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REVIEW ARTICLE

Pancreaticoduodenectomy for locally advanced gastric cancer: Results from a pooled analysis

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Summary Little is known about the clinical outcome of pancreaticoduodenectomy (PD) for locally advanced gastric cancer invading the duodenum and/or pancreas. The aim of this study was to define the clinical outcome and prognostic determinants of PD for locally advanced gastric cancer through a systematic review and pooled analysis of relevant data in the literature. A total of 13 articles involving 69 patients were eligible for inclusion. Postoperative morbidity and mortality were 59.4% and 1.4%, respectively. Overall 5-year survival and median survival were 39.3% and 26 months, respectively. Positive peritoneal lavage cytology represented the only independent prognostic factor for the poor outcome at multivariate analysis (hazard ratio 3.470, 95% confidence interval 1.011–11.909; $P = 0.048$). In summary, PD is a feasible option for locally advanced gastric cancer invading the duodenum and/or pancreas with an acceptable operative risk and offers survival benefits in selected patients.
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1. Introduction

Although the global incidence of gastric cancer has decreased, it remains the fourth most common cancer worldwide and the second leading cause of cancer-related mortality. Curative resection with negative microscopic margins is essential to achieve long-term survival.[1] In patients with locally advanced gastric cancer invading the duodenum and/or pancreas, pancreaticoduodenectomy

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(PD) is warranted to achieve oncological clearance. However, most currently available publications are limited to a small number of patients,[2–11] and no specific factors to predict the long-term survival. The aim of the present study was to assess the clinical outcome and prognostic determinants of locally advanced gastric cancer following PD by retrieving a relatively large cohort of cases based on a systematic literature search.

2. Methods

2.1. Systematic search strategy

In accordance with the guidelines of preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009,[12] a systematic literature search was carried out using PubMed and Chinese Biomedical Literature database to identify relevant articles published from January 1990 to June 2018. The following MeSH headings and keywords were used: pancreaticoduodenectomy, stomach cancer, and gastric cancer. Studies published in English, Chinese, or Japanese were considered eligible. The references of relevant articles were reviewed to identify additional articles. Studies reporting the outcomes following PD for locally advanced gastric cancer were included for analysis. Reviews, conference abstracts, non-human studies, studies that did not provide individual patient data were excluded. The patient demographics, pathologic tumor characteristics, adjuvant treatments, morbidity, mortality, and long-term survival were collected. Mortality was defined as any death occurring within 30 days after surgery or during the same hospital admission.

2.2. Statistical analysis

Descriptive statistics were performed and data are expressed as mean or median (range) where appropriate. Overall survival (OS) was analyzed by means of the Kaplan–Meier method, and the log rank test was used for univariate analysis of prognostic factors. Variables with *P* value of <0.10 in univariate analysis were entered in the multivariable Cox proportional hazards regression to investigate independent predictors of survival. Hazard ratio (HR) was reported with 95% confidence interval (CI). All statistical analyses were performed using SPSS version 18.0 (SPSS, Chicago, Illinois).

3. Results

3.1. Study populations

The literature search identified 13 articles containing 69 individual patients who met the inclusion criteria.[3,5,6,8,10,11,13–19] The process for selection of relevant studies is shown in Fig. 1. Clinicopathological and operative data of the 69 selected patients are summarized in Table 1. A total of 49 complications occurred in 38 (59.4%) of 64 evaluable patients. The most frequent complication was pancreatic fistula (31.2%), followed by anastomotic leakage (14.1%), and abdominal abscess (9.3%). Re-operations were required for two of those patients. One (1.4%) patient died of postoperative complications. Thirty-two (57.1%) of 56 evaluable patients received adjuvant chemotherapy, including 5-fluorouracil + mitomycin (n = 10); oxaliplatin, 5-fluorouracil and folinic

