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ORIGINAL ARTICLE

Retrospective Study

Retrospective analysis of surgically treated pT4b gastric cancer with pancreatic head invasion

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Abstract

BACKGROUND

For advanced gastric cancer patients with pancreatic head invasion, some studies have suggested that extended multiorgan resections (EMR) improves survival. However, other reports have shown high rates of morbidity and mortality after EMR. EMR for T4b gastric cancer remains controversial.

AIM

To evaluate the surgical approach for pT4b gastric cancer with pancreatic head invasion.

METHODS

A total of 144 consecutive patients with gastric cancer with pancreatic head invasion were surgically treated between 2006 and 2016 at the China National Cancer Center. Gastric cancer was confirmed in 76 patients by postoperative pathology and retrospectively analyzed. The patients were divided into the gastrectomy plus *en bloc* pancreaticoduodenectomy group (GP group) and gastrectomy alone group (GA group) by comparing the clinicopathological features, surgical outcomes, and prognostic factors of these patients.

RESULTS

There were 24 patients (16.8%) in the GP group who had significantly larger lesions ($P < 0.001$), a higher incidence of advanced N stage ($P = 0.030$), and less neoadjuvant chemotherapy ($P < 0.001$) than the GA group had. Postoperative morbidity (33.3% *vs* 15.3%, $P = 0.128$) and mortality (4.2% *vs* 4.8%, $P = 1.000$) were not significantly different in the GP and GA groups. The overall 3-year survival rate of the patients in the GP group was significantly longer than that in the GA group (47.6%, median 30.3 mo *vs* 20.4%, median 22.8 mo, $P = 0.010$). Multivariate

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analysis identified neoadjuvant chemotherapy [hazard ratio (HR) 0.290, 95% confidence interval (CI): 0.103–0.821, P = 0.020], linitis plastic (HR 2.614, 95% CI: 1.024–6.675, P = 0.033), surgical margin (HR 0.274, 95% CI: 0.102–0.738, P = 0.010), N stage (HR 3.489, 95% CI: 1.334–9.120, P = 0.011), and postoperative chemoradiotherapy (HR 0.369, 95% CI: 0.163–0.836, P = 0.017) as independent predictors of survival in patients with pT4b gastric cancer and pancreatic head invasion.

CONCLUSION
Curative resection of the invaded pancreas should be performed to improve survival in selected patients. Invasion of the pancreatic head is not a contraindication for surgery.

Key Words: Gastric cancer; T4; R0 resection; Prognostic factors; Extended multiorgan resection; Pancreatectomy

Core tip: This was a retrospective study to evaluate the surgical approach for pT4b gastric cancer with pancreatic head invasion. The overall 3-year survival rate of the patients in the gastrectomy plus *en bloc* pancreaticoduodenectomy group was significantly longer than that in the gastrectomy alone group. Curative resection of the invaded pancreas should be performed to improve survival after balancing the risk and survival benefit.

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INTRODUCTION

Gastric cancer is the fifth most common cancer worldwide and the third leading cause of cancer-related mortality[1]. Advanced disease at presentation accounts for 39%–44% of newly diagnosed gastric cancer cases[2]. Despite improvements in early diagnosis and neoadjuvant or adjuvant chemotherapy, radical surgery is still the conventional curative treatment for gastric cancer. In patients with advanced gastric cancer, extended multiorgan resection (EMR) may be needed to achieve R0 resection. Some studies have suggested that EMR improves the survival rate of T4b patients[3-5]. However, other studies have shown high rates of morbidity and mortality after EMR [6]. Therefore, EMR for T4b gastric cancer remains controversial.

In advanced gastric cancer, the pancreas is the most frequently invaded organ. Min *et al*[7] reported that patients with pancreatic invasion had worse survival when they underwent pancreaticoduodenectomy. Postoperative pancreatic fistula is the most frequently reported complication after combined surgery. The performance of additional partial pancreatectomy and splenectomy to facilitate D2 lymphadenectomy was abandoned. This is because it increased the postoperative morbidity significantly without positive overall survival benefits[8,9]. The benefits of *en bloc* partial pancreatectomy for advanced gastric cancer with pancreatic invasion should be critically evaluated, given its potential of increased morbidity. However, only a few reports evaluating partial or total pancreatectomy for these patients have been published[5,10-13]. The aim of this study was to investigate the clinicopathological features, surgical outcomes, and prognostic factors of these patients.

