

Superior mesenteric artery-first approach for resectable pancreatic head cancer

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Received April 20, 2022; Accepted August 4, 2022

DOI: 10.3892/wasj.2022.169

Abstract. Superior mesenteric artery-first approach has been proposed for the surgical treatment of pancreatic head cancer. However, little is known about its effects on resectable pancreatic head cancer. In the present study, data from patients with resectable pancreatic head cancer, who underwent radical pancreatoduodenectomy with or without the superior mesenteric artery-first approach at from January, 2014 to December, 2019, were retrospectively collected and analyzed. A total of 204 patients were included in the study. The blood loss and blood transfusion of the arterial approach group (n=94) were less than those of the conventional approach group (n=110). Diarrhea occurred in 31 cases (15.2%) of the arterial approach group and in 18 cases (8.8%) of the conventional approach group (P<0.05). A higher rate of R0 resection and a higher number of lymph nodes harvested were achieved in the arterial approach group (P<0.05). The 1-, 2- and 3-year tumor-free survival rates of the patients in the arterial approach group were 60.9, 43.2 and 37.9%, respectively, and those of the patients in the conventional approach group were 64.2, 24.9 and 15.6%, respectively (P<0.05). Moreover, the 1-, 2-, and 3-year overall survival rates of the patients in the arterial approach group were 79.5, 49.7 and 36.7%, and those of the patients in the conventional approach group were 75.9, 38.6 and 18.7%, respectively (P<0.05). On the whole, the present study demonstrates that the superior mesenteric artery-first approach can reduce intraoperative blood loss and consequent blood transfusion, facilitate the achievement of an R0 resection, and thus

prolong the survival of patients, despite resulting in a higher rate of diarrhea.

Introduction

Pancreatic head cancer is one of the most malignant digestive system tumors worldwide, which greatly contributes to the increasing overall morbidity and mortality (1). Radical resection remains the potential curative treatment for long-term survival. If the margins of the specimens are all negative, an R0 resection may be achieved (2-4). Local recurrence around the superior mesenteric artery (SMA) is a frequent outcome following resection, even in patients with resectable pancreatic head cancer, which is defined as a tumor which does not touch the artery, according to the National Comprehensive Cancer Network (NCCN) guidelines (5). Therefore, radical dissection with a reticular pattern around the SMA in resectable cancer of the pancreatic head is vital in order to achieve a better prognosis.

Due to the difficulty of the procedure and the complex anatomical association of the organs and tissues around the head of pancreas, the traditional surgical resection often causes incomplete tumor resection and a high recurrence rate (6-8). In order to avoid the shortcomings of conventional surgery, the superior mesenteric arterial approach is recommended; this involves the exploration of the mesenteric vessels first, and subsequently to determine whether radical pancreaticoduodenectomy (PD) can be performed (9). In the 1990s, Nakao and Takagi (10) and Leach *et al* (11) first described the application of priority artery exposure in PD. In 2001, Machado *et al* (12) tried the posterior approach for PD, and indicated that this approach had great advantages for patients with portal vein invasion who required resection and reconstruction. In 2006, Pessaux *et al* (13) first proposed the application of the priority artery approach for PD. After this time, the term 'arterial priority approach' was used worldwide, and this procedure was adopted in PD to evaluate the main vascular invasion before entering the irreversible surgical procedure.

The superior mesenteric arterial approach has been reported to have the advantage of improving the R0 resection rate; however, little is known about its effects on resectable pancreatic head cancer. Thus, the present study aimed to determine the function and efficacy of the superior mesenteric artery-first approach for resectable pancreatic head cancer by comparing the post-operative complications and patient survival.

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Key words: resectable pancreatic head cancer, superior mesenteric artery-first approach, conventional approach, radical pancreatoduodenectomy, prognosis

Patients and methods

Patient screening. Data from patients with resectable pancreatic head cancer were retrospectively collected and analyzed based on the relevant inclusion/exclusion criteria. The patients underwent radical PD with or without the superior mesenteric artery-first approach at Beijing Chaoyang Hospital (Beijing, China) from January, 2011 to December, 2019. Informed consent was obtained from the patients and their family members. The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Chaoyang Hospital (No. 2020-D-302). The participants provided written informed consent to participate in this study.

