

## Pancreatico-Duodenectomy for Pancreatic Ductal Adenocarcinoma: from Artery-First Approaches to TRIANGLE Operation

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### Rezumat

#### *Duodenopancreatectomia cefalică pentru carcinom ductal pancreatic: de la abordul arterial primar la operația TRIANGLE*

Duodenopancreatectomia cefalică este singura speranță de supraviețuire pe termen lung la un pacient cu adenocarcinom ductal al capului pancreatic. Din păcate, chiar și după duodenopancreatectomia cefalică cu intenție curativă, supraviețuirea pe termen lung a pacienților cu adenocarcinom ductal rămâne sub așteptări, cu rate ridicate de recurență, inclusiv cele loco-regionale. Marginile de rezecție pozitive după rezecția unui adenocarcinom ductal sunt frecvente și au un efect negativ atât asupra recidivei, cât și asupra ratelor de supraviețuire pe termen lung, în special asupra celor R1 (directe), către mezopancreas. În ultimii ani, s-au depus eforturi sporite de către chirurghi pentru a introduce în practica clinică mai multe perfecționări în tehnica standard de duodenopancreatectomie cefalică pentru a rezeca mai bine tumora, inclusiv o disecție precisă a ganglionilor, în speranța de a crește rata marginilor negative de rezecție, pentru a scădea ratele de recurență locală și pentru a îmbunătăți prognosticul. Mai mult, pentru a extinde numărul de pacienți cu boală rezecabilă, câteva tehnici chirurgicale au fost, de asemenea, destinate convertirii la rezecabilitate a pacienților cu boala regională (adenocarcinom ductal anatomic la limita rezecabilității și local avansat) în contextul terapiilor multimodale, în special al terapiilor neoadjuvante. Aici, discutăm pe scurt câteva perfecționări tehnice care abordează timpul de rezecție al duodenopancreatectomiei cefalică, cum ar fi abordul arterial primar și operația TRIANGLE. Ambele tehnici

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chirurgicale vizează o mai bună curățare a spațiului retroperitoneal pentru nervi, ganglioni limfatici și vase, inclusiv excizia totală a mezopancreasului.

**Cuvinte cheie:** duodenopancreatectomie cefalică, carcinom ductal pancreatic, abord arterial primar, operația TRIANGLE, rezultate postoperatorii

## Abstract

Pancreatico-duodenectomy (PD) is the single hope for long-term survival in a patient with pancreatic head ductal adenocarcinoma (PDAC). Unfortunately, even after curative intent PD, the long-term survival of patients with PDAC remains under expectations, with high recurrence rates, including the loco-regional ones. Positive resection margins after resection of PDAC are frequent, and they have a detrimental effect on both recurrence and long-term survival rates, particularly the R1 (direct) ones, toward the mesopancreas. In the last years, there were made increased efforts by surgeons to introduce in clinical practice several technical refinements to the standard technique of PD better to resect the tumor, including an accurate lymph node dissection, hoping to increase the rate of negative resection margins, to decrease local recurrence rates and to improve prognosis. Furthermore, to extend the number of patients with resectable disease, a few surgical techniques were also intended to convert to resectability the patients with the regional disease (i.e., anatomical borderline resectable and locally advanced PDAC) in the context of multimodal therapies, particularly neoadjuvant therapies. With this, we briefly discuss a few technical refinements addressing the resection time of PD, like the artery-first approaches and the Triangle operation. Both surgical techniques aim for better clearance of the retroperitoneal space for nerves, lymphatic nodes, and vessels, including total mesopancreas excision.

**Key words:** pancreatico-duodenectomy, pancreatic ductal adenocarcinoma, artery-first approach, TRIANGLE operation, outcomes

## Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest types of cancer worldwide. In the United States, PDAC represents the 10<sup>th</sup> most frequent type of cancer in men and the 8<sup>th</sup> most frequent type of cancer in women, but the 4<sup>th</sup> leading cause of death by cancer both in men and women (1). PDAC is the 4<sup>th</sup> leading cause of death by cancer in both men and women in Europe (2).

