Comparative study between Artery-first approach and classic approach in pancreatoduodenectomy with mesopancreas dissection

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Received: 11 May 2021
Revised: 11 May 2021
Accepted: 16 May 2021
Published: 11 January 2022

The Egyptian Journal of Surgery 2021, 40:959–967

Background
Cancer pancreas ranks the fourth cause of death in the cancer list in the USA. Surgical resection with negative margins is one of the most important factors influencing the survival, hence, it is considered the only and best modality of choice for achieving curative treatment.
Objective
The aim was to check the feasibility of Artery-first approach and to check the impact of R0 mesopancreatic margin as a prognostic factor on recurrence.
Patients and methods
Between 2017 and 2020, 40 patients underwent pancreatoduodenectomy for periampullary carcinoma. Of these 40 patients, 22 cases underwent classic standard approach and 18 cases underwent Artery-first approach, they were followed up for postoperative morbidity and mortality, with histopathological data focusing on R margins, especially mesopancreatic margin and postoperative recurrence.
Results and conclusion
Artery-first approach is a safe and feasible technique in comparison with standard classic approach in pancreatoduodenectomy with mesopancreas dissection as regards operative time, blood loss, postoperative morbidity, mortality, and hospital stay. There is no significant difference between the two groups as regards recurrence.
Margins in this triangle for periampullary carcinoma in univariate and multivariate analysis.

Keywords:
artery-first, mesopancreas, pancreatoduodenectomy classic approach, R0 margin cancer pancreas, superior mesenteric artery-first approach

Egyptian J Surgery 40:959–967

1110-1121

Introduction

Cancer pancreas ranks the fourth cause of death in the cancer list in USA. Surgical resection with negative margins is one of the most important factors influencing the survival, hence, it is considered the best modality of choice for achieving curative treatment [1].

In 1993, Nakao and Takagi were the first who proposed the mesenteric approach where superior mesenteric artery (SMA) and superior mesenteric vein (SMV) were approached from the mesentery of the jejunum at the transverse mesocolon base to early ligate the inferior pancreaticoduodenal artery. Then Weitz and colleagues were the first to propose the term 'artery-first approach.' After that, many other methods were proposed by other surgeons using 'Artery-first' approach for pancreatoduodenectomy (PD) [2].

Previously the periampullary cancer resectability depended on portal vein (PV)/SMV axis involvement, However, now, it is well known that the posteromedial resection margin is an important prognostic factor to confirm or abandon resectability and SMA involvement is a contraindicating factor for cancer pancreas resection. So 'Artery-first' technique is a promising and important approach to avoid 'point of nonreturn' in PD [3].

Adham and Singhirunnusorn [1] delineated the anatomical boundaries of 'The mesopancreatic triangle' bounded by the anterior surface of the aorta between the celiac trunk (CT) and the origin of SMA from below, the SMV and PV axis above, and SMA as the medial boundary.

After evolution of the concept of mesorectum and the important prognostic outcome of total mesorectal

excision in cancer rectum, Gockel *et al.* [4] in 2007 proposed the concept of mesopancreas.

Retropancreatic 'mesopancreatic' margin is the commonest resection margin to be involved and mesopancreas was proposed in analogy with mesorectum, which is considered as a fusion fascia formed embryologically during the development of pancreas [5].

A systematic review of histopathological data confirms that retropancreatic margin 'mesopancreatic margin' in special and resection margin involvement in general are poor prognostic factors as regards the intention of curative cancer pancreas resection [6].

Aim

The aim was to assess the feasibility of Artery-first approach in comparison with classic approach in PD and its impact on recurrence after mesopancreatic dissection in periampullary cancer.

And also to assess if the histopathological parameters include mesopancreatic margin, in particular, as prognostic factors for periampullary carcinoma influencing recurrence.

Patients and methods

The study was conducted at Assiut and Mansoura Universities in Egypt with periampullary carcinoma during the period between 2017 and 2020. I have the acceptance of the ethics committee approval at Assiut University faculty of medicine to conduct this study and the informed consent of the patients to share in the study.

