Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
In partnership with Paradigm Publishing Services, Warsaw, Poland
Open Access Macedonian Journal of Medical Sciences. 2026 Jun 14; 14(1):53-59.
https://doi.org/10.3889/oamjms.2026.12162
eISSN: 1857-9655
Category: *B – Clinical Sciences*
Section: *Surgery*

Divestment–Adventitia Resection in Order to Decrease Morbidity and Mortality and Improve R0/R1 Ratio in Curative Pancreatoduodenectomy for Advanced Pancreatic Head Carcinoma

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Citation: Shumkovski A, Ognjenovic Lj, Shumkovski R, Kolari A. Divestment–Adventitia Resection in Order to Decrease Morbidity and Mortality and Improve R0/R1 Ratio in Curative Pancreatoduodenectomy for Advanced Pancreatic Head Carcinoma. Open Access Maced J Med Sci. 2026 Jun 14; 14(1):53-59. https://doi.org/10.3889/oamjms.2026.12162
Keywords: Pancreatic head carcinoma; Pancreatoduodenectomy; Arterial divestment; Borderline resectable pancreatic cancer; R0 resection
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Received: 03-May-2026
Revised: 04-Jun-2026
Accepted: 12-Jun-2026

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Pancreatic head carcinoma (PHC) is a highly aggressive malignancy associated with substantial morbidity, mortality, and poor long-term survival. Achieving an R0 resection margin during pancreatoduodenectomy (PD) is crucial for improving oncological outcomes. However, in borderline resectable (BRPHC) and locally advanced pancreatic head carcinoma (LAPHC), arterial involvement often necessitates complex arterial resections associated with high perioperative risks. Periarterial sub-adventitial divestment has emerged as a potential alternative to arterial resection, aiming to improve radicality while reducing complications.

AIM: To evaluate whether sub-adventitial arterial divestment during curative pancreatoduodenectomy decreases perioperative morbidity and mortality and improves the R0/R1 resection ratio in patients with BRPHC and LAPHC.

METHODS: A retrospective study was conducted on 50 consecutive patients with BRPHC or LAPHC treated between 2009 and 2017 following neoadjuvant therapy when indicated. All patients underwent extensive pancreatoduodenectomy with triangle operation, extended lymphadenectomy, and periarterial sub-adventitial divestment of the superior mesenteric, common hepatic, and/or celiac arteries. Clinicopathological data, perioperative morbidity, mortality, length of hospital stay, and R0/R1 resection status were analyzed.

RESULTS: Among the 50 patients, 27 (54%) were male and 23 (46%) were female, with a mean age of 63.1 ± 8.97 years. Overall mortality was 8% (4/50). Major complications included postoperative pancreatic fistula (24%), postoperative biliary fistula (2%), postpancreatectomy hemorrhage (4%), reoperation (6%), necrotizing pancreatitis (4%), thromboembolism (4%), cardiac failure (2%), and pulmonary complications (8%). Venous resection was required in 12% of patients. Postoperative pain relief was achieved in 92% of cases. Mean hospital stay was 10.56 ± 6.09 days. Histopathological examination demonstrated R0 resection in 28 patients (56%) and R1 resection in 22 patients (44%). Morbidity and mortality rates were comparable to standard PD and appeared lower than those reported for PD combined with arterial resection.

CONCLUSION: Sub-adventitial arterial divestment during pancreatoduodenectomy is a feasible and safe technique for selected patients with borderline resectable and locally advanced pancreatic head carcinoma. The procedure provides acceptable morbidity and mortality rates while achieving favorable R0 resection outcomes, representing a promising alternative to arterial resection in specialized high-volume centers.

Introduction

Pancreatic carcinoma is one of the most potential malignancies with high morbidity, mortality and poor prognosis concerning postoperative overall survival (OS) and postoperative disease-free survival (DFS). Incidence has risen in the last decades, affected by increase of the risk factors, from 9 to 12,2-13,6 per 100 000. It is now forth cause of death related to cancer in the west and sixth in the world [1], [2], [3]. In the meanwhile, the advance in surgical technique, procedures and devices for early precise screening, diagnosis and staging, also postoperative oncological treatment has not significantly improved the outcome after treatment of pancreatic carcinoma [4]. Morphological pattern is over 2/3 appearance on the head of the pancreas and 1/3 body and tail. The

diagnosis is often lately because of insidious and torpid clinical course at early stages. This particularly matters for pancreatic cancer of the body and tail. On the other hand, the pancreatic head carcinoma (PHC) appears to have more imminent clinical pattern and is likely to be diagnosed in the earlier stage, thus has generally better prognosis. This is still a controversial issue to be confirmed, though further prospective clinical trials are to be conducted [5], [6], [7].