In Romania, the age-standardized incidence rates (per 100,000) for PDAC are 20.7 in men and 13.8 in women for the incidence and 19.6 for men and 12.9 in women for the mortality, in line with the mean European rates (2).

Among the other types of cancer, PDAC appears to have the lowest survival (less than

11% five-year survival for the combined stages) (1). For localized PDAC, the five-year survival is around 42%, while for regional diseases, only 14%. Unfortunately, only 13% of PDACs have localized disease at the time of diagnosis, while a regional or distant metastases disease is encountered in 29% and, respectively, 47% (1).

Surgical resections are the single hope for long-term survival in patients diagnosed with PDAC in the multimodal approach (with adjuvant chemotherapy, with neoadjuvant therapies (NAT) when indicated). Most patients with PDAC have the tumor at the level of the pancreatic head. Thus, pancreatico-duodenectomy (PD) represents these patients' single curative intent option. A curative intent surgery is indicated for fit patients with

localized disease and a few with regional disease: borderline resectable (BRPC) and potentially resectable locally advanced pancreatic cancer (LAPC).

Unfortunately, even after curative intent PD, the long-term survival of patients with PDAC remains under the expectations (median survival times around 28 months), with high recurrence rates (up to 80%), including the loco-regional ones (up to 45%) (3,4). Positive resection margins after resection of PDAC are a frequent event (between 16% and 79%) and have a detrimental effect on both recurrence and long-term survival rates (3-5), particularly the R1 (direct) ones (3,5), toward the major vascular structures and mesopancreas. Thus, obtaining negative resection margins after curative intent PD for PDAC is of utmost importance for the prognosis.

Adjuvant chemotherapy has been proven to increase survival after curative intent surgery for PDAC, as few recent randomized trials have shown (6,7). NAT appears to increase the survival of patients with BRPC and LAPC converted to resectability (8,9). Recently, few studies have shown the benefits of NAT, even for localized PDAC (8,10).

Considering PD as the single hope for long-term survival in a patient with pancreatic head PDAC, in the last years, there were made increased efforts by surgeons to introduce in clinical practice several technical refinements to the standard technique of PD better to resect the tumor, including an accurate lymph node dissection, hoping to increase the rate of negative resection margins, to decrease local recurrence rates and to improve prognosis. Furthermore, to extend the number of patients with resectable disease, a few surgical techniques were also intended to convert to resectability the patients with the regional disease (i.e., anatomical BRPC and LAPC) in the context of multimodal therapies, particularly NAT.

The artery-first approaches and the Triangle operation are the most widely proposed technical refinements addressing the resection time of PD. Both surgical techniques

aim for better clearance of the retroperitoneal space for nerves, lymphatic nodes, and vessels, including total mesopancreas excision.

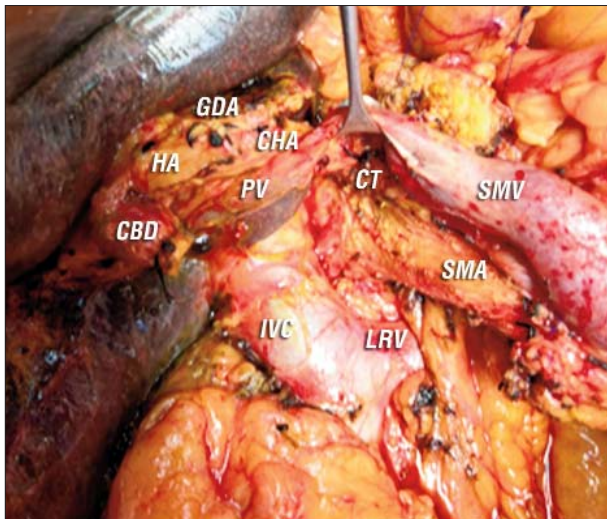
### *Artery-First Approaches*

Several PD techniques are grouped in the artery-first approaches, with different indications, advantages, and disadvantages. All these techniques put the superior mesenteric artery (SMA) in its primary place, particularly for the early assessment of resectability (11). It is worth mentioning that inability to clear the SMA margin is the most frequent cause of positive resection margins PD (5).