The inclusion criteria were as follows: i) An age range between 18-80 years; ii) a pathologically confirmed diagnosis of pancreatic ductal adenocarcinoma; iii) no distant metastasis; iv) the pre-operative assessment of resectable pancreatic cancer according to the NCCN 2020 guidelines (5); v) the provision of informed consent; vi) complete availability of clinical and pathological data. The exclusion criteria were as follows: i) Portal vein invasion $>180^\circ$ or celiac artery invasion; ii) pathologically confirmed non-adenocarcinoma pancreatic cancer; iii) pre-operative neoadjuvant therapy; iv) incomplete clinicopathological data.

Patient grouping and definition. According to the surgical technique, the patients were divided into two groups as follows: The arterial approach group and the conventional approach group.

The inferior infracolic superior mesenteric artery-first approach was performed as previously reported (14): A transverse arc incision was performed in the superior abdomen followed by exploration. The SMA was gradually separated and exposed after opening the serosa of the mesenteric root in the lower colon. The first jejunal artery and the inferior pancreaticoduodenal artery were then ligated. The SMA was separated from the tumor and skeletonized. The 14th group lymph nodes and retroperitoneal nerve connective tissue were removed. If the SMA could be dissociated to its origin in abdominal aorta smoothly, it was concluded that a radical resection could be achieved. If the SMA was found to be seriously invaded and difficult to dissociate, the surgery was abandoned. The choice of modus operandi needed to be individualized according to the patient's situation. Finally, the gastrocolic ligament was incised and the anterior lobe of transverse mesocolon was dissociated to enter the lesser omental cavity. The stomach, pancreas, jejunum and bile duct were resected accordingly, and pancreaticojejunostomy, choledochojejunostomy, gastrointestinal anastomosis and enterojejunostomy were performed in turn.

The conventional approach was performed as follows: Kocher incision exploration was performed to free the pancreatic head and duodenum area, to evaluate the resectability of the tumor, to skeletonize the common hepatic artery, celiac trunk, superior mesenteric transarterial in turn, and to clean the surrounding lymph tissue. The gastric body and pancreatic body, and jejunum and bile duct were cut off, respectively. Subsequently, pancreaticojejunostomy, choledochojejunostomy, gastrointestinal anastomosis and enterojejunostomy were performed.

Parameters and follow-up. The intraoperative parameters were as follows: Duration of surgery, intraoperative blood loss and intraoperative blood transfusion. The post-operative conditions examined were the following: Pathological examination results, complications and recovery. The follow-up protocol included telephone and outpatient follow-up. The follow-up time was as of March, 2021 to June, 2021.

Statistical analysis. Normal quantitative parameters are expressed as the mean \pm standard deviation, while the median (interquartile range) was used for non-normal quantitative parameters. Fisher's exact test was used for categorical variables, while the independent samples unpaired t-test and Mann-Whitney U test were employed for normal quantitative variables and non-normal quantitative variables, respectively. The Kaplan-Meier method was used to calculate the survival curve. The log-rank test was used to compare the differences in the survival rates of patients between the two groups. All data were analyzed by SPSS 24.0 software (IBM Corp.). A value of $P < 0.05$ was considered to indicate a statistically significant difference.

Results

A total of 204 patients were enrolled in the present study, including 122 males and 82 females with an average age of 63.9 years. The most common symptoms noted were asymptomatic jaundice (65.2%), abdominal pain (27.9%) and atypical gastrointestinal symptoms (1.5%); a total of 5.4% of the patients underwent routine checkups. The pre-operative characteristics of the patients are summarized in Table I. There was a similar distribution of sex, age, smoking stats, diabetes, biliary drainage and carbohydrate antigen 19-9 between the two groups ($P > 0.05$).

The operative parameters and post-operative complications of the two groups are presented in Table II. All patients completed the surgery successfully and no peri-operative mortality occurred. Blood loss and blood transfusion in the arterial approach group were less than those in the conventional approach group. The differences in the duration of the surgery between the two groups was not statistically significant. A total of 82 cases (40.2%) had post-operative complications. Diarrhea occurred in 31 cases (33.0%) in the arterial approach group and in 18 cases (16.4%) in the conventional approach group ($P < 0.05$). The incidence of the total rate of post-operative complications, pancreatic fistula, gastric emptying disorder, abdominal infection, abdominal hemorrhage, biliary fistula, pulmonary infection, gastrointestinal bleeding and liver abscess in the two groups was similar.