Treatment of diagnosed PHC nowadays is a complex procedure consisting of neo adjuvant therapy (NAT), surgery and adjuvant therapy. NAT as a protocol varies among the centers, consisting of chemotherapy or chemo radio therapy. According to ISGPS, for resectable PHC the consensus is upfront surgery and then adjuvant therapy. On the other hand, for borderline resectable pancreatic (BRPHC) there is still unclear evidence of the predicted benefit. Though, after NAT radiologically can't be confirmed shrinkage or down staging. On the other hand, after NAT for BRPHC the studies expose lower rate of resections (lower resectability) but improvement in R0/R1 ratio, also OS after curative resections. Locally Advanced pancreatic head carcinoma (LA PHC) is determined by abutment of the arterial vessels (SMA, CHA, CT), and NAT is standard treatment, improving R0vR1 rate, also OS [8], [9], [10], [11]. Affecting this issue, hereby to mention, biopsy before NAT theoretically may cause seeding, and with radiation local desmoid inflammation which could cause worsening of the operative site. This could be the reason why majority of the surgeons prefer upfront surgery for resectable PHC, also BRPHC.

Standard surgical for PHC is pancreatoduodenectomy (PD), Whipple procedure. It is a complex and demanding procedure, which is to be performed in a high-volume tertiary center. The curative PD should provide R0 resection line, also certain number of lymph nodes to be retrieved. Recently there is a consensus reached by ISGPS for the extension of the procedure, either lymphadenectomy [12].

One of the most important goals for PD for PHC is R0, resection free margin. It is gross factor to determine future prognosis of the patient. In our series R0 was defined as minimum distance 1 mm of malignancy [13], [14], [15].

In certain cases, particularly in BRPHC or LAPHC achievement for R0 can be extremely difficult affecting the vascular abutment. For the veins is less demanding, skilled and trained surgeon is capable to resect and reconstruct the SMV or Portal Vein without excessive increase of the perioperative risk. PD with venous resection of the Portomesenteric trunc can be done safely without or with venous graft. The benefit of PD with venous resection compared to non-resected patients for OS is clear, but surprisingly, there is no difference in risk benefit with patients undergone PD without venous resection. More than that, there are studies reporting worst results in patients with venous resections compared with those without. This may be explained by the higher stage of the PHC at the time of resection, either worse biological malignant behavior of the tumor, or higher rate of R1 resection [16], [17], [18], [19], [20].

Speaking about arteries is quite another issue, the perioperative risk for morbidity and mortality is high, also postoperative quality of life (QOL) is poor. Present dilemma for arterial resection is the lack of benefit concerning the OS, also undesired rate of R0 resections, 65-75 % [21]. The most often arteries resected in this extensive PD are Celiac Trunk (CT), Superior Mesenteric Artery (SMA), Common Hepatic Artery (CHA). Concerning the disappointingly objective reality upon desired outcome, arterial resections during PD are not widely accepted. It should be done in high volume centers and in carefully selected patients, which can decrease perioperative morbidity, mortality and improve the OS. The assessment of the risk/benefit preoperatively and perioperatively should be done by angiography and peroperative dopler estimation of the arterial blood flow. The technique is meticulous microsurgery with obtaining sufficient blood flow [22], [23], [24], [25].

High morbidity and mortality with PD with arterial resection (PD AR), followed by unsatisfactory results in OS and DFS, encouraged the surgeons to find another way to obtain radicality-R0 resection margin, with decrease of the perioperative adverse events following arterial resection. Though, a delicate and meticulous procedure was invented by Nakao and Del Chiaro, divestment of the arteries with malignant abutment. Essentially, it is a complete resection of the adventitia of the arteries, altogether with the fat, fibrous, lymphatic and nervous tissue-peri arterial nervous plexus. This procedure provides additional layer and distance upon malignancy, reaching R0 in over 80 % of resections. Depicted procedure upon the arteries, resection or divestment, should be estimated preoperatively by the CICT, MRI, angiography, ai-PC estimation, finally intra operatively, meticulously defining the degree-layer of the malignant invasion to the arterial wall [21], [26], [27], [28]. So far recent studies suggest great options to use adventitia resection, meanwhile maintaining radical PD and reducing of perioperative morbidity and mortality imposed by arterial resection and reconstruction [29], [30]. In our opinion, not to defy the fact this procedure undoubtedly facilitates surgeon's effort either abbreviates operative time.