The total cases were 40 that are 22 cases of classic approach and 18 cases of Artery-first approach. The study was prospective and the cases undergoing 'Artery-first' approach were those with a larger preoperative tumor size by imaging.

Inclusion criteria

Surgically fit patients according to American Society of Anesthesiologists classification with resectable cancer head and nearby body of pancreas, ampullary carcinoma, second-part duodenal adenocarcinoma, and distal cholangiocarcinoma.

Exclusion criteria

Metastatic cases.

Surgical techniques

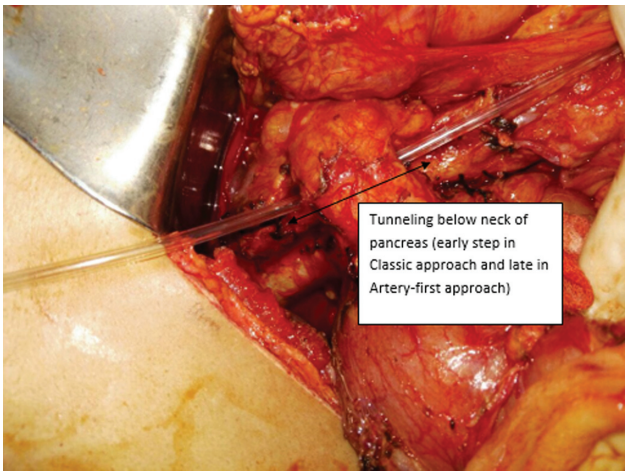
Varieties of operations, including whipple operation, total pancreatectomy with splenectomy, with or without vascular resections for indicated infiltrated cases, or to get a proper oncologic safety margin, for example, PV and SMV.

Open and laparoscopic-assisted cases were among the approaches.

In classic approach, after kocherization of the duodenum and dissection of portal triade and cholecystectomy, we start to assess the tunnel under the neck of the pancreas whether tumor-infiltrating the PV/SMV axis, and if not, we cut the neck of pancreas early in the procedure, then we continue to dissect the uncinate process and control pancreatoduodenal vessels as the latter steps and draining lymph nodes, including periportal lymph nodes and up to the hepatic artery, and we will add to the standard procedure the mesopancreatic dissection that lies between SMA caudal, celiac artery cranial, and PV/SMV axis anterior, and the specimen will be marked and sent for histopathology. There is no difference as regards further steps of whipples or total pancreatectomy operations (Fig. 1).

While in the Artery-first approach, a craniocaudal dissection at the origin of the SMA and the CT, all along their right semicircumference versus standard approach. We will fully kocherize the duodenum until reaching inferior vena cava (IVC) and entrance of the left renal vein, then we will hang the left renal vein with a vascular loop or a small foley catheter (Fig. 2).

Figure 1



Tunneling below the neck of pancreas (early step in the classic approach may lead to point of nonreturn).

Then continue dissection medially and in a cranial position, until we will find the origin of SMA from the aorta, then we will sharply dissect the right side of the vertical portion of SMA, no branches arise from this short vertical portion, then the SMA curves forward caudally, making an angle to start its horizontal part that passes over the left renal vein, and at this position, we can early control the inferior pancreatoduodenal artery at its origin and assess resectability by confirming the absence of involvement of the vertical angle and horizontal parts of SMA from uncinate process of the pancreas and to delineate any vascular anomalies at this step (Fig. 3).

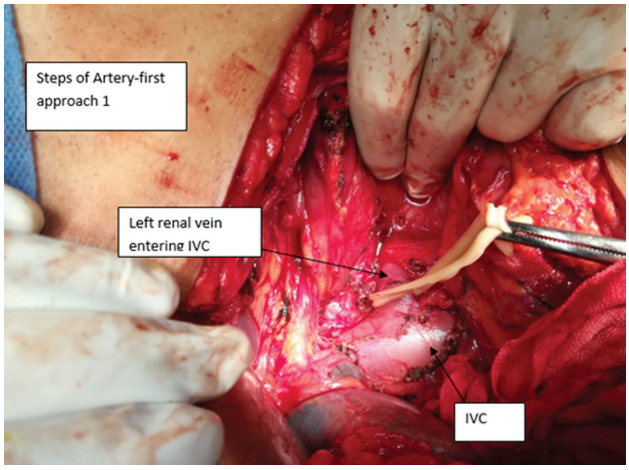
Once resectability is confirmed, all the tissues that lay in this triangular space (SMA caudal, CT cranial, and SMV-PV at the roof of the triangle) are cleared (Figs 4–7).