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MATERIALS AND METHODS

Patients

A total of 144 consecutive gastric cancer with pancreatic head invasion were surgically treated from January 2006 to December 2016 at our hospital. Of these patients, 76 who underwent surgery [gastrectomy combined with pancreatectomy (GP) or gastrectomy alone (GA)] with pancreatic invasion confirmed by postoperative pathology were enrolled. The remaining 68 patients underwent palliative bypass or exploratory surgery or with pancreas body/tail invasion, or with pancreas invasion after radical surgery. The study group consisted of 65 men (85.5%) and 11 women (14.5%) aged 28–74 years (mean 56.0 ± 10.7 years). The inclusion criteria were: (1) gastric cancer patients diagnosed with pancreatic head invasion who underwent curative gastrectomy combined with GP or GA; (2) patients without distant metastasis or other malignancies; and (3) patients with complete clinicopathological and follow-up records. The exclusion criteria were: (1) patients who underwent palliative gastrojejunostomy or exploratory surgery; (2) patients who presented with pancreatic metastasis after radical gastrectomy; and (3) patients with pancreatic body or tail invasion (Figure 1). T4 gastric cancer is defined according to the American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) system. Our study was performed in accordance with the Declaration of Helsinki, which was approved by the Institutional Review Board of our hospital (No. 14-067/857).

Surgical procedures

In cases where pancreatic invasion was considered during surgery, the curative-intent GP procedures were performed with *en bloc* gastrectomy combined with pancreaticoduodenectomy and D2 or D2+ lymphadenectomy. In contrast, *en-bloc* gastrectomy with D2 or D2+ lymphadenectomy without pancreatectomy (GA) was performed when the surgeon considered macroscopically inflammatory reactions, but postoperative pathology confirmed pancreatic invasion.

Clinicopathological features and surgical outcomes

Clinicopathological variables included: age, gender, body mass index (BMI), preoperative albumin, preoperative hemoglobin, neoadjuvant chemotherapy, postoperative treatment, tumor size, Borrmann type, histological type, lymphovascular invasion, perineural invasion, surgical margin (R0 or R1), and pathological stage (T, N or M). Surgical outcomes included the type of surgery, operation time, blood loss, postoperative hospital stay, morbidity, mortality, and overall survival rates. Postoperative morbidity and mortality were graded with a modified Clavien–Dindo classification. Postoperative mortality was defined as death within 30 d after surgery. The TNM stage was evaluated according to the 8th TNM AJCC/Union for International Cancer Control guidelines. The presence or absence of gross residual disease was classified as negative resection margin (R0), microscopic tumor infiltration (R1), and macroscopic residual tumor (R2).

Adjuvant therapy

Perioperative neoadjuvant or adjuvant chemotherapy (AC) after surgery was mainly based on fluorouracil in combination with platinum chemotherapy. The regimens were based on widely accepted studies[14,15]. Fifty-four patients who underwent neoadjuvant chemotherapy (NAC) and 43 patients who underwent AC were included: 20 received S-1 plus oxaliplatin; 15 docetaxel, oxaliplatin and S-1; and eight capecitabine plus oxaliplatin. The median number of courses of AC was six (5–8), while that of NAC was three (2–4). A total of 33 patients received postoperative concurrent chemoradiotherapy, the dose of which was the same as that used in a previous study[16]. In case of recurrence, patients were advised to consult an oncologist to adjust the treatment plan.

Follow up

Patients were asked to re-examination every 3 mo for the first 2 years after surgery, then every 6 mo for 3 years, and annually thereafter. Clinicopathological features and survival data were obtained from electronic medical records, outpatient clinical visits and telephone interviews by the authors. Patients were followed up until death or December 31, 2020.