Primary end point of the study is to compare if there is decrease in perioperative morbidity and mortality for DP, and secondary end point, comparison of R0/R1 ratio to series with arterial resection.

Material and method

In our study from 2009 to 2017, we enrolled 50 consecutive patients with BRPHC, and LAPHC after

NAT. inclusion criteria for the population were radiologically resectable PHC, absence of liver metastases or peritoneal dissemination. All patients were preoperatively examined and staged with MRI, CICT, Ca19-9. For patients staged LAPHC, preoperatively was provided US guided or EUS biopsy and patients were referred and passed NAT.

Surgery was extensive Whipple procedure, PD, triangle operation. Pancreatic resection was not at the neck of the pancreas, but extended to the left, over the left margin of Superior Mesenteric Artery (SMA) (Figure 1).

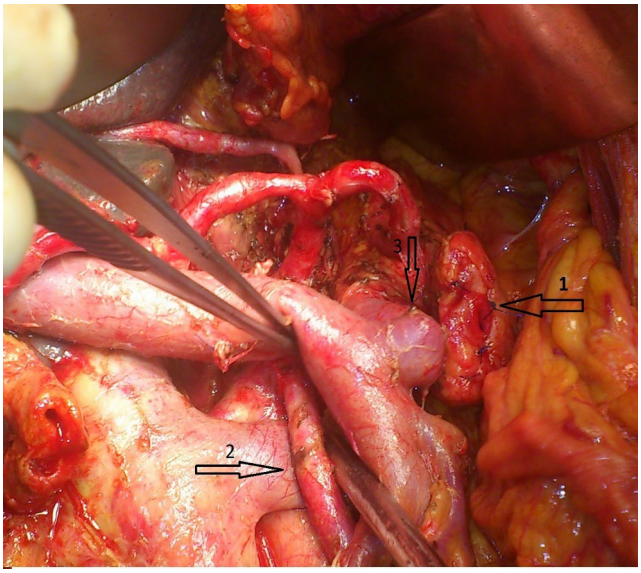

Figure 1: a) arrow 1: Pancreas respected to the left of SMA, over dissected Splenic Vein, b) arrow 2: dissected SMA; c) arrow 3: Splenic Vein

Procedure also contained hemigastrectomy, cholecystectomy followed with high resection of the common bile duct obtaining broad biliar resection margin.

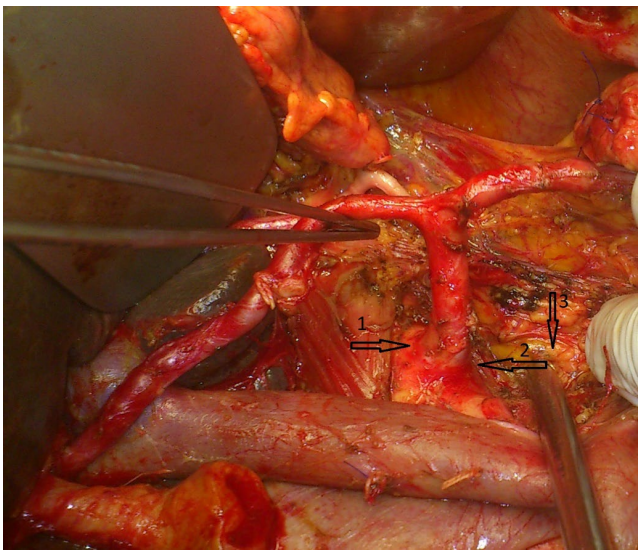

Figure 2: a) arrow 1: site of the resected right coeliac ganglion, b) arrow 2: site of resected left coeliac ganglion, c) arrow 3: suprarenal gland

Lymphadenectomy was also extended D3, beyond the consensus of the ISGPS, intended for staging with right renal hilys, interaortocaval dissection, 14th and 15th station also to the left surface of SMA, 11th station-Splenic Artery cleaning, 12th station-complete dissection of the hepatoduodenal ligament. Added procedure was bilateral Coeliac gangliectomy, at our opinion mitigating the adventitia resection-divestment of the CA, also pain relief (Figure 2).