Then the dissection continues along the right and then anterior surface of the SMV and PV, until reaching the dissected posterior surface of the neck of the pancreas. Here, pancreaticoduodenal veins can be controlled and divided electively to reach the posterior surface of the neck of the pancreas. Tunneling under the PV is now done.

The last step in the Artery-first approach is the division of the neck of the pancreas (the point of nonreturn), unlike classic approach where this is one of the earliest steps in the procedure.

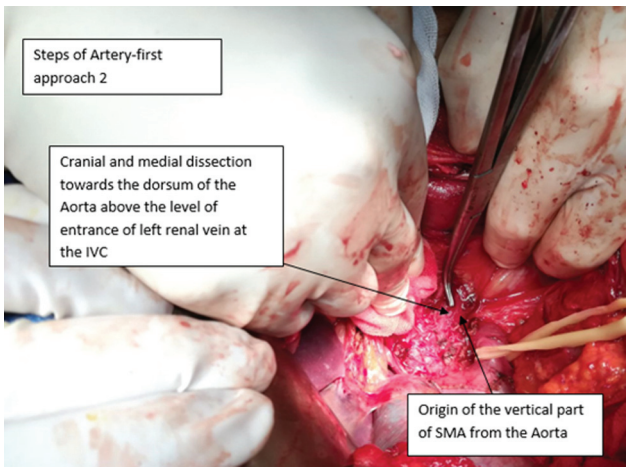
PV resection en-block with the specimen is done whenever this is feasible. Sidewall (sleeve) resection

Figure 2



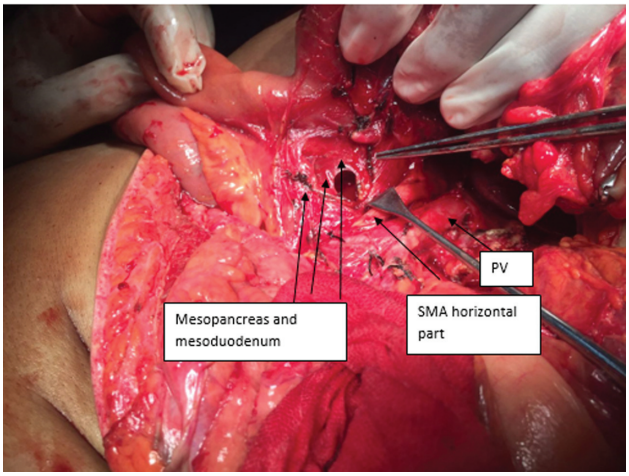
First step of Artery-first technique with dissection till visualizing the left renal vein entering IVC after fully kocherization of the duodenum.

Figure 3



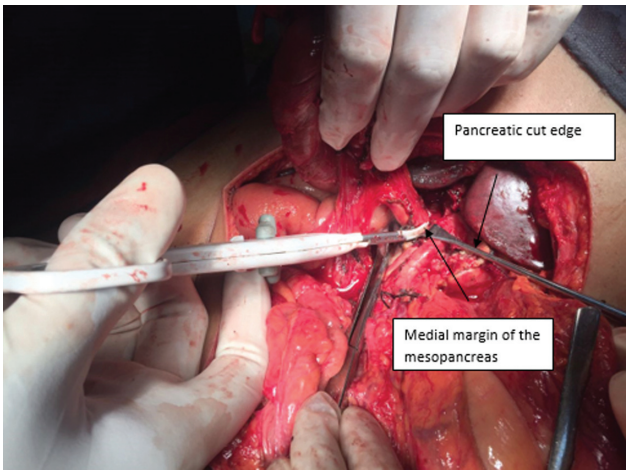
Second step of Artery-first technique with cranial and medial dissection toward the dorsum of the aorta above the level of entrance of the left renal vein at the IVC.