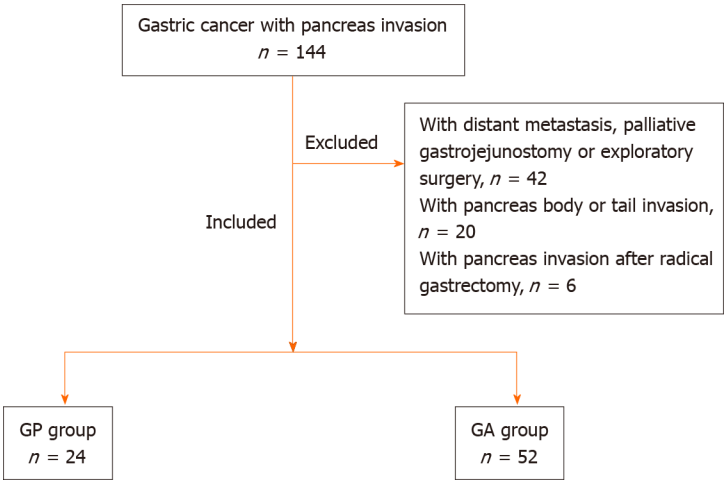

Figure 1 Flowchart of study inclusion.

Statistical analysis

Statistical analyses were calculated with SPSS version 22.0. All continuous variables were assessed using the *t* test. Categorical variables were compared using the Fisher's exact or χ^2 tests. The Kaplan–Meier method was used to calculate cumulative survival rates and the log-rank test was used to evaluate statistically significant differences. Multivariate analysis of prognostic significance was performed using Cox's proportional hazard model. $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological features

In total, 76 gastric cancer patients with pancreatic head invasion who underwent surgical operation were enrolled from 2006 to 2016 in our hospital. Age, gender, BMI, American Society of Anesthesiologists scores, AC, histological type, Borrmann types, lymphatic and venous invasion, perineural invasion, preoperative albumin, and hemoglobin levels were comparable between the two groups. The percentage of patients receiving postoperative chemotherapy or chemoradiotherapy in the GA and GP groups had no significant difference ($P = 0.199$). However, NAC was administered more in the GA group than in the GP group (84.6% *vs* 41.7%, $P < 0.001$). Small tumor diameter ($P < 0.001$) was associated with the GA group. The GP group had a high N stage ($P = 0.030$), although the median number ($n = 29$) of harvested lymph nodes was similar between the two groups. The clinicopathological features of the 76 patients are summarized in Table 1.

Surgical outcomes

The overall perioperative 30-d mortality (4.2% *vs* 4.8%, $P = 1.000$) and postoperative morbidity (33.3% *vs* 15.3% $P = 0.128$) were similar in the GP and GA groups. Those in the GP group had longer operation times (223.3 ± 41.6 *vs* 192.9 ± 29.6, $P = 0.003$) and postoperative hospital stays (18.2 ± 5.9 *vs* 10 ± 3.6, $P < 0.001$) than those in the GA group. The details of the operation and postoperative complications are summarized in Table 2. The overall 3-year survival rate of the pT4 patients in the GP group was significantly longer than that in the GA group (47.6%, median 30.3 mo *vs* 20.4%, median 22.8 mo, $P = 0.010$) (Figure 2).

Prognostic factors of the pT4b patients

Of all the prognostic factors evaluated, tumor type (linitis plastica/not), tumor diameter, NAC (yes/no), N stage, operation type, lymphovascular invasion (yes/no), surgical margin (R0/R1), and postoperative treatment (chemotherapy/chemoradiotherapy) were statistically significant by univariate analysis. Only NAC ($P = 0.020$), tumor type (linitis plastica/not) ($P = 0.033$), N stage ($P = 0.011$), surgical margin (R0/R1) ($P = 0.010$), and postoperative treatment ($P = 0.017$) were identified as independent prognostic factors by multivariate survival analysis (Table 3). Surgical margin (R0/R1) was identified as the most powerful prognostic factor.