The sub-adventitia resection-divestment was performed between the tunica adventitia (resected) and elastic lamina-tunica media of the artery. The procedure was delicate and meticulous, particularly to avoid lesion and consecutive post-traumatic pseudo aneurism of the artery.

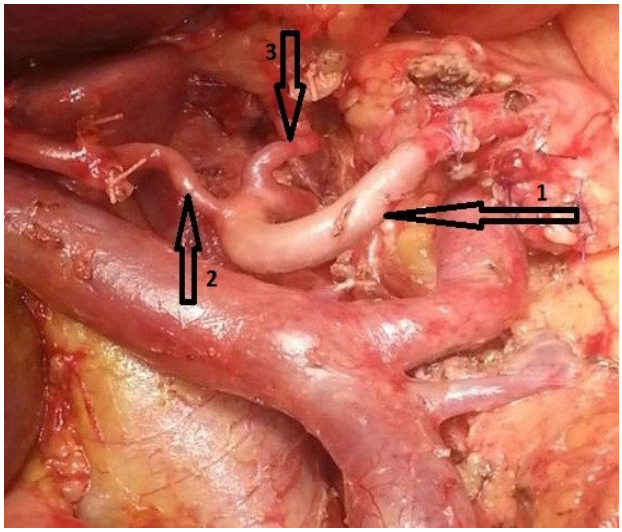

Figure 3: Subadvetitia resection, divestment of the arteries; a) arrow 1: Splenic artery, b) arrow 2: Hepatic artery, c) arrow 3: Right gastric artery, below CA

For SMA the procedure was completed en-block with the specimen altogether with the Uncinate process, and proceeded separately for CHA, CT (Figure 3, 4, 5).

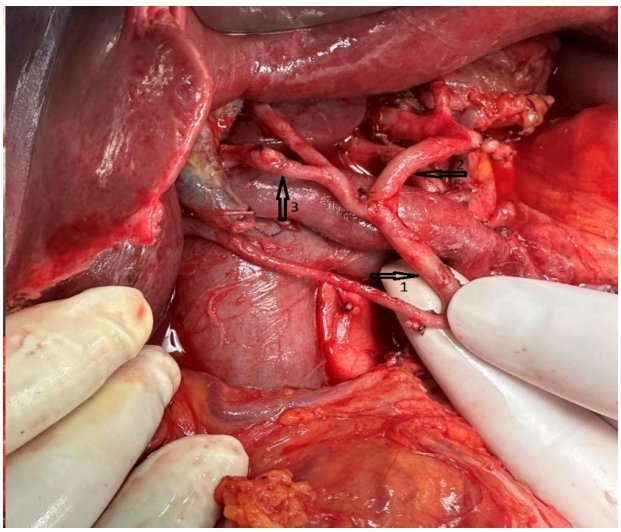

Figure 4: Subadvetitia resection, divestment of the arteries, anatomical arterial pattern with aberrant right hepatic artery; a) arrow 1: Right hepatic artery, b) arrow 2: Splenic artery; c) arrow 3: Left Hepatic artery

Reconstruction consisted of dunking T-L pancreatojejunostomy with interrupted sutures, T-L hepaticojejunostomy with interrupted sutures, retrocolic gastrojejunostomy, and jejunojejunostomy for exclusion of the omega loop.

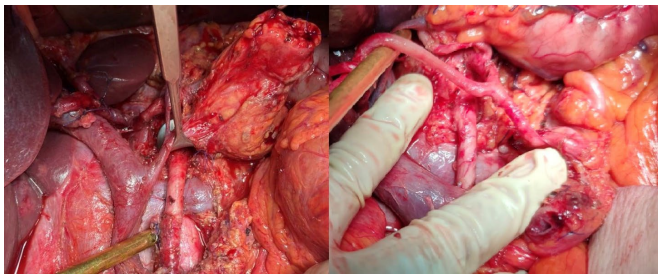

Figure 5: Subadvetitia resection, divestment of the arteries, SMA

Criterion for R0, free resection margin was ≥1 mm distance from the malignancy.

Results

In our group of 50, 27 patients were male (54 %), while 23 (46 %) were female. The age was 42 to 79, interval 63.10 ± 8.97.