The histological and post-operative parameters are summarized in Table III. A higher rate of R0 resection and a higher number of lymph nodes harvested were achieved in the arterial approach group ($P < 0.05$). The comparison of the tumor diameter, tumor differentiation, tumor stage, lymph node metastasis, adjuvant chemotherapy and post-operative hospitalization duration did not yield significant differences. In addition, regional recurrence in the arterial approach group was significantly less than that in the conventional approach group. The comparison of hepatic, peritoneal, pulmonary and skeletal metastases did not reveal any significant differences.

Table I. Comparison of the pre-operative parameters of the patients in the two groups.

Parameter	Arterial approach group (n=94)	Conventional approach group (n=110)	P-value
Sex, n (%)			0.425
Male	59 (62.8%)	63 (57.3%)	
Female	35 (37.2%)	47 (42.7%)	
Age, years; n (range)	64 (57-67)	66 (57-72)	0.671
Symptom, n (%)			
Asymptomatic jaundice	63 (67.0%)	70 (63.6%)	0.613
Abdominal pain	27 (28.7%)	30 (27.3%)	0.818
Atypical gastrointestinal symptoms	1 (1.1%)	2 (1.8%)	0.656
Routine checkups	3 (3.2%)	8 (7.3%)	0.198
Smoking status, n (%)			0.822
Yes	37 (39.4%)	45 (40.9%)	
No	57 (60.6%)	65 (59.1%)	
Diabetes, n (%)			0.570
Yes	24 (25.5%)	32 (29.1%)	
No	70 (74.5%)	78 (70.9%)	
Biliary drainage, n (%)			0.095
Yes	35 (37.2%)	29 (26.4%)	
No	59 (62.8%)	81 (73.6%)	
Carbohydrate antigen 19-9 (U/ml), n (%)			0.148
≤37	19 (20.2%)	14 (12.7%)	
>37	75 (79.8%)	96 (87.3%)	

In total, the most common symptoms noted were asymptomatic jaundice (65.2%), abdominal pain (27.9%) and atypical gastrointestinal symptoms (1.5%); a total of 5.4% of the patients underwent routine checkups.

Table II. Comparison of operative details and complications between the two groups.

Parameters	Arterial approach group (n=94)	Conventional approach group (n=110)	P-value
Blood loss, ml; amount (range)	500 (400,600)	600 (400,800)	0.001
Blood transfusion			0.001
Yes	14 (14.9%)	54 (49.1%)	
No	80 (85.1%)	56 (50.9%)	
Duration of surgery (h)	9.4±2.0	9.0±1.7	0.173
Post-operative complications, n (%)	38 (40.4%)	44 (40.0%)	0.951
Pancreatic fistula, n (%)	13 (27.1%)	18 (16.4%)	0.615
Biochemical leakage, n (%)	6 (6.4%)	8 (7.3%)	0.802
Grade B pancreatic fistula, n (%)	3 (3.2%)	5 (4.5%)	0.620
Grade C pancreatic fistula, n (%)	4 (4.3%)	5 (4.5%)	0.920
Gastric emptying disorder, n (%)	14 (14.9%)	27 (24.5%)	0.086
Abdominal infection, n (%)	4 (4.3%)	7 (6.4%)	0.506
Abdominal hemorrhage, n (%)	2 (2.1%)	9 (8.2%)	0.056
Biliary fistula, n (%)	1 (1.1%)	5 (4.5%)	0.142
Pulmonary infection, n (%)	1 (1.1%)	1 (0.9%)	0.911
Gastrointestinal bleeding, n (%)	0	2 (1.8%)	0.189
Liver abscess, n (%)	0	1 (0.9%)	0.354
Diarrhea, n (%)	31 (33.0%)	18 (16.4%)	0.006

Table III. Comparison of the histological and post-operative parameters between the two groups.