Table 1 Clinicopathological features of patients undergoing gastrectomy plus pancreatectomy and palliative gastrectomy alone

Variable	GP group, (*n* = 24) (%)	GA group, (*n* = 52) (%)	*P* value
Gender			0.486
Male	22 (91.7)	43 (82.7)	
Female	2 (8.3)	9 (17.3)	
Age (yr)			0.254
< 65	16 (66.7)	41 (78.8)	
≥ 65	8 (33.3)	11 (21.2)	
BMI (kg/m^2)	23.5 ± 3.5	23.2 ± 3.3	0.779
ASA score			0.45
< 3	16 (66.7)	39 (75.0)	
≥ 3	8 (33.3)	13 (25.0)	
Neoadjuvant chemotherapy			< 0.001
Yes	10 (41.7)	44 (84.6)	
No	14 (58.3)	8 (15.4)	
Postoperative therapy			0.199
Chemotherapy	11 (45.8)	32 (61.5)	
Chemoradiotherapy	13 (54.2)	20 (38.5)	
Preoperative albumin (g/L)	37.9 ± 4.9	36.3 ± 5.1	0.083
Preoperative hemoglobin (g/L)	119.0 ± 28.2	108.3 ± 26.5	0.058
Linitis plastica			0.059
Yes	1 (4.2)	11 (21.2)	
No	23 (95.8)	41 (78.8)	
Borrmann type			0.312
I	1 (4.2)	1 (1.9)	
II	8 (33.3)	18 (34.6)	
III	14 (58.3)	23 (44.2)	
IV	1 (4.2)	10 (19.2)	
Tumor size (cm)	9.3 ± 2.3	6.7 ± 1.9	< 0.001
Histological type			0.945
Poorly differentiated	20 (83.3)	43 (82.7)	
Well–moderately differentiated	4 (16.7)	9 (17.3)	
Pathological N stage			0.03
N0	0 (0.0)	0 (0.0)	
N1	0 (0.0)	0 (0.0)	
N2	5 (20.8)	17 (32.7)	
N3a	5 (20.8)	16 (30.8)	
N3b	14 (58.3)	19 (36.5)	
Lymphovascular invasion			0.168
Yes	22 (91.7)	41 (78.8)	
No	2 (8.3)	11 (21.2)	
Neural invasion			0.638
Yes	17 (70.8)	34 (65.4)	

No	7 (29.2)	18 (34.6)	
Surgical margin			< 0.001
R0	21 (87.5)	0 (0.0)	
R1	3 (12.5)	52 (88.5)	

Values are percentages or mean ± SD. GA: Gastrectomy alone; GP: Gastrectomy plus pancreatectomy; BMI: Body mass index; ASA: American Society of Anesthesiologists.

Table 2 Surgical outcome of patients undergoing gastrectomy plus pancreatectomy and gastrectomy alone

Variable	GP group, (*n* = 24) (%)	GA group, (*n* = 52) (%)	*P* value
Intraoperative blood loss (mL)	443.8 ± 104.6	144.2 ± 64.7	< 0.001
Operation time (min)	223.3 ± 41.6	192.9 ± 29.6	0.003
Postoperative hospital stay (d)	18.2 ± 5.9	10 ± 3.6	< 0.001
Postoperative mortality	1 (4.2)	2 (3.8)	1
Postoperative morbidity	8 (33.3)	8 (15.3)	0.128
Local complications	5 (20.8)	6 (11.5)	0.324
Abdominal infection	1	0	
Anastomotic fistula	0	1	
Abdominal hemorrhage	1	0	
Gastrointestinal hemorrhage	0	1	
Disruption of wound	1	0	
Pancreatic fistula	2	3	
Duodenal stump fistula	0	1	
Systemic complications	3 (12.5)	2 (3.8)	0.177
Pulmonary infection	1	0	
Pneumothorax	1	1	
Renal failure	0	0	
Diabetic ketoacidosis	1	0	
Cardio- and cerebrovascular event	0	1	
Clavien–Dindo classification			0.309
II	1	3	
IIIa	2	1	
IIIb	3	1	
IVa	1	0	
IVb	0	1	
V	1	2	

GA: Gastrectomy alone; GP: Gastrectomy plus pancreatectomy.

