3	No
Patient 6	Female	72	November 12, 2014	23	22.9	Yes
Patient 7	Female	62	December 18, 2014	34	20.4	Yes
Patient 8	Female	67	August 11, 2016	13	20.3	Yes
Patient 9	Female	51	November 17, 2016	11	18.0	Yes

NA, not available

comparable in TNM staging. Hence, it is practicable to compare the prognosis of the two groups. The findings of the present study demonstrated no significant difference in operative time, blood loss, and blood transfusion. Although the CP group had higher overall morbidity, overall POPF, and grade B + C POPF rate, the difference was not statistically significant. Moreover, no difference was found in the DGE, chyle leak, hemorrhage, abdominal collections, pulmonary complications, postoperative hospital stay, readmission, reoperation, and R0 resection rate. Several reasons might be responsible for our result. First, a statistically significant difference was difficult to obtain due to the limited number of CP cases ($n = 9$). Second, most of the published studies focused on CP resecting benign or low-grade malignant tumors, and these tumors were usually in the soft pancreas, which is a known risk factor for pancreatic fistula. In the present series, all patients were diagnosed with PDAC and the parenchyma of the pancreas with PDAC was often hard.

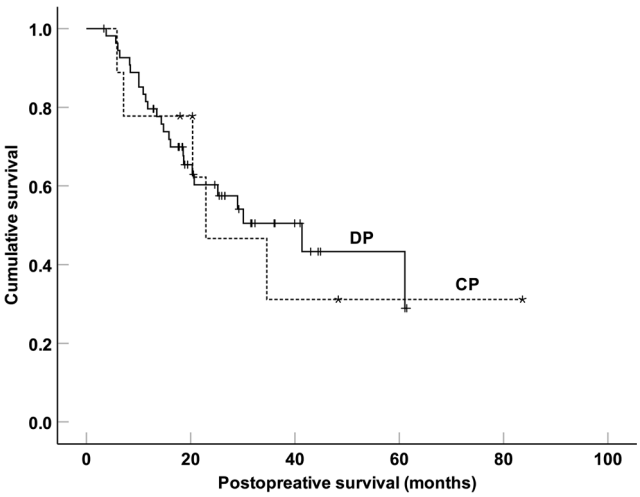

Fig. 1 The Kaplan–Meier survival curves of patients with PDAC undergoing CP and DP. The CP group had a median postoperative overall survival of 20.4 (12.6–41.5) months, whereas the survival for the DP group was 19.4 (12.9–31.5) months. Log-rank $P = 0.842$

The main benefit of CP is the preservation of endocrine and exocrine functions because it spares more pancreatic parenchyma than DP. However, limited tissue resection and inadequate lymph node dissection may be potentially noncurative for patients with PDAC [16, 17]. Thus, CP is not considered an oncologically appropriate procedure for PDAC. As a matter of fact, very few studies reported treatment of PDAC using CP, especially for early-stage PDAC, let alone high-quality evidence of evidence-based medicine, such as prospective studies or randomized controlled trials.

Given that CP was a limited resection, R0 resection should be guaranteed by performing an intraoperative frozen-section biopsy to obtain sound oncologic safety. The DP group had a higher trend of R0 rate compared with the CP group. Due to the dissatisfactory widespread of intraoperative frozen-section biopsy before and relatively smaller tumors of the CP group, it was more likely for the surgeons to misjudge that sufficient resection had been made, resulting in significantly higher positive margin in the CP group. The rate of adjuvant chemotherapy was reported to be different [32–34], varying from 29 to 78%. In this study, the rate of adjuvant chemotherapy was 45% in the CP group and 67% in the DP group. In our study, tumors in the CP group were confined to pancreatic parenchyma with no infiltration to the pancreatic capsule. The findings of this study indicated that for small PDAC (greatest tumor diameter ≤ 2 cm) confined to pancreatic parenchyma in the neck of the pancreas, patients undergoing CP could obtain similar long-term survival as patients treated using DP (20.4 months for CP vs 19.4 months for DP, $P = 0.842$).

This was the first series to evaluate the safety and feasibility of the CP procedure for PDAC. This retrospective study had some limitations. First, data on adjuvant chemotherapy were incomplete. Their impact on survival was not included in the statistical analysis. Second, the size of patient cohort limited the statistical analysis between the CP and DP groups.

Table 4 Characteristics of recent studies on CP ($n \geq 30$)

Authors	Year	Cases of CP/DP	Overall morbidity% (CP/DP)	Overall POPF% (CP/DP)	Grade B + C POPF% (CP/DP)	Mortality% (CP/DP)	Endocrine insufficiency% (CP/DP)	Exocrine insufficiency% (CP/DP)
Sauvanet et al. [24]	2002	53/–	41/–	30/–	NA	2/–	6/–	8/–
Balzano et al. [25]	2003	32/21	62/29	50/14	NA	0/0	10/15.8	6.2/4.8
Müller et al. [26]	2006	40/40	27.5/25	7.5/10	NA	2.5/0	15/42	46/41
Crippa et al. [1]	2007	100/45	58/46.7	44/29	17/13	0/0	4/38	5/15.6
Adham et al. [27]	2008	50/–	38/–	8/–	NA	0/–	0/–	NA
Lavu et al. [28]	2008	34/–	47.1/–	29.4/–	11.8/–	NA	5/–	NA
DiNorcia et al. [16]	2010	50/50	42/40	24/20	18/14	0/0	14/46	0/0
Du et al. [29]	2013	36/26	NA	42/31	17/–	0/0	2.8/21.7	8.3/8.7
Goudard et al. [5]	2014	100/–	72/–	63/–	44/–	3/–	7/–	6/–
Dokmak et al. [30]	2017	35/165	74/55	51/40	23/27	0/0	NA	NA
Iacono et al.* [10]	2013	359/480	47.1/29.4	30.8/14.3	NA	0.9/0	5.5/23.6	11.9/19.1
Sean et al.* [31]	2016	586/–	50.3/–	34.1/–	NA	0.7/–	3.2/–	6.5/–
Xiao et al.* [11]	2018	539/869	51/26	35/21	NA	0.5/0.1	4/31	5/13

CP, central pancreatectomy; *DP*, distal pancreatectomy; *POPF*, postoperative pancreatic fistula; *NA*, not available

*Systematic review and meta-analysis

Conclusions

CP is safe for patients with small PDAC at the neck of the pancreas. The rate of postoperative morbidity and clinically significant POPF after CP did not differ from those after DP. Considering the good preservation of pancreatic endocrine and exocrine functions, CP could be considered as an alternative procedure for single small PDAC (greatest tumor diameter ≤ 2 cm) confined to pancreatic parenchyma in the neck of the pancreas. This result should be verified by well-designed studies with large samples.

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Authors' contributions Jishu Wei and Yi Miao participated in study conception and design. Guangfu Wang, Yong Gao, and Lingdi Yin participated in acquisition of data. Yunpeng Peng, Nan Lyu, and Kai Zhang participated in analysis and interpretation of data. Hao Gao and Tongtai Liu participated in drafting of manuscript. Wentao Gao, Junli Wu, and Kuirong Jiang participated in critical revision of manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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