Figure 4



Mesopancreas and mesoduodenum.

Figure 5



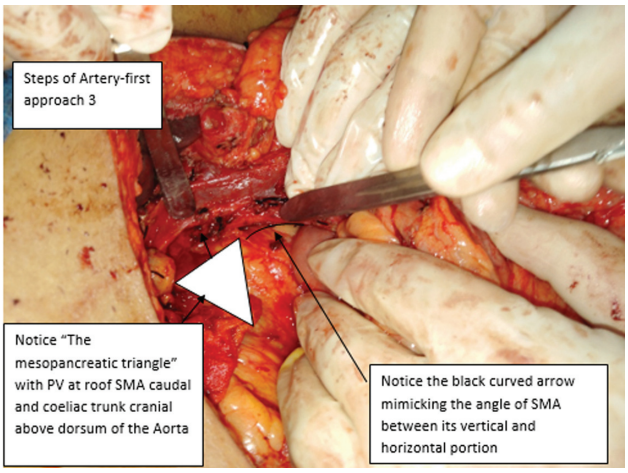
Mesopancreatic margin of the mesopancreas.

of the PV in indicated cases was done en-block with the mass.

Postresection reconstruction of hepaticojejunostomy, gastrojejunostomy, and either pancreatojejunostomy or pancreatogastrostomy in whipple cases for both techniques.

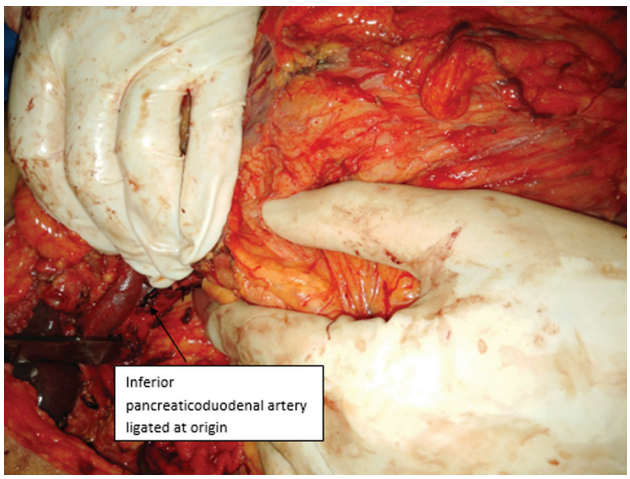
After the specimen is removed in both procedures and before it is sent to the pathology unit, each margin of the specimen is marked. This can guide the pathologist to identify the retropancreatic margins and define whenever there is an R1 resection and the exact area of invasion. Microscopic margin involvement (R1) will be defined as tumor within 1 mm of the resection margin (Figs. 8 and 9).

Figure 6



Demonstration of the junction between vertical and horizontal parts of superior mesenteric artery+demonstration of the boundaries of mesopancreatic triangle.

Figure 7



Inferior pancreaticoduodenal artery ligated at the origin.

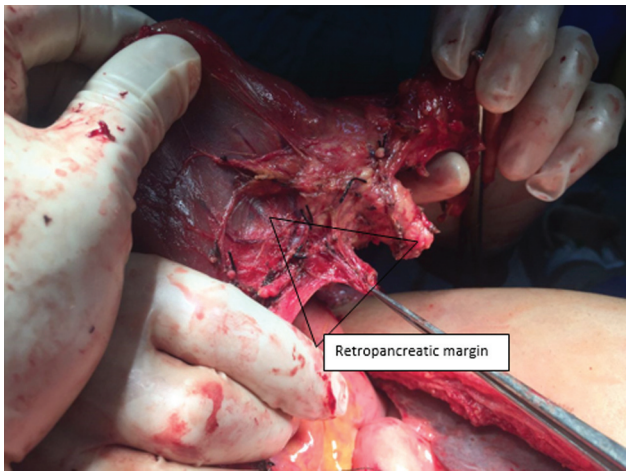
Histopathological evaluation

The margins will be examined as the following:

