COMPARISON BETWEEN DUNKING (INVAGINATION) PANCREATICOJEJUNOANASTOMOSIS AND DOUBLE LAYER DUCT TO MUCOSA ANASTOMOSIS AFTER CEPHALIC DUODENOPANCREATECTOMY-WHIPPLE PROCEDURE FOR PANCREATIC CEPHALIC CARCINOMA

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ABSTRACT

Introduction: Pancreatic cancer is malignancy with poor prognosis for quality of life and overall survival. The incidence is variant, 7.7/100,000 in Europe, 7.6/100,000 in the USA, 2.2/100,000 in Africa. The only real benefit for cure is surgery, duodenopancreatectomy. The key points for this procedure are radicality, low morbidity and low mortality, the follow up and the expected overall survival. The benchmark of the procedure is the pancreaticojejunostomy, with its main pitfall, postoperative pancreatic fistula B or C. Subsequently, the manner of creation of pancreaticojejunostomy defines the safety, thus the postoperative morbidity and mortality. Finally, this issue remarkably depends on the surgeon and the surgical technique creating the anastomosis. We used 2 techniques with interrupted sutures, dunking anastomosis and duct-to-mucosa double layer technique. The objective of the study was to compare these 2 suturing techniques we applied, and the aim was to reveal the risk benefit rationale for dunking either duct to mucosa anastomosis.

Material and method: In our last series of 25 patients suffering pancreatic head carcinoma we performed a standard duodenopancreatectomy. After the preoperative diagnosis and staging with US, CECT, tumor markers, they underwent surgery. Invagination-dunking anastomosis was performed in 15, whereas, duct-to-mucosa, double layer anastomosis was performed in 10. In the first group with dunking anastomosis, we had 6 patients with soft pancreas and 8 with narrow main pancreatic duct, less than 3 mm. In the duct-to-mucosa group there were 5 patients with soft pancreas and 4 with narrow main pancreatic duct. All other stages of surgery were unified, so the only difference in the procedure remained on the pancreaticojejunostomy. The onset of the postoperative pancreatic fistula was estimated with revelation of 3 fold serum level of alpha amylases from the third postoperative day in the drain liquid.

Results: In the duct to mucosa group there wasn't a clinically relevant postoperative pancreatic fistula, while in the dunking anastomosis group we had 4 postoperative pancreatic fistula B, 26 %. One of these 4 patients experienced intraabdominal collection – abscess, conservatively managed with lavation through the drain. Comparing the groups, there was no significant difference between the groups concerning the appearance of postoperative pancreatic fistula: $p > 0.05$, $p = 0.125$. From all 25 patients, in 21 patients biliary stent was installed preoperatively to resolve the preoperative jaundice. All 21 suffered preoperative and postoperative reflux cholangitis, extending the intra-hospital stay.

Conclusion: So far, there have been many trials referring to opposite results while comparing these 2 techniques in creation of the pancreaticojejunostomy. In our study, the duct to mucosa anastomosis prevailed as a technique, proving its risk benefit rationale. However, further large randomized clinical

studies have to be conducted to clarify which of these procedures would be the prime objective in the choice of the surgeon while creating pancreatojejunoanastomosis.

Keywords: pancreatic head carcinoma, pancreaticoduodenectomy, postoperative pancreatic fistula, dunking anastomosis, duct to mucosa anastomosis, mortality, intra-hospital stay

INTRODUCTION

Pancreatic cancer (PC) is one of the most severe malignancies with quite unfavorable prognosis, affecting both, quality of life and survival. It occurs in 7.7/100,000 in Europe, 7.6/100,000 in the USA, while the incidence in Africa is 2.2/100,000, decreasing in Guinea to 0.35/100,000 population. It is the seventh cause of death in Europe, and the fourth in the USA. The etiology mentions many factors, like age, alcohol, helicobacter pylori, but definitely the tobacco abuse and genetic hereditary as factors are emphasized. Although the treatment and the prognosis in the last decades have been improved, the global outcome is still unsatisfactory. The prognosis mainly depends on the stage of the disease at the diagnosis. The studies in the USA reveal the overall survival rate with pancreatic carcinoma for 5 years to be 9%. Unfortunately, 52% of the patients are diagnosed at stage IV, and only 3% have a 5-year survival; on the other hand, if the cancer is diagnosed at stage I, presenting 10% of the sample population, the 5-year survival is 32%. These facts suggest that if the screening and the diagnosis improve generally, delivering higher rate of early stage at the time of diagnosis, there is a hope for successful treatment and desired outcome.