Mortality rate in our study was 4 patients, 8%.

Morbidity was manifested in: 1. Postoperative Pancreatic Fistula (POPF); 2. Postoperative Biliar Fistula (POBF); 3. Perioperative blood loss/transfusion; 4. Postpancreatectomy hemorrhage (PPH); 5. Reoperation-revision; 6. Postoperative-post pancreatectomy necrotizing pancreatitis (PPNP); 7. Postoperative thromboembolism; 8. Cardiac failure insufficiency; 9. Pulmonary failure, pulmonary oedema, pleural effusion; 10. Added procedure-hemicolectomy, venous resections; and 11. Postoperative pain.

1. POPF: a) POPF B 9 patients, 18 %; b) POPF C 3 patients, 6 %.

2. POBF: 1 patient, 2 %.

3. Blood loss/Transfusion: a) 6 patients, 12 % received 350 ml, b) one patient, 2 %, received 700 ml transfusion;

4. PPH in 2 patients, 4 %.

5. reoperation-revision in 3 patients, 6 %.

6. PPNP suffered 2 patients, 4 %.

7. postoperative thromboembolism in 2 patients, 4 %,

8. cardiac failure-insufficiency with cardiac arrest in 1 patient, 2 %,

9. Pulmonary failure, pulmonary oedema, pleural effusion in 4 patients, 8 %.

10. Added procedure, a) in 2 patients, 4 %, right hemicolectomy was performed; b) 6 patients, 12 %, received portomesenteric venous resection, 3 with autologous graft from falciform hepatic ligament, 1 patient underwent resection of inferior vena cava (Figure 6, 7).

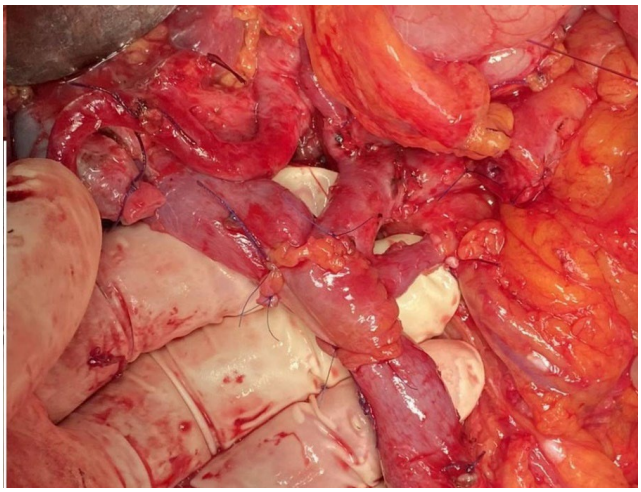

Figure 6: Resection of the portomesenteric vein with autologous free graft, falciform ligament

11. postoperative pain relief: in 4 patients 8% there was postoperative pain present, while 46, 92%, had pain relief.

Postoperative Intra hospital stay was from 8 to 31 postoperative days (POD). Average interval 10.56 ± 6.09.

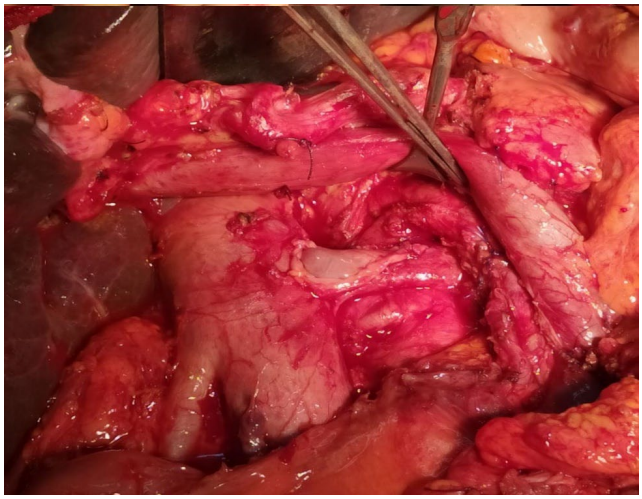

Figure 7: Resection of the Inferior vena cava, autologous free graft, falciform ligament.

R0/R1 was the second point. In our series we had 22 patients (44%), with R1 resection and 28 (56 %) with R0 resection margin.