(1) Mesopancreatic R0 greater than or equal to 1 mm of free margin.
(2) Mesopancreatic margin R1 less than 1 mm of free margin.
(3) Mesopancreatic margin R2=0 mm of free margin.
(4) Transection margin R0 greater than or equal to 1 mm of free margin.
(5) Transection margin R1 less than 1 mm of free margin.
(6) Transection margin R2=0 mm of free margin.
(7) Anterior margin R0 greater than or equal to 1 mm of free margin.
(8) Anterior margin R1=0 mm of free margin.
(9) The T-stage and N-stage will be evaluated.

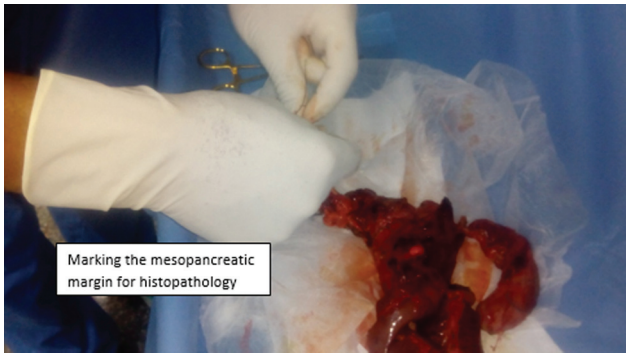
Operative outcome data, including operative time in minutes, blood loss, and blood transfusion.

Figure 8



Retropancreatic margin.

Figure 9



Marking the mesopancreatic margin for histopathology.

Table 1 Preoperative and operative analysis of data

Outcomes	Classic approach (*n*=22) [*n* (%)]	Artery-first approach (*n*=18) [*n* (%)]	*P* value
Sex			
Male	14 (63.64)	11 (61.11)	0.870 (NS)
Female	8 (36.36)	7 (38.39)	0.870 (NS)
Mean age (years)	60.77±12.016	63.44±12.890	0.502 (NS)
Operation time (min)	462.14 ±123.089	507.11±103.474	0.225 (NS)
Blood loss (ml)	645.45±315.062	661.11±223.314	0.860 (NS)
Blood transfusion	14 (63.64)	13 (72.22)	0.434 (NS)
Delayed gastric emptying	5 (22.37)	2 (11.11)	0.336 (NS)
Pancreatic fistula	4 (18.18)	1 (5.56)	0.230 (NS)
Hematemesis and melena	0	1 (5.56)	0.263 (NS)
Bile leak	0	1 (5.56)	0.263 (NS)
Postoperative bleeding	0	1 (5.56)	0.263 (NS)
Reoperation	0	1 (5.56)	0.263 (NS)
Acute severe pancreatitis	0	1 (5.56)	0.263 (NS)
Wound infection	1 (4.55)	2 (11.11)	0.433 (NS)
Pulmonary embolism	1 (4.55)	0	0.360 (NS)
Mean hospital stay (days)	18.27±7.735	14.56±6.233	0.108 (NS)
Mortality	1 (4.55)	2 (11.11)	0.433 (NS)

Table 2 Age×sex cross-tabulation

	Age				
	<55	55–54	65–74	≥75	Total
Sex					
Male	1	9	11	4	25
Female	0	4	7	4	15
Total	1	13	18	8	40

Postoperative short-term outcomes will be evaluated, including postoperative complications (pancreatic fistula, bleeding, delayed gastric emptying, and wound infection) and hospital stay in days.

Postoperative mortality

Postoperative follow-up for recurrence at 6-month intervals and shorter periods in case of symptomatic or suspicious cases of recurrence.

Results

Tables 1–6 and Fig. 10.

Discussion

Pancreatic cancer is associated with poor prognosis and surgery remains the main modality of treatment. Mesopancreas was proposed in analogy with mesorectum, which is considered as a fusion fascia formed embryologically during the development of pancreas [7].