The only beneficial treatment is the radical surgery, duodenopancreatectomy (DP), Whipple procedure. It's a complex and demanding surgery, advocated and reserved for experienced surgical teams in high volume centers. Key points for this procedure are radicality, low morbidity and low mortality. Also, the postoperative follow-up of the patients should expose acceptable postoperative overall survival, of course, comparable and dependent on the preoperative radiology staging and postoperative TNM (p-TNM). One of the most important elements of the surgical management, determining the morbidity and mortality of the procedure, is the pancreaticojejunostomy (PJA). This is the most demanding and delicate sequence of the operation, conducting the entire postoperative course of the patient.

The objective of this prospective study was the comparison between 2 operative techniques, dunking or telescopic anastomosis on one hand, and duct to mucosa anastomosis on the other hand. The aim of the study is to define the rationale of the prevailing anastomosis, obtaining the benefit for the patients affecting their postoperative course, based on the measurable parameters used during the study. This objective measurable parameters were postoperative pancreatic fistula (POPF), associated with the morbidity and mortality in the groups. Radicality was similar in both groups, only 1 patient with R1, and mortality – 1 patient (4%) due to pulmonary embolism, in the duct to mucosa anastomosis group.

MATERIALS AND METHOD

During the last 14 months we operated 25 patients with pancreatic cephalic carcinoma (PCC), performing standard duodenopancreatectomy (SDP). All of the patients were recruited from the Clinic for GHE. Inclusive criteria for the sample population were:

1. US, with tumor in the head of the pancreas or periampullary region;
2. ERCP, in 21 for diagnosis and stenting in order to solve the jaundice, 4 without ERCP, 2 of them with unsuccessful attempt for ERCP and direct transfer to surgery, and 2 anicteric, no present jaundice, with processus uncinatus carcinoma;
3. CE angio CT scan, verifying operability and resectability of the carcinoma;
4. Laboratory findings, tumor markers: CEA, Lewis CA 19-9, VEGF.
5. Three patients underwent EUS guided biopsy and neoadjuvant therapy due to locally advanced cancer – 2 patients and borderline resectable cancer, 1.

The patients were accepted to surgery, and after the preparation submitted to surgery. They all received SDP. In 8 cases the resection of the Portal Vein/Superior Mesenteric Vein (PV/SMV) was done, because of the malignant infiltration-shift of the vein. Four resections of the vein were tangential, and 4 with transversal resection and direct anastomosis, without graft. The procedure also included, cholecystectomy, hemigastrectomy, jejunectomy of the first 2 jejunal loops. The reconstruction was classical, with PJA end to side with interrupted sutures, hepaticojejunostomosis termino lateral – also interrupted, side-to-side enteroenteroanastomosis – Braun, and side-to-side gastrojejunoanastomosis, denuovo on the anterior wall of the stomach, both double layer technique.

Depending on the pancreatic anastomosis, we had 2 groups, one with dunking anastomosis (DA) – 15 patients, and second with duct to mucosa anastomosis (DMA), 10 – patients. In the first DA group, there were 6 patients with soft pancreas and tin-week capsule, 8 patients with small-narrow main pancreatic duct (MPD), 3 mm or less. In the second DMA group, 5 patients had soft pancreas and week-tin capsule, and 4 patients small-narrow MPD. In the DA group 5 patients received PV/SMV resection, while in the DMA group 3 received resection of the vein. These variables are shown in Table 1.

Group	DA	DMA
No.ofpatients	15	10
Softpancreas/tin-weekcapsule	6	5
Small-narrowMPD	8	4
PV/SMVresection	5	3

The extension of the dissection and reconstruction technique, except the PJA was uniformed to avoid the influence while comparing the results. Gastroenteroanastomosis (GEA), was created after hemigastrectomy, de nuovo, side-to-side, on the anterior surface of the stomach, with double layer technique. Same technique was used for enteroenteroanastomosis for the omega loop. Biliodigestive anastomosis –hepaticojejunoanastomosis (HJA) was created in end-to-side fashion, interrupted sutures.

Nevertheless, the resection of the vein in both groups could not be unique, inevitably depending on the operative finding, dictated and demanded by the intention for R0 resection of the specimen. In the DA group, there were 5 resections of the PV/SMV, 2 longitudinal and 3 transversal with direct anastomosis, while in the DMA group, we did 3 resections

of the vein, 2 longitudinal and 1 transversal, also direct reconstruction without prosthesis or autologous graft. Fortunately, this distinction between the groups didn't affect the morbidity neither mortality during the study.

The creation of PJA in the DA group was with 4-0 prolene interrupted sutures, 3-5 mm distance of the resection margin, on the capsule of the pancreas. On the jejunum the suture was seromuscular. This technique enables inverting the pancreatic stump in to the lumen of the jejunum. This anastomosis was facilitated with a splinting catheter – internal stent placed in the MPD (Figure 1).