Parameters	Arterial approach group (n=94)	Conventional approach group (n=110)	P-value
Tumor diameter (cm)	3.0±1.2	3.1±1.1	0.517
Tumor differentiation, n (%)			0.860
Low	31 (33.0%)	35 (31.8%)	
Medium-high	63 (67.0%)	75 (68.2%)	
Tumor stage, n (%)			
I	47 (50.0%)	42 (38.2%)	0.090
II	23 (24.5%)	37 (33.6%)	0.152
III	24 (25.5%)	31(28.2%)	0.671
Lymph node metastasis, n (%)			0.160
Yes	57 (60.6%)	77 (70.0%)	
No	37 (39.4%)	33 (30.0%)	
R0 resection, n (%)			0.003
Yes	91 (96.8%)	93 (84.5%)	
No	3 (3.2%)	17 (15.5%)	
Lymph nodes harvested, n (range)	19 (11-24)	13 (8-20)	0.024
Adjuvant chemotherapy, n (%)			0.711
Yes	42 (44.7%)	52 (47.3%)	
No	52 (55.3%)	58 (52.7%)	
Post-operative duration of hospitalization (days), n (range)	17 (15,22)	17 (16,24)	0.285
Type of recurrence, n (%)	64 (68.1%)	93 (84.5%)	0.005
Regional recurrence, n (%)	9 (9.6%)	28 (25.5%)	0.003
Hepatic metastasis, n (%)	33 (35.1%)	35 (31.8%)	0.620
Peritoneal metastasis, n (%)	17 (18.1%)	23 (20.9%)	0.613
Pulmonary metastasis, n (%)	3 (3.2%)	4 (3.6%)	0.862
Skeletal metastases, n (%)	2 (2.1%)	3 (2.7%)	0.783

Univariate analysis and multivariate analysis of long-term survival for patients with pancreatic head cancer are summarized in Table IV. In the univariate analysis, sex, age, blood loss, blood transfusion and adjuvant chemotherapy had no significant effect on the prognosis of patients. Carbohydrate antigen 19-9, tumor differentiation, the nature of resection, tumor stage and the artery-first approach were included in the multivariate analysis. The results revealed that tumor differentiation, tumor stage and the artery-first approach could influence the prognosis of patients.

As of March 2021, the overall median survival rate was 24 months, and the median tumor-free survival rate was 17 months. The 1-, 2- and 3-year overall tumor-free survival rates were 62.8, 35.2 and 27.9% (Fig. 1A); and the 1-, 2- and 3-year overall survival rates were 77.6, 46.3 and 29.2% (Fig. 1B). The median survival of the two groups was 26 and 23 months, and the median tumor-free survival of the two groups was 18 and 16 months, respectively. The 1-, 2- and 3-year tumor-free survival rates of the patients in the arterial approach group were 60.9, 43.2 and 37.9%, respectively, and those of the patients in the conventional approach group were 64.2, 24.9 and 15.6%, respectively (P=0.017; Fig. 2A). Moreover, the 1-, 2- and 3-year overall survival rates of the patients in the arterial approach group were 79.5, 49.7 and 36.7%, respectively,

and those of the patients in the conventional approach group were 75.9, 38.6 and 18.7%, respectively (P=0.034; Fig. 2B).

Discussion

In the present study, it was found that patients from the artery-first approach group had less bleeding and blood transfusion, but a prolonged duration of surgery. However, the number of lymph nodes dissected and the R0 resection rate were higher, which could lead to the lower incidence of regional recurrence, but to a higher incidence of post-operative diarrhea. Furthermore, the present study demonstrated that tumor differentiation, tumor stage and the artery-first approach could independently affect the prognosis of patients. The lower the differentiation, the higher the staging, the worse the prognosis. Finally, the prolonged tumor-free time and overall survival time of the patients in the artery-first approach group was observed.

According to the statistics of the American Cancer Society in 2020, the 5-year survival rate of patients with pancreatic head cancer was only 9% (15-17). The only curative treatment for resectable pancreatic head cancer is surgical resection, namely pancreatoduodenectomy. However, An R0 resection is usually difficult to achieve, and local recurrence is related to a positive SMA margin. Kalisvaart *et al* (18) retrospectively reviewed

Table IV. Univariate analysis and multivariate analysis of the long-term survival of patients with pancreatic head cancer.

Factor	Univariate analysis			Multivariate Cox regression analysis		
	Median survival time (months)	χ^2 value	P-value	RR value	95% CI	P-value
Sex	20	2.418	0.120			
Male	17					
Female	31					
Age (years)	20	0.029	0.864			
≤ 60	20					
> 60	20					
Carbohydrate antigen 19-9 (U/ml)	22	4.627	0.031	1.198	0.729-1.969	0.476
≤ 37	41					
> 37	21					
Blood loss (range, ml)	20	1.821	0.110			
≤ 500	23					
> 500	19					
Blood transfusion	21	0.202	0.821			
Yes	29					
No	14					
Tumor differentiation	20	1.778	0.037	0.645	0.455-0.916	0.014
Low	18					
Medium-high	27					
Nature of resection	20	11.952	0.001	1.069	0.548-2.085	0.845
R0	28					
R1	8					
Adjuvant chemotherapy	20	0.120	0.729			
Yes	20					
No	19					
Tumor stage	22	51.018	0.000	0.431	0.281-0.662	0.001
I	30					
II	23					
III	15					
Artery-first approach	24	10.824	0.017	1.694	1.2-2.391	0.003
Yes	34					
No	19					