Table 3 Histopathological data for the two approaches

Outcomes	Classic approach (*n*=22)	Artery-first approach (*n*=18)	*P* value
Mesopancreatic R0	13 (59.09)	13 (59.09)	0.386 (NS)
Mesopancreatic R1	8 (36.36)	1 (5.56)	0.020**
Mesopancreatic R2	1 (4.55)	4 (22.22)	0.093 (NS)
Transection R0	18 (81.82)	18 (100)	0.057 (NS)
Transection R1	2 (9.09)	0	0.189 (NS)
Transection R2	2 (9.09)	0	0.189 (NS)
Anterior R0	19 (86.36)	18 (100)	0.103 (NS)
Anterior R1	3 (13.64)	0	0.103 (NS)
T1	2 (9.09)	2 (11.11)	0.832 (NS)
T2	11 (50)	6 (33.33)	0.289 (NS)
T3	9 (40.91)	7 (38.89)	0.897 (NS)
T4	0	3 (16.67)	0.046**
N0	5 (22.73)	9 (50)	0.072 (NS)
N1	9 (40.91)	3 (16.67)	0.096 (NS)
N2	8 (36.36)	6 (33.33)	0.842 (NS)
Tumor size mean (cm)	1.73±0.550	2.17±6.18	0.023**
Recurrence	7 (31.21)	6 (33.33)	0.919

**$P<0.05$, statistically significant.

The mean age of patients for the classic approach was 60.77±12.016 years, and for the 'Artery-first' approach, it was 63.44±12.890 years, with no significant difference between the two groups.

Table 4 Sites of recurrence and metastasis

	Approach		
	Classic approach (*n*=22)	Artery-first approach (*n*=18)	*P* value
Recurrence			
No recurrence	15 (68.18)	12 (66.67)	0.919 (NS)
Locoregional	2 (9.09)	5 (27.78)	0.122 (NS)
Liver	6 (27.27)	3 (16.67)	0.424 (NS)
Lymph nodes	1 (4.55)	0	0.368 (NS)
Lungs	1 (4.55)	1 (5.56)	0.884 (NS)

Table 5 Univariate analysis of histopathological data versus recurrence using χ^2

	P value
Mesopancreatic margin	0.020**
Transection margin	0.091 (NS)
Anterior margin	0.974 (NS)
Grade of tumor	0.153 (NS)
T-stage	0.467 (NS)
N-stage	0.043**
Operative approach	0.919 (NS)

***P*<0.05, statistically significant.

Table 6 Multivariate linear regression analysis of histopathological data versus recurrence (dependent variable)

	P value
Mesopancreatic margin	0.024**
Transection margin	0.480 (NS)
Anterior margin	0.728 (NS)
Grade of tumor	0.410 (NS)
T-stage	0.821 (NS)
N-stage	0.212 (NS)
Operative approach	0.320 (NS)

***P*<0.05, statistically significant.

The risk of cancer pancreas is directly proportional with the increase in age. More than 50% of pancreatic adenocarcinoma cases occur after the age of 70 [8].

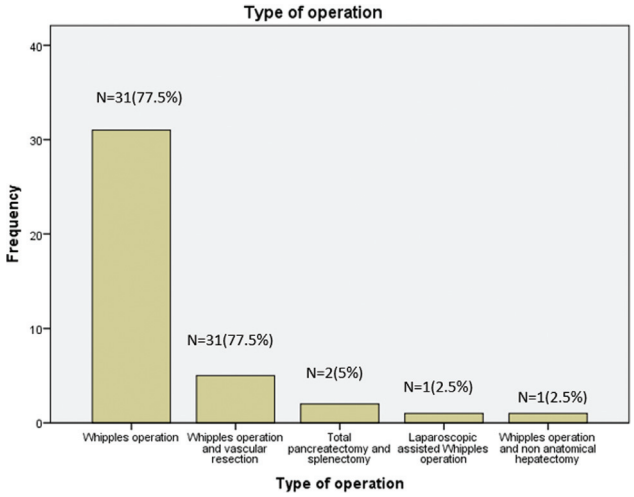
In our study, 45% of cases were among the age group between 65 and 74 years and 32.5% between the age group of 55 and 64 years. So, the incidence increases with age.