The PJA in DMA group, was created in 2 layers, interrupted sutures, prolene 4-0. The external layer was on the capsule of the pancreas and seromuscular layer of the jejunum. The second, internal layer was sawn with prolene 5-0, 4-6 interrupted sutures, depending on the caliber and topography of the MPD. The sutures were placed on the wall of the MPD and the jejunal mucosa (Figure 2).

In both groups we placed 3 abdominal tubes, silicon drains, first, right in the subhepatic space, second left in the bursa omentalis, and third, bellow, in the excavation rectovesicalis/uterina. These drains were the source for retrieving liquid for laboratory investigation on alfa amylasemia. We estimated to place 3 drains in order to decrease the possibility of fistulization on the wound, particularly in case of obturation of a placed single drain only.

The control of the anastomosis and the eventual onset of POPF was investigated with the alfa amylasemia in the drain liquid, 3rd and 6th postoperative day. As the definition by the ISGPS is that pancreatic fistula is presence of alfa amylases in the drained liquid 3 or more times higher concentration than normal serum level (normal serum concentration is 30-110 U/L), more than 330 U/L from the third postoperative day. This is independent from the outlet volume of the fistula, which means for any volume of the liquid, ml/24 h.

RESULTS

In the DMA group, there was no clinically relevant POPF, only one patient experienced biochemical-pancreatic leakage, 0 % of POPF. On the other hand, in the DA group, there were 2 cases of biochemical-pancreatic leakage and 4 patients suffering POPF B, 26.7 %, all treated conservatively. One of these 4 patients with POPF B exposed in-

Figure 1. A) Placement of the sutures, seromuscular on the jejunum, external capsular sutures on the pancreas. B) created dorsal wall of the anastomosis. C) Placed internal anastomotic stent-splinting catheter. D) completion of the anastomosis.

Figure 2. A) Position after sutured dorsal external wall of the DMA. B) Position after sutured dorsal internal layer – dorsal wall of the MPD with the dorsal jejunal mucosa. C) Suturing anterior internal wall. D) Position before noting the placed sutures on the anterior internal wall of the DMA.

traabdominal collection in the operative site (OS) on US investigation, just adjacently where the drain was. Thus, we estimated the malfunction of the drain amid occlusion by thick clough of fibrin exudatus. The resolving treatment was aspiration of the clough trough the drain, lavation of the OS and maintaining of the functional drain for 3 weeks. Statistically, concerning the occurrence of the POPF, there was not significant difference between the groups, $p>0.05$, $p=0.125$. The morbidity of the DA group consisted also in 5 wound infections. In the DMA group there were 2 infections of the wound.

Of the total sample population of 25, as mentioned, 21 were with ERCP and installed stent in order to resolve the jaundice and liver lesion preoperatively. Consecutive bacterial cholangitis appeared in all 21, 12 in DA group and 9 in the DMA group. This complication was managed in 3 ways, preoperative flushing irrigation and washing of the biliary stamp carried throughout with re-duodenoscopy, peroperative flushing irrigation, finally with antibiotics according to the antibiogram. We didn't have further postoperative morbidity associated with the biliary infection, like jaundice, liver abscess, fever, prostration, scathing tender in the upper right quadrant. Out of 21 patients with cholangitis, 20 overwhelmed the disease and the surgery successfully, but one with alcoholic liver cirrhosis who died on the 7th postoperative day.

Commenting the intrahospital stay, in the DA group the median stay was 11, 9 to 21 days, while in the DMA group – 9, 8 to 11 days. There was no difference in the peroperative blood lose and the units of blood administered. The mortality was 1 patient in the whole series, 4 %, due to pulmonary embolism. It was a patient who suffered alcoholic liver cirrhosis, diagnosed and treated long before this surgery. Nevertheless, he was accepted by the anesthesiology team and referred for surgery. He was in the DMA group.

The radicality of the resection was similar, in the DA group 14 were R0, and one was R1 resection. In the DMA group all 10 pTNM referred R0 resection.

DISCUSSION

As mentioned before, PC is the seventh cancer related reason for death in Europe, and fourth in the USA. The incidence is variable, from 7.7/100 000 in Europe and USA, to 2.2 in Africa

(1). This could be caused and partially explained by the presented high incidence of diseases characteristic for undeveloped countries, also low level of economic and health protection, leading to low level of capacity and ability for diagnosis and treatment of PC.

As the main role in the treatment for PC remains for surgery, the essential factor which determinates the morbidity and mortality is the onset of POPF, without neglecting the other challenging stages and reasons, like liver cirrhosis is (2, 3.). In order to unify the definition of the POPF, in 2016 the ISGPS-ISGPF redefined the stages of pancreatic leak. The former POPF A is nowadays a biochemical-pancreatic leak without impact of the leakage on the general status of the patient, except the prolonged presence of the drain. POPF B, affects the outfit performance of the patient, and beside the additional or intensive means of