23/617 evaluated studies (n=3,815); local recurrence was observed in 7-69% of the studies and the SMA margin (six studies) was positive in 15-35% of the studies. Moreover, local recurrence was more frequently observed with a positive SMA margin (66 vs. 45%; P=0.005). In addition, the abnormal origin and direction of the artery can easily increase the risk of intraoperative injury, massive hemorrhage and post-operative hepatic, intestinal and biliary ischemia. The postoperative survival rate is not ideal (19-21). The aim of the artery-first approach is to explore the superior mesenteric artery in the inferior infracolic to determine the resectability of the tumor, cut off the blood supply of the tumor, and then resect the specimen for routine anastomosis. It gives priority to the evaluation of vascular invasion, and directly determines whether radical resection can be implemented, which is of utmost importance for the prognosis of patients (22,23).

In the present study, the inferior superior mesenteric artery-first approach was performed, as previously described (24). In the study by Vallance *et al* (25), 80 patients underwent the posterior superior mesenteric artery-first approach and the half-year survival rate was significantly higher in these patients than those in the conventional approach group (95 vs. 80%), which was similar to the results of the present study. Furthermore, according to the study by Du *et al* (26), the R0 resection rate was improved by the artery-first approach (85.71 vs. 62.50%), and the post-operative tumor recurrence rate was significantly lower in this group than that in the conventional approach group (7.14 vs. 28.13%); these findings were also in accordance with those of the present study.

The mesenteric approach was first developed for pancreatoduodenectomy by Professor Akimasa Nakao (27). This approach

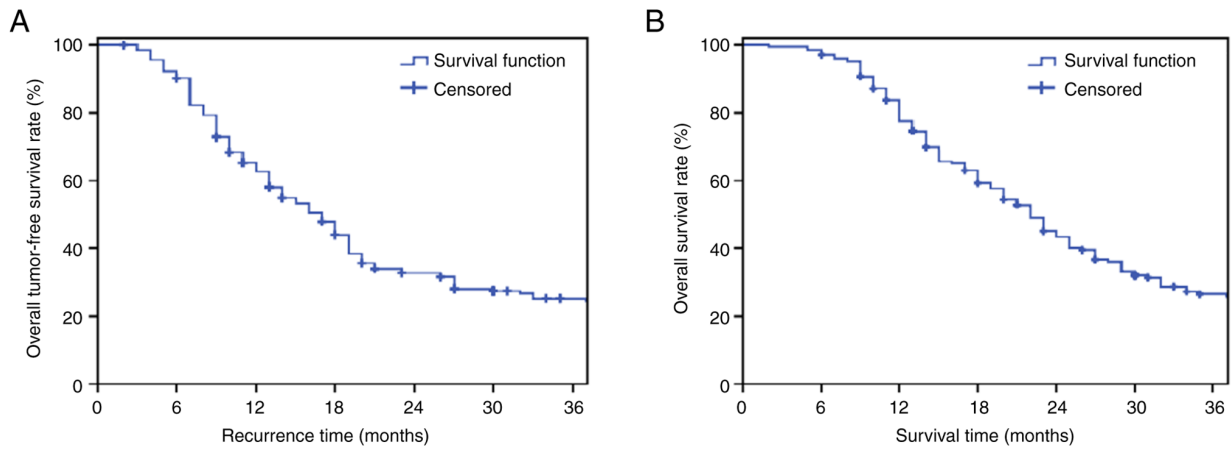


Figure 1. Long-term prognosis of patients with resectable pancreatic head cancer undergoing radical pancreatoduodenectomy (n=204). (A) Tumor-free survival curve; (B) overall survival curve.