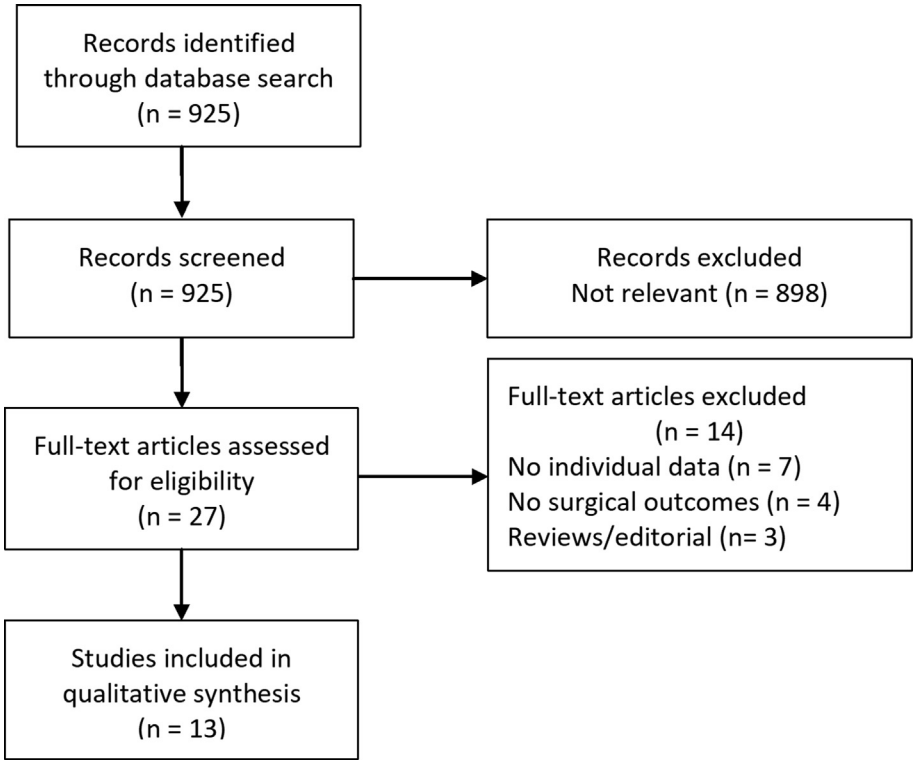

Figure 1 PRISMA flow diagram.

Table 1 Clinicopathological and operative data of documented patients.

Parameters	N[a]	Median or %
Sex	59	
Male	42	76.3
Female	17	23.7
Age, years	59	61 (37–79)
Disease	69	
Primary tumor	59	85.5
Tumor of the gastric remnant	10	14.5
Combined organ resection	59	
No	34	57.6
Yes	25	42.4
Colon	24	40.6
Liver	2	3.4
Spleen	1	1.7
Differentiation	33	
Well–moderate	15	45.4
Poor–undifferentiated	18	54.6
pT 4	68	
No	12	17.6
Yes	56	82.4
Lymph node metastasis	65	
No	20	30.7
Yes	45	69.3
Peritoneal lavage cytology	30	
No	26	86.7
Yes	4	13.3
Morbidity	64	
No	26	40.6
Yes	38	59.4
Pancreatic fistula	20	31.2
Anastomotic leakage	9	14.1
Abdominal abscess	6	9.3
Cholangitic infection	2	3.1
Bleeding	2	3.1
Wound infection	2	3.1
Anastomotic or jejunal stenosis	1	1.5
Reoperation	2	3.1
Pneumonia	2	3.1
Liver dysfunction	1	1.5
MRSA-induced enterocolitis	1	1.5
Colocolic leakage	1	1.5
Mortality	69	
No	68	98.6
Yes	1	1.4
Adjuvant chemotherapy	56	
No	24	42.8
Yes	32	57.1

MRSA = methicillin-resistant *Staphylococcus aureus*.
[a] No. of patients for whom data were provided.

acid (n = 8); 5-fluorouracil (n = 2); tegafur/gimeracil/oteracil potassium (n = 3); docetaxel + cisplatin (n = 1); cisplatin + 5-fluorouracil (n = 1), and unknown (n = 7).

3.2. Survival

Thirty-nine patients (56.5%) died during a median follow-up period of 17 (range 1–210) months, with a median survival time of 26 months and a 1-, 3- and 5-year OS rate of 75.3%, 41.9% and 39.3%, respectively (Fig. 2). Univariate analysis of OS revealed positive peritoneal lavage cytology (PLC) as the only factor associated with poor prognosis ($P = 0.014$, Table 2). After multivariable analysis, together with disease (primary tumor or tumor in the gastric remnant) and lymph node metastasis (both $P < 0.10$), positive PLC remained the only independent prognostic factor for poor outcome (HR 3.470, 95% CI 1.011–11.909; $P = 0.048$).

4. Discussion

Pancreaticoduodenectomy is generally accepted as a safe and appropriate operation for periampullary malignancies. In the setting of non-periampullary tumors, a recent study of 81 cases clearly demonstrated that PD could be performed safely and offered good survival for patients with locally advanced colon cancer, with an operative mortality rate of 3.7% and 5-year OS of 55.2%.[20] However, the role of PD for locally advanced gastric cancer remains poorly defined, mainly due to the limited number of patients. In this study, we pooled individual patient data identified from the literature to constitute the largest collective report to date to evaluate the clinical outcome and prognostic determinants of patients with locally advanced gastric cancer treated with PD.

It was found in the present study that the overall morbidity was high as 59.4%, which emphasizes the extensive and difficult nature of PD for gastric cancer. First, in more than 40% cases, PD employed additional organ resection in pursuit of negative margins. Second, most patients with gastric cancer have a fragile pancreatic texture and a non-dilated pancreatic duct, rendering pancreatic fistula a major postoperative complication. However, this high morbidity did not translate into fatal outcomes in most cases, with a mortality rate of 1.4% only. The safety of PD for gastric cancer also has been described in several