As regards sex, Ilic and Ilic [8] found that some findings showed that the difference that is higher in favor for men over women, may be due to more exposure of men to environmental factors, especially tobacco smoking than women, making the incidence of pancreatic cancer higher in men.

In our study, men represented about 62.5% of periampullary carcinoma, while women represented 37.5% with a higher incidence in males than in females, but the exact reason for this difference is not sufficiently known till now. There was no statistical difference between the two groups as regards sex *P* value that was 0.870.

The mean operative time for the Artery-first approach was 462.14±123.089 min, while for the classic approach, it was 507.11±103.474 min, with no statistical difference between both groups. The mean operative time for the artery-first approach with uncinate process dissection was 457.5 min by Shrikhande *et al.* [9].

Figure 10



Bar chart showing the types of operations done.

The rates of complications in our study were 45.45 and 50% for classic and Artery-first approach, respectively, with *P* value .377 showing no significant difference between the two groups. While the rate of complications in the Artery-first approach for Shrikhande *et al.* was 40% [9].

The mean blood loss for Artery-first approach was 661.11±223.314 ml, and for the classic group, it was 645.45±315.062 ml, and the need for blood transfusion was 72.22 and 63.64% for Artery-first and classic

approaches, respectively, with no significant difference between both groups as regards blood loss or transfusion. There may be an increase in blood loss of the Artery-first approach due to the learning curve for the technique. Takaori and Uemoto [2] found that the estimated blood loss volume and operative time were lower after the right posterior approach PD.

We have found that other complications between the two groups, including delayed gastric emptying, pancreatic fistula, bile leak, wound infection, pulmonary embolism, acute pancreatitis, hematemesis, melena, pulmonary embolism, postoperative bleeding, and reoperation, were statistically insignificantly different.

There were four (18.18%) cases and one (5.56%) case of pancreatic fistula among classic group and the SMA-first approach, respectively, with *P* value of 0.230, and one case of the classic approach was Clavien–Dindo classification grade I pancreatic fistula and managed conservatively and the other three cases were Clavien–Dindo grade II managed by total parenteral nutrition (TPN) conservatively. Clavien–Dindo grades III and IV present in 11 (32.3%) were found by Roshan *et al.* in his study [10].

One case of the SMA-first approach developed Clavien–Dindo grade I pancreatic fistula and managed conservatively.

The case of reoperation was among the 'Artery-first' group limb, and exploration was done, and bleeding from uncinate process bed was found and controlled.

There was an insignificant difference in postoperative mortality among both groups. In total, one case (4.55%) for classic approach and two cases (11.11%) for 'Artery-first' approach were decreased with *P* value of 0.433.

The case of classic approach decreased due to pulmonary embolism, and as regards the Artery-first approach, one case decreased after developing acute severe pancreatitis and the second case developed melena and PV thrombosis after sleeve resection of PV en-bloc with the mass. Postoperative mortality was insignificantly different between classic and the SMA approach with *P* value of 1.00, found by Vallance *et al.* [11].

The mean hospital stay in days was 14.56±6.233 for the Artery-first approach and 18.27±7.735 for classic approach, with an insignificant difference, and the mean hospital stay was 14 days found by Shrikhande *et al.* [9], and was 16±9 days for Roshan *et al.* [12].

As regards histopathological data, each group has yielded R0 mesopancreatic margin by 72.22 and 59.09%, R1 mesopancreatic margin 5.56 and 36.36%, and R2 mesopancreatic margin 22.2 and 4.55% for Artery-first and standard approaches, respectively, with *P* values 0.386, 0.020, and 0.093, respectively, between the two groups, which shows no significant difference between yielding R0 by the two techniques, yet the Artery-first approach generates more R0 margins. But there was a significant difference in yielding R1 mesopancreatic margins more in standard approach than in Artery-first approach.