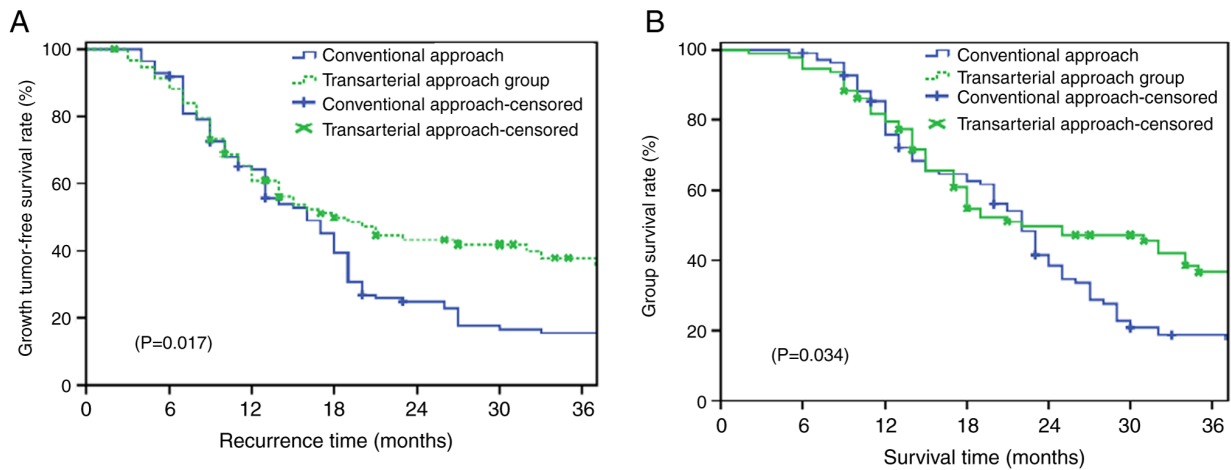


Figure 2. Long-term prognosis of patients with resectable pancreatic head cancer undergoing radical pancreatoduodenectomy in the arterial approach group (n=94) and the conventional approach group (n=110). (A) Tumor-free survival curve; (B) overall survival curve.

allowed for the dissection from the non-cancerous side and the determination of both cancer-free margins and resectability followed by systematic lymphadenectomy around the superior mesenteric artery. It also enables the early ligation of the inferior pancreatoduodenal artery and dorsal pancreatic artery branches from the superior mesenteric artery, as well as the complete excision of the total mesopancreas, which is considered to be the second portion of the pancreatic head nerve plexus (27). Similar to the present study, the artery-first approach was to explore along the artery and in turn, dissect the perivascular tissue and lymph node dissection during the exploration. Moreover, it was found that the artery-first approach could make lymph node dissection more thorough and comprehensive, expand the scope of lymph node dissection, allow for an easier R0 resection, avoid residual lesion tissue, reduce the risk of post-operative recurrence, improve the tumor-free survival rate and improve the prognosis of patients. At the same time, it reduced the times of moving tissues and organs, which could reduce the tumor cell diffusion caused by moving.

Furthermore, the present study also demonstrated that the patients who underwent the superior mesenteric artery-first approach in the inferior infracolic region had less intraoperative

bleeding and blood transfusion. These results may be due to the fact that the blood supply of the resected tissue was ligated and cut first, which facilitated the subsequent organ resection, reduced the bleeding caused by separating the venule between uncinate process of pancreas and portal vein, and reduced the blood transfusion. Moreover, the artery-first approach could not only facilitate the judgement of its anatomical structure, but also increased the accuracy of the operation for surgeons. However, there were also some shortcomings in artery-first approach, such as the prolonged duration of surgery and post-operative diarrhea; in terms of the shortcomings, the general condition of the patients during the surgery could be monitored, cooperating with anesthesiologists to timely apply drugs, thus reducing the impact of the long duration of the surgery on patients.

The main limitation of the present study was that it presented the experience of a single center. The number of patients in each subgroup was relatively small, which may limit the accuracy of the assessment. Further studies, preferably random clinical trials from multi-centers, are thus required to further confirm the preliminary outcomes observed herein.

In conclusion, the present study demonstrated that the inferior superior mesenteric artery approach improved the R0 resection

rate, prolonged the post-operative survival time, reduced recurrence and improved the prognosis of patients. It also reduced intraoperative blood loss and blood transfusion, although it increased the incidence of post-operative diarrhea. Further studies are warranted in the future to validate these findings.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JQZ conceived the study. SCL and FFW performed the research and wrote the first draft of the manuscript. All authors (FFW, SCL, ZYR, XZ, JQZ and QH) contributed to the design of the study and to the interpretation of the results, and to further drafts. JQZ and QH confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Chaoyang Hospital (No. 2020-D-302). The participants provided written informed consent to participate in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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