Discussion

In our series morbidity was broadly dispersed affecting the clinical course and pattern. The most frequent complication was POPF, from total of 12, 9 patients (18%) suffered POPF B, which led to prolonged intra hospital stay, administration of antibiotic therapy, and parenteral hyper alimentation. There was no need for radiologically guided intervention, due to controlled fistula with by drain. The discharged volume of the drain gradually decreased, finally diminished, patients went well. This morbidity concerning POPF B in our patients with adventitia resection is in range to other series in high volume centers. The incidence, treatment, outcome are comparable and satisfactory [28], [29], [30], [31], [32], [33], [34], [35].

On the other hand, 3 of our patients suffered POPF C. They were all with prolonged hospital stay, re operated. The first one with POPF C was re operated, impair suture line was found, in the harsh operative environment subtotal pancreatectomy proceeded. The patient was discharged on the 31st POD. The second patient suffered simultaneously POPF C and POBF. The revision led to completion of pancreatectomy, and reconstruction of the biliodigestive anastomosis. Several days later patient developed sepsis, multi organ failure, leading to death. The last patient with POPF C was re operated on 8th POD, postoperative necrotizing pancreatitis was the background, leading also to PPH and lethal outcome [32], [33], [34], [35], [36], [37].

One patient suffered PPH devoid from another pathology, angiography was done, the source for bleeding couldn't be spotted. At the re reoperation, we didn't find the reason either, but postoperatively the patient had uneventful course, discharged in good condition.

Mortality in our series was 4 (8%). As mentioned before, 1 patient died from simultaneous POPF and POBF. The second reason for death was POPF C, postoperative necrotizing pancreatitis with PPH. The third and fourth lethal outcome were pulmonary thromboembolism and acute cardiac failure in patients with preoperative present risk factors, chronic myocardiopathy [37], [38], [39].

All these odds from our series we have analyzed are quite comparable superior to standard PD without adventitia resection-divestment. Since, when we match the results from our study with the results from centers and studies performing PD with arterial resection, we remain with another impression. Namely, morbidity is significantly higher than 30% [40]. Further studies with bigger number of patients observe also unsatisfying results, morbidity 54 %, mainly depending on POPF or PPH. In the same study, mortality was 13 %, grossly impacted by PPH [41].

One big systematic review and meta-analysis confirmed high morbidity, high mortality compared to divestment procedure. In this big study is also emphasized poor OS, thus barely justifying PD associated with arterial resections, particularly SMA [42].

The second end point of the study was R0/R1 ratio, particularly concerning it's high impact to OS. The pTNM findings among our patients confirmed 22 patients with R1 resection (44 %). This is barely satisfying but understandable while speaking for BRPHC and LAPHC. Several years earlier, when divestment began to be introduced, R1 resections we unacceptable high, some studies refer to over 80 %. In our early series the rate of R1 was also higher, and it decreased during the years by the enhance of the turnover [28], [29], [39], [43], [44]. The outcome for R0/R1 ratio in our series may appear better than reported results from some other high turnover centers, but it's necessary to mention we had lower number of patients with LAPHC after NAT than patients with BRPHC.

On the other hand, R0/R1 resection rate in PD with arterial resections remains high, generally unsatisfactory, particularly concerning morbidity, mortality and prognosis after arterial resections. According to some recent trials, total neo adjuvant therapy (TNT) may improve R0/R1 resections for BRPHC and LAPHC [45], [46].

Finally, in accordance with our opinion, it could be important to advance the radiological accuracy for preoperative distinction between BRPHC and LAPHC. This could precisely define the difference in R0/R1 ratio between BRPHC and LAPHC after adventitia resection-sub-adventitia divestment. More than that, it could enable accurate separate comparing of the R0/R1 ratio of both, BRPHC LAPHC after sub-arterial divestment to R0/R1 ratio after PD with arterial resection. Though, it may be particularly interesting to reveal the equity R0/R1 ratio after PD for LAPHC with sub-adventitia divestment to R0/R1 ratio after PD for LAPHC with arterial resection.

Conclusion

The sub-adventitia resection, divestment of the arteries for borderline resectable and locally advanced pancreatic head carcinoma so far delivered comparable improved result upon arterial resections. We consider the procedure safe, feasible, obtaining promising results concerning perioperative morbidity, mortality and R0/R1 ratio. Further broad adoption of the procedure by high volume centers may lead to desired avoidance of arterial resections.

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