DISCUSSION

There are few reports that have directly evaluated partial or total pancreatectomy due to confined tumor invasion to the pancreas. Most studies evaluated EMR as one group. Some patients underwent radical gastrectomy with extended *en bloc* resection of the head or tail of the pancreas to achieve R0 resection. However, with macroscopic assessment of organ involvement in preoperative and intraoperative staging, it is sometimes difficult to distinguish histological invasion from peritumoral inflam-

Table 3 Univariate and multivariate analysis of prognostic factors for pT4 gastric cancer with pancreatic head invasion

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age ≥ 65/< 65 yr	1.19 (0.567–2.505)	0.644	–	–
Gender (male/female)	1.01 (0.369–2.101)	0.346	–	–
Preoperative hemoglobin < 35 g/L (yes/no)	1.09 (0.423–3.205)	0.524	–	–
Preoperative anemia	1.18 (0.523–2.985)	0.502	–	–
(hemoglobin < 90 g/L) (yes/no)				
Neoadjuvant chemotherapy (yes/no)	0.180 (0.073–0.446)	< 0.001	0.29 (00.103–0.821)	0.02
Operation type (GP/GA)	0.393 (0.188–0.819)	0.013	0.689 (0.157–3.019)	0.621
Borrmann type		0.159	–	–
I	1			
II	1.399 (0.266–7.358)	0.692		
III	0.479 (0.164–1.403)	0.179		
IV	0.398 (0.144–1.100)	0.076		
Tumor diameter > 7/≤ 7 cm	0.380 (0.190–0.758)	0.006	–	–
Tumor type (linitis plastica/not)	2.764 (1.127–6778)	0.026	2.614 (1.024–6.675)	0.033
Intraoperative blood loss > 400mL (yes/no)	1.089 (0.347–2.102)	0.154		
Operation time > 240 min	1.021 (0.233–3.112)	0.423		
Surgical margin (R0/R1)	2.501 (1.177–5.314)	0.017	0.274 (0.102–0.738)	0.01
Lymphovascular invasion (yes/no)	2.512 (1.066–5.921)	0.035	1.517 (0.930–2.476)	0.095
Perineural invasion (yes/no)	1.545 (0.781–3.054)	0.211	–	–
Differentiation type (poor/well–moderate)	1.358 (0.610–3.021)	0.454	–	–
N stage(N0/N1/N2/N3a/N3b)	1.708 (1.103–2.644)	0.016	3.489 (1.334–9.120)	0.011
Postoperative treatment (chemotherapy/chemoradiotherapy)	0.347 (0.159–0.757)	0.008	0.369 (0.163–0.836)	0.017

HR: Hazard ratio; CI: Confidence interval; GP: Gastrectomy combined with pancreatectomy; GA: Gastrectomy alone.

mation. Some patients who underwent gastrectomy alone, were identified to be pT4b with pancreatic invasion in the final postoperative histological examination. The present study is novel in that it directly assessed the prognostic factors for the patients in the two groups.

The predictive value of computed tomography in identifying T4 disease was found to be ≤ 50%[17]. The accuracy of endoscopic ultrasound was only 46.2% for T stage and 66.7% for N stage. The incidence of pathologically confirmed T4 cancers was found to be 38.1% by intraoperative assessment. Previous studies reported that pathological invasion was confirmed in only 14%–65% of gastric cancer patients treated with EMR [4,18-20]. All patients who underwent EMR were confirmed with pancreatic invasion in our study. Comparison between the GP and GA groups demonstrated that patients with larger lesions, higher N stage and less NAC were associated with a higher possibility of receiving GP. Given the significantly poorer survival with R1/R2 resection and the difficulty of perioperative assessment, we recommend that GP should be performed in patients with T4b gastric cancer for curative resection. The alternative of "peeling" an adherent tumor off of the pancreas carries a high risk of leaving behind a positive margin.

Of the prognostic factors evaluated, only NAC, N stage, surgical margin (R0/R1), tumor type, and postoperative treatment were identified as independent prognostic factors by multivariate analysis (Table 3). The cumulative 3-year survival rate of the T4b patients in the GP group was significantly longer than that in the GA group. Previous reports demonstrated that the 5-year survival rate of the patients with the R0 resection was 30.6%–37.8%. The percentage of R0 resection after multivisceral resection was 38%–100%. Tran *et al*[18] reported that R0 resection rate reached 100% in 34