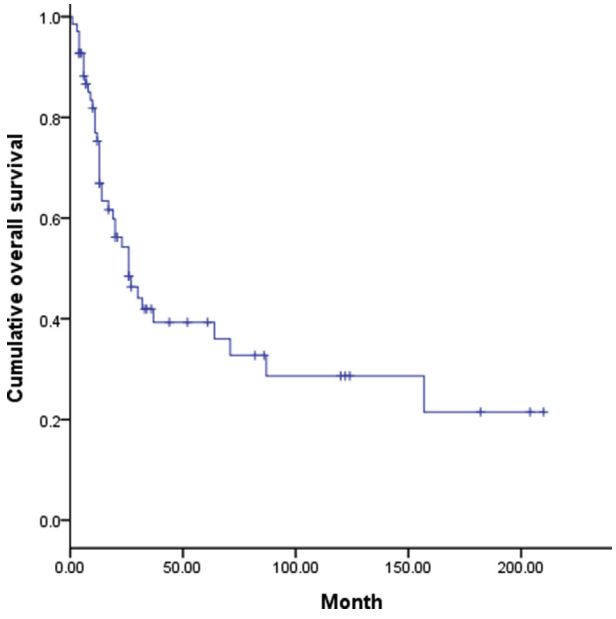

Figure 2 Kaplan–Meier curve of overall survival.

Table 2 Univariate analysis for prognostic factor of overall survival after surgery.

Characteristics	N[a]	1-year OS (%)	3-year OS (%)	5-year OS (%)	*P*-value
Sex					
Male	42	82.3	47.9	43.9	0.164
Female	17	57.4	30.6	30.6	
Age, years					
<60	25	77.1	40.6	34.8	0.990
≥60	34	72.7	44.5	44.5	
Disease					
Primary	59	75.0	45.3	42.3	0.092
Remnant	10	77.1	17.1	17.1	
Combined organ resection					
No	34	75.8	46.9	41.7	0.463
Yes	25	66.9	31.8	31.8	
pT 4					
No	12	91.7	64.4	64.2	0.240
Yes	56	71.1	35.3	31.9	
Lymph node metastasis					
No	20	76.2	59.3	59.3	0.078
Yes	45	72.6	36.1	31.6	
Peritoneal lavage cytology					0.014
No	26	73.9	45.4	45.4	
Yes	4	25.0	0	0	
Differentiation					
Well—moderate	15	78.3	47.7	47.7	0.280
Poor—undifferentiated	18	76.7	36.0	27.0	
Adjuvant chemotherapy					
No	24	65.8	37.6	37.6	0.511
Yes	32	78.8	38.1	31.7	

OS = overall survival.
[a] No. of patients for whom survival data were provided.

studies,[2,4,7,9,21–23] they were not included in this study for analysis because they did not provide individual patient data (Table 3). These encouraging results are largely related to the careful patient selection, improved surgical techniques and perioperative care.

The 5-year OS following PD of gastric cancer in our pooled analysis was 39.3%. The figure varies from 15.8% to 35% in the reported articles (Table 3). This survival difference may be attributable to the wide variety of tumor biological behavior. The present study revealed that positive PLC was the only independent prognostic factor for poor survival. Patients with PLC negative tumors was associated with a 45.4% 5-year survival rate, whereas no 5-year survivors were noted in patients with cytology positive tumors, indicating that PLC positive tumors represent a contraindication for PD. Currently, the Japanese Research Society for Gastric Cancer has classified positive PLC as M1 or stage IV disease.[24] Minimally invasive procedures, including diagnostic laparoscopy with cytological examination of peritoneal lavage fluid, should be useful to avoid futile surgery.

Table 3 Outcome in series not providing individual patient data.

Reference	Year	N	Morbidity (%)	Mortality (%)	5-year OS (%)
Yonemura[2]	1991	26	23.1	0	—
Shchepotin[4]	1998	37	—	—	17.0
Aijisaka[7]	2001	22	—	0	35.0
Lee[9]	2007	25	32.0	0	15.8
Nunobe[21]	2008	31	45.1	12.9	22.3
Wang[22]	2008	17	70.6	0	—
Ryu[23]	2013	16	31.3	6.2	16.7

OS = overall survival.

Theoretically, PD should be reserved for T4 lesions, with true histological invasion into adjacent organs. Unfortunately, large inflammatory perigastric lymph nodes or desmoplastic reaction around gastric cancer can be inaccurately assessed to be tumor invasion. In the present study, overstaging was found in 17.6% of patients on the final pathologic review. When the real nature of invasion is unclear, *en bloc* resection of the stomach and adjacent organs should be considered.[4]

Although the role of adjuvant chemotherapy is now clearly established in patients with resected gastric cancer,[25] the present study failed to show its efficacy, probable due to the varied regimens and the small number of patients.

Our study has several limitations. First, this is a retrospective study, which may be critically influenced by selection bias. Second, due to the different tumor staging systems applied during the study period, we could not assess the prognostic importance of lymph node stations or the number of lymph nodes involved. Third, we had no

control group of patients undergoing palliative treatment to compare with PD in terms of long-term outcomes. In fact, such work has been done by Wang et al,[22] who reported a significant difference in 3-year survival between patients undergoing PD and those receiving palliative treatment (34% vs. 5.6%, $P = 0.0064$). Finally, there was a lack of recurrence data, which precluded assessment of disease-free survival.

In conclusion, PD is a feasible option for locally advanced gastric cancer invading the duodenum and/or pancreas with an acceptable operative risk and offers survival benefits in selected patients.

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Conflicts of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2018.09.005.

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