Nakao described the first artery-first PD as the mesenteric approach in 1993 (12). Afterward, Pessaux and Arnaud presented the posterior approach PD in 2003 (13). A group from Heidelberg described in 2007 an artery-first PD to better resect PDAC with venous invasion (14). Inoue and co-workers communicated in 2015 about the supracolic artery-first approach combined with systematic mesopancreas excision (15). Starting from the techniques mentioned above, many other artery-first PD techniques were developed (11).

All the artery-first techniques PD are intended better to resect a patient with PDAC, including total mesopancreas excision. The mesopancreas is the space between the SMA, celiac trunk (CT), portal-superior mesenteric veins (PV/ SMV), and posterior surface of the pancreatic head. It includes nerves, lymph nodes, and vessels and represents the primary site for R1 resections (16,17). Thus, total mesopancreas excision (*Fig. 1*) is a must during PD for PDAC because it is of utmost importance for the radicality of the procedure (18); with an artery-first PD, one might expect to increase the negative resection margins and decrease loco-regional recurrence rates hoping to improve the prognosis of a patient resected for PDAC.

A group from Lyon has shown that the posterior approach PD facilitates total mesopancreas excision, with high rates of negative resection margins (80.7%) (16). Interestingly, the tissue resected by the Lyon's technique



**Figure 1.** Total mesopancreas excision during PD for PDAC, intraoperative aspects after resection

(PV – portal vein; SMV – superior mesenteric vein; IVC – inferior vena cava; LRV – left renal vein; SMA – superior mesenteric artery; CT – celiac trunk; CHA – common hepatic artery; HA – hepatic artery; GDA – gastro-duodenal artery stump; CBD – common bile duct; PD – pancreatico-duodenectomy; PDAC – pancreatic ductal adenocarcinoma) (images from authors' personal experience).

(16) appears to be quite similar to the one described in the TRIANGLE technique (19). Furthermore, a triangular space is also described in Lyon's technique (16).

Our group has adopted in an early setting the posterior approach PD, particularly but not exclusively for the patients with PDAC and suspected vascular invasion (20). Our data have shown no morbidity or long-term survival differences between the posterior approach and the standard PD. However, a posterior approach PD was associated with decreased operative times and blood loss (21).

To date, there is only one randomized controlled trial comparing the artery-first approach with the standard PD. No significant differences were observed between the groups for the operative time, intraoperative blood loss and transfusions, postoperative complications, and negative resection margins rates (22).

Several comparative studies and meta-analyses comparing the artery-first with the standard PD have reached conflicting results (15,22-25). Thus, a meta-analysis published in 2017 associated an artery-first approach with less intraoperative blood loss and need for transfusions, lower pancreatic fistula and

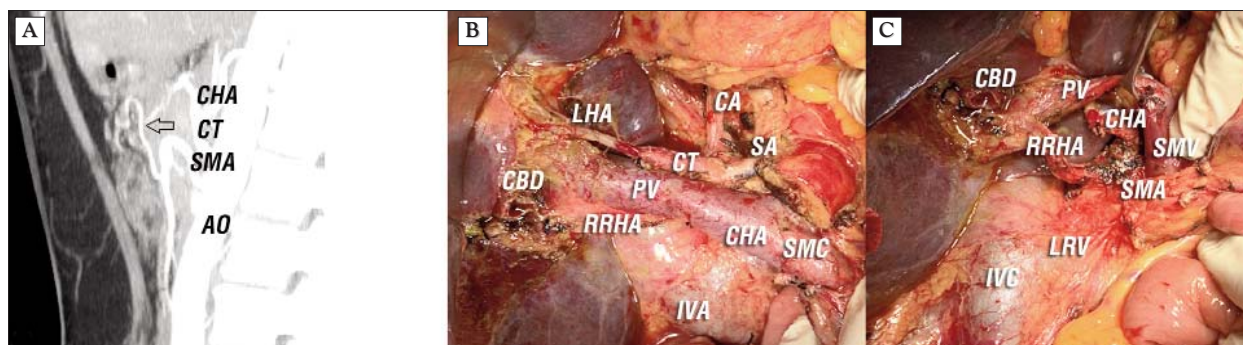
delayed gastric emptying rates, and lower local recurrence rates. However, no differences were observed between the groups for the negative resection margins and survival rates (25). Few other meta-analyses associated an artery-first approach with less intraoperative blood loss, need for transfusions, lower morbidity, and pancreatic fistula rates. Furthermore, increased negative resection margins and survival rates were observed in the artery-first group of PDs (23,24). Nevertheless, the current evidence is scarce about the role of an artery-first PD in increasing margin negative and survival rates (26).