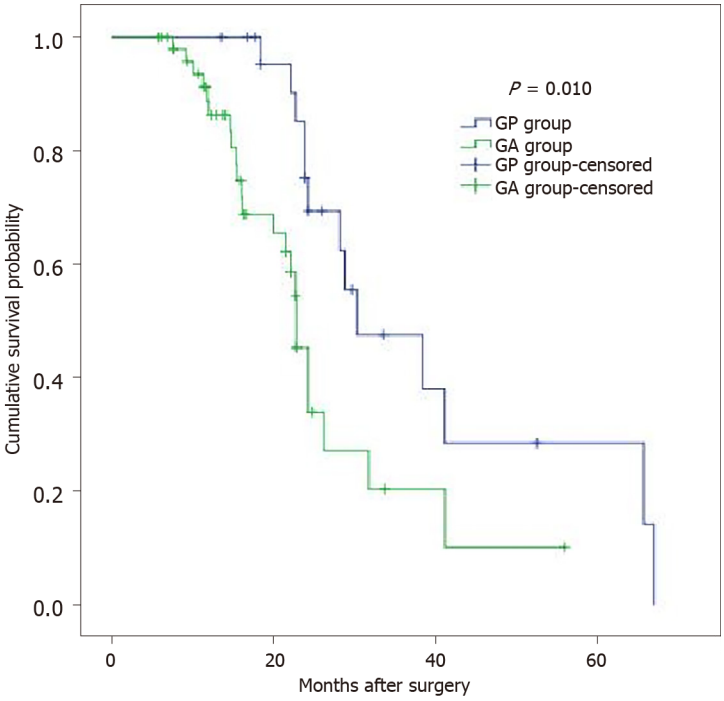

Figure 2 Overall 3-year survival rate of the pT4 patients in the GP group was significantly longer than that in the GA group (47.6%, median 30.3 mo *vs* 20.4%, median 22.8 mo, *P* = 0.010). GP group: Gastrectomy plus *en bloc* pancreaticoduodenectomy group; GA group: Gastrectomy alone group.

patients after additional partial pancreatectomy. Our results also suggested that R0 resection was an important prognostic factor associated with improved survival for T4b gastric cancer with pancreatic invasion.

Lymph node metastasis was reported to be one of the important prognostic factors in patients with gastric cancer. Yasuo reported that patients with pN3 lymph node metastasis have dismal prognosis even if R0 resection is achieved and thus those patients may be not suitable candidates for GP. In the present study, the prognosis of patients with N2 lymph node metastasis was significantly better than the prognosis of those with N3 lymph node metastasis.

With major advances in systemic chemotherapy for advanced gastric cancer, the median survival of patients has been prolonged to > 12 mo. In particular, NAC has been used as a treatment option. In our study, patients treated with NAC had significantly better survival. However, as a national cancer center, we have patients from all over the country. Different patients received different treatments, which was a limitation of our study. Becker *et al*[21] reported that nearly 50% of patients with locally advanced gastric cancer were downstaged by NAC. Recently, a meta-analysis showed morbidity and perioperative mortality were not influenced by NAC[22]. Therefore, we recommend that NAC should be considered first, followed by GP in patients with pancreatic invasion. Furthermore, patients presenting with progression on perioperative therapy or who cannot tolerate chemotherapy should be excluded from GP.

Tran *et al*[18] reported a significantly higher percentage of Clavien–Dindo grade ≥ III complications for patients with gastric cancer undergoing gastrectomy with partial pancreatectomy. Another study showed that patients with postoperative complications had a threefold increased likelihood of not receiving AC[23]. In our study, the overall perioperative 30-d mortality (4.2% *vs* 4.8%, $P = 1.000$) and postoperative morbidity (33.3% *vs* 15.3% $P = 0.128$) were similar in the GP and GA groups. There were no surgery-related deaths in our study. Therefore, we recommend an algorithm for the management of the related patients as Figure 3 showed.