On the other hand, there was an increase in yielding R2 mesopancreatic margin by the Artery-first approach, yet not statistically significant, and this can be explained may be due to the increased tumor size mean, which is 2.17±6.18 cm in the Artery-first approach, compared with that of classic approach, which is 1.73±0.550 cm, with *P* value 0.023 that is a significant difference. Besides that, the univariate analysis showed that the mesopancreatic margin was statistically significant with *P* value of 0.020 with recurrence that was the dependent variable. While transection margin, anterior margin, grade of the tumor, T-stage, and the two operative approaches were insignificantly different over recurrence outcomes in univariate analysis.

Luis *et al.* found that there is no difference as regards R0 resection for the Artery-first approach compared with standard approach in his multicenter randomized controlled trial [13].

The mesopancreas was found to be the commonest site of positive resection margins, especially for cancers, which were resected noncuratively. However, R0 resection pancreatic cancer patients experience frequent locoregional recurrence and metastasis, unlike other gastrointestinal tract solid tumors [14].

There is controversy as regards the definition of Ro/R1 safety margins of cancer pancreas with marked heterogeneity in survival outcomes, with 5-year survival 5–20% in the case of R0 negative resection margin. Modified pathological examination (R1/R2) increased the rate of R1 resection ranging from 76 to 85%, instead of older noncurative resection data ranging only from 15 to 35% [15].

The 1-mm negative margin is underestimating the definition of R1 in cancer pancreas, however, it is an adequate definition in the case of rectal cancer [16].

Another important reason for the diversity of the definition of R1 resections in cancer pancreas is that in the USA, pathologists will report a margin as positive only if tumor cells are present at the surface, that is, if the clearance equals 0 mm, unlike many pathologists in Europe and the UK using a definition based on a 1-mm clearance [17].

N-stage was statistically significant using recurrence as a dependent variable and the *P* value was 0.043. But, in multivariate analysis, N-stage was statistically insignificant and the *P* value was 0.212, yet the mesopancreatic R margin was the statistically significant variable affecting recurrence with *P* value 0.024 in multivariate analysis with other constant variables, including transection margin, anterior margin, tumor grade, T-stage, N-stage, and operative approach. Tummers *et al.* [18] found that recurrence, especially in cases with N1 disease, disease recurrence patterns were similar between R1 and R0 groups. There was no significant difference between the two groups as regards N0-, N1-, and N2-stage distribution among the two groups.

There were seven (31.82%) recurrences and metastasis among the 22 cases of the classic approach, and six (33.33%) cases developed recurrences and metastasis out of the 18 cases of 'Artery-first' approach with an insignificant difference between the two groups, *P* value 0.919.

The most common sites of metastasis and recurrences were liver, locoregional, lymph nodes, and lungs.

The most common recurrence type in patients after resection of cancer pancreas was locoregional recurrence along cardinal arteries by Kovač *et al.* [19].

As regards early postoperative mortality, one case (4.55%) decreased among the classic approach group after pulmonary embolism and two cases (11.11%) decreased among the 'Artery-first approach' group, one with acute severe pancreatitis underwent pancreatogastrostomy reconstruction and the other case underwent sleeve resection of PV and developed postoperative PV thrombosis and mesenteric venous occlusion treated by anticoagulants, and there was an insignificant difference as regards mortality between the two groups, *P* value 0.433.

Conclusion

According to our study, the Artery-first approach is a safe and feasible technique in comparison with standard classic approach in PD with mesopancreas dissection as regards operative time, blood loss, postoperative morbidity, and mean time of hospital stay. There is no significant difference between the two groups as regards recurrence.

R0 mesopancreatic margin was the most important factor for recurrence postperiampullary carcinoma resection.

More studies should be done with longer periods of follow-up with multicenter studies to help delineating the anatomy of the mesopancreatic margin and stratification of sites of positive margins in this triangle for periampullary carcinoma.

Acknowledgments

The authors would like to thank Professor Farouk A. Mourad who was my vice supervisor and supported me a lot to get this work done.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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