Based on the current literature data and our personal experience, we consider that an artery-first PD (particularly a posterior approach) could be a valuable option or even a standard approach of PD for PDAC because it has several advantages: identification in an early setting of the tumor resectability mainly to the SMA avoiding the point of no return (decreasing the risk for an R2 resection), proper identification and sparing of an arterial anatomical variant (i.e., replaced or accessory right hepatic artery, replaced common hepatic artery (CHA)) (Fig. 2), facilitates total mesopancreas excision including loco-regional lymph node dissection, facilitates associated venous resections with reduced times of venous occlusion, and reduced operative time and blood loss due to early ligation of the vessels of the pancreatic head (Fig. 3).

### *TRIANGLE Operation*

To increase the resectability and negative resection margin rates for PDAC, a group from Heidelberg has introduced in the clinical practice the TRIANGLE operation (19,27). This new technique was initially proposed for patients with LAPC without disease progression after NAT (19), but afterward, the indications were extended to BRPC (27-31) or even localized PDAC (27;28;30).

TRIANGLE technique combines the advantages of artery-first approaches in terms of proper assessment of major arterial invasion and facilitation of venous resections. Thus,



**Figure 2.** A posterior approach PD facilitates identification and sparing of an RRHA originating from SMA: **(A)** contrast-enhanced computed tomography reconstruction showing an RRHA originating from the SMA (the black arrow marks the RRHA); **(B-C)** intraoperative aspects after resection

(PV – portal vein; SMV – superior mesenteric vein; IVC – inferior vena cava; LRV – left renal vein; SMA – superior mesenteric artery; CT – celiac trunk; CHA – common hepatic artery; HA – hepatic artery; SA – splenic artery; CA – coronary artery; RRHA – replaced right hepatic artery; AO – aorta; CBD – common bile duct; PD – pancreatico-duodenectomy) (images from authors' personal experience).

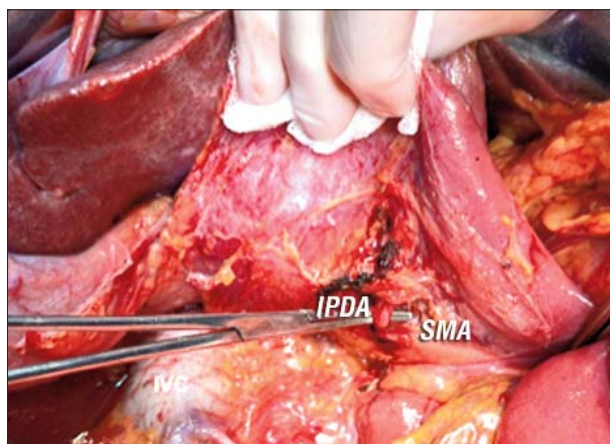
when arterial involvement is suspected, a frozen section is mandatory to exclude viable tumor cells at this site and further perform the PD (19). This is particularly important in the context of NAT because in a large proportion of patients with BRPC or LAPC after NAT, the imaging explorations cannot predict the resectability. If there is only fibrous tissue at the arterial level, an arterial resection is not required (19). TRIANGLE technique implies dissection of the major arterial structures such as SMA, CT, and CHA at the adventitial layer to make a complete resection at this level (including nerves, lymph nodes, and vessels) without an arterial resection, increasing the

chances of negative resection margins and avoiding the morbidity and mortality of an arterial resection (19).

The triangle is defined anatomically by the SMA, PV-SMV, and CHA. All tissues inside the triangle should be wholly removed after circumferential skeletonization of the CHA and right sides of the SMA and CT (19). A total mesopancreas excision is also performed during TRIANGLE operation (27) (*Fig. 4*). It is worth mentioning that loco-regional lymph node dissection is complicated in the context of NAT, and TRIANGLE operation appears to facilitate lymphadenectomy in these situations (19).

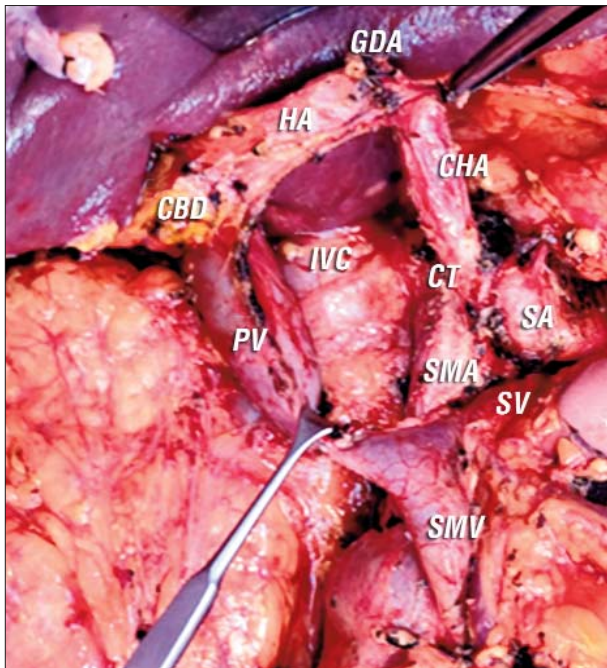
Although the Heidelberg group has demonstrated the feasibility and safety of the TRIANGLE operation (19) and other surgical teams (30,31), including the robotic (28,32) and laparoscopic approaches (29), however, at the moment, there are few data about its real clinical value.

One of the main advantages of the TRIANGLE operation appears to be the avoidance of an arterial resection (19,31). However, a venous resection can be associated with the TRIANGLE operation if required (*Fig. 5*). A recent meta-analysis has shown that an arterial resection increases morbidity and mortality rates to pancreatectomies (33). The technique of arterial skeletonization during TRIANGLE operation has the background of the arterial divestment technique, a surgical procedure previously



**Figure 3.** A posterior approach PD for PDAC facilitates early identification and ligation of the IPDA, intraoperative aspects during resection

(IVC – inferior vena cava; SMA – superior mesenteric artery; IPDA – inferior pancreatico-duodenal artery; PD – pancreatico-duodenectomy; PDAC – pancreatic ductal adenocarcinoma) (images from authors' personal experience).



**Figure 4.** TRIANGLE operation, intraoperative aspects after removal of all soft tissues including lymph nodes and vessels, nerves in the space between the SMA, CT, and PV-SMV (PV – portal vein; SMV – superior mesenteric vein; IVC – inferior vena cava; SMA – superior mesenteric artery; CT – celiac trunk; CHA – common hepatic artery; HA – hepatic artery; SA – splenic artery; GDA – gastro-duodenal artery stump; CBD – common bile duct) (images from authors' personal experience).

proposed by a few surgical teams to avoid arterial resections (34,35).

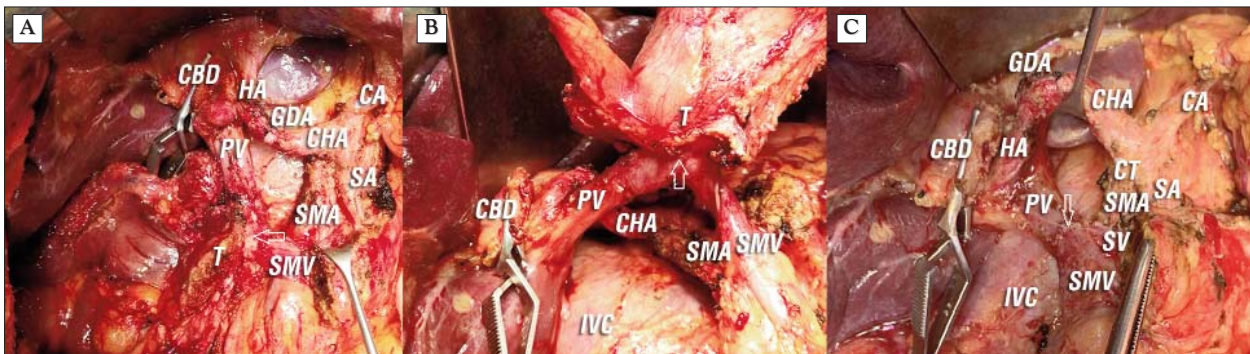
The initial data from the Heidelberg group have shown nil mortality rates and severe

morbidity rates of 47% after TRIANGLE operation. Negative resection margins were obtained in 40% of the resected patients with PDAC. Persisting diarrhea rate was 7% (19).

A study from Pisa, including 127 patients with robotic TRIANGLE PD, has shown mortality and severe morbidity rates of 7.1% and, respectively, 22%. Negative resection margins rates were 55.9% (28).

A study from China included 30 patients with TRIANGLE operations showing mortality and severe morbidity rates of 6.7% and, respectively, 10%. Negative resection margins rates were 30% (30).

To date, only one comparative study has assessed the potential benefits of TRIANGLE operation over the standard techniques. Thus, TRIANGLE operation was associated with statistically significantly higher operative times, intraoperative blood loss, and the number of harvested lymph nodes compared with the standard PD. No significant differences were observed between the groups for the overall and severe morbidity, mortality, and specific post-pancreatectomy complications rates, except for diarrhea, which was observed in a higher number of patients from the TRIANGLE group (34.4% vs. 14.4%). No significant differences were observed between the groups for the negative resection margins rates (36). Few



**Figure 5.** TRIANGLE operation combined with a posterior approach PD for PDAC with PV invasion, intraoperative aspects (A-B) during the resection time showing the tumor attached only to the venous invasion, after total mesopancreas excision, facilitating venous resection and reconstruction, reducing the time of venous occlusion (the white arrow marks the tumor invasion into the PV); (C) after removal of the operative specimen of PD and all soft tissues including lymph nodes and vessels, nerves in the space between the SMA, CT, and PV-SMV (the white arrow marks the end-to-end PV anastomosis)

(PV – portal vein; SMV – superior mesenteric vein; IVC – inferior vena cava; SV – splenic vein; SMA – superior mesenteric artery; CT – celiac trunk; CHA – common hepatic artery; HA – hepatic artery; SA – splenic artery; CA – coronary artery; GDA – gastro-duodenal artery stump; CBD – common bile duct; T – tumor; PD – pancreatico-duodenectomy; PDAC – pancreatic ductal adenocarcinoma) (images from authors' personal experience).

other studies have compared the arterial divestment with the standard technique showing increased rates of R1 resection margin (86% vs. 60%) and mortality rates (6% vs. 0.4%) for the divestment technique (34).

In conclusion, TRIANGLE operation is a feasible and safe technique to resect patients with PDAC, particularly but not exclusively those with BRPC and LAPC after NAT, sparing the major arteries without compromising the radicality of PD and avoiding the complications of major arterial resections. Although TRIANGLE operation appears to improve the local control in patients resected for PDAC, the actual impact on the long-term prognosis of PDAC remains to be established by future research.

## Conclusions

Artery-first approaches and TRIANGLE operation are valuable tools in a pancreatic surgeon's armamentarium. An artery-first PD has several advantages: identification in an early setting of the tumor resectability mainly to the SMA, avoiding the point of no return (decreasing the risk for an R2 resection), proper identification and sparing of an arterial anatomical variant (i.e., replaced or accessory right hepatic artery, replaced CHA), facilitates total mesopancreas excision including loco-regional lymph node dissection, facilitates associated venous resections with reduced times of venous occlusion, and reduced operative time and blood loss due to early ligation of the vessels of the pancreatic head. TRIANGLE operation is a feasible and safe technique to resect patients with PDAC, particularly but not exclusively those with BRPC and LAPC after NAT, sparing the major arteries without compromising the radicality of PD and avoiding the complications of major arterial resections. Although both artery-first approaches and the TRIANGLE operation appear to improve the local control in patients resected for PDAC, the actual impact on the long-term prognosis of PDAC remains to be established by future research.

## Conflicts of Interests

The authors declare that they have no conflict of interest.

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