CONCLUSION

NAC followed by a curative resection including radical gastrectomy, extensive lymph node dissection, and *en bloc* resection of invaded pancreas plus postoperative chemora-

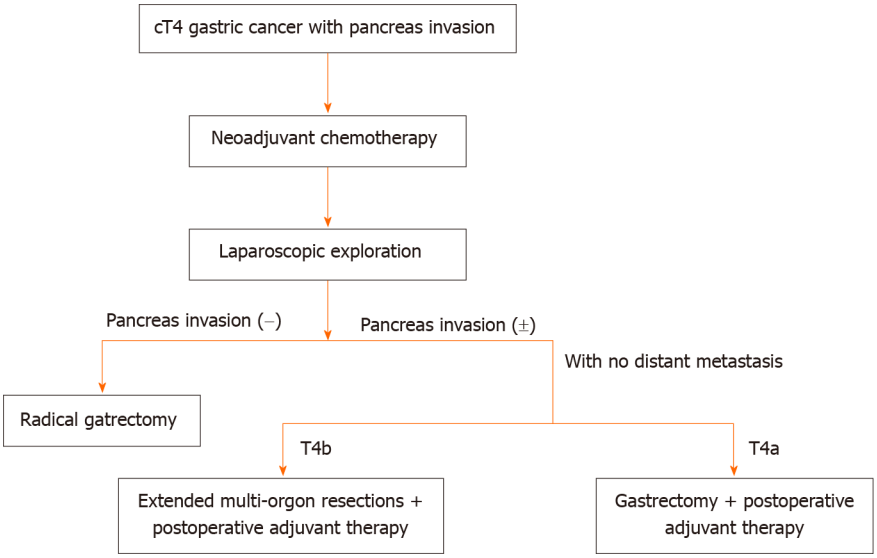

Figure 3 Flowchart of suggested treatment for cT4 gastric cancer with pancreatic head invasion.

diotherapy might be considered as a valid treatment option to improve the survival rate of patients with pT4b gastric cancer with pancreatic head invasion. However, it should be cautiously performed in selected patients. It may be worthwhile to perform a pR0 resection after balancing the risk and survival benefit. Large randomized control trials are needed to confirm the results.

ARTICLE HIGHLIGHTS

Research background

For advanced gastric cancer patients with pancreatic head invasion, extended multiorgan resection remains controversial.

Research motivation

This study investigated the clinicopathological features, surgical outcomes, and prognostic factors of these patients.

Research objectives

This study aimed to evaluate the surgical approach for pT4b gastric cancer with pancreatic head invasion.

Research methods

A total of 143 consecutive gastric cancer with pancreatic head invasion were surgically treated between 2006 and 2016 at the China National Cancer Center. Of these patients, 76 confirmed by postoperative pathology were retrospectively analyzed. They were divided into the gastrectomy plus *en bloc* pancreaticoduodenectomy group (GP group) and gastrectomy alone group (GA group). The clinicopathological features, surgical outcomes, and prognostic factors of these patients were compared.

Research results

The GP group had significantly larger lesions ($P < 0.001$), higher incidence of advanced N stage cancer ($P = 0.030$), and less neoadjuvant chemotherapy (NAC) ($P < 0.001$) than the GA group. Postoperative morbidity (33.3% *vs* 15.3% $P = 0.128$) and mortality (4.2% *vs* 4.8%, $P = 1.000$) were not significantly different in the GP and GA groups. The overall 3-year survival rate of the patients in the GP group was significantly longer than that in the GA group (47.6%, median 30.3 mo *vs* 20.4%, median 22.8 mo, $P = 0.010$). Multivariate analysis identified NAC [hazard ratio (HR) 0.290; 95% confidence interval (CI): 0.103–0.821; $P = 0.020$], linitis plastic (HR 2.614; 95% CI: 1.024–6.675, $P = 0.033$), surgical margin (HR 0.274; 95% CI: 0.102–0.738; $P = 0.010$), N stage (HR 3.489; 95% CI: 1.334–9.120, $P = 0.011$), and postoperative chemoradiotherapy (HR 0.369; 95% CI: 0.163–0.836, $P = 0.017$) as independent predictors of survival in patients with pT4b

gastric cancer and pancreatic head invasion.

Research conclusions

NAC followed by curative resection including radical gastrectomy, extensive lymph node dissection, and *en bloc* resection of invaded pancreas plus postoperative chemoradiotherapy might be considered as a valid treatment option to improve the survival rate of patients with pT4b gastric cancer with pancreatic head invasion.

Research perspectives

Surgical role for T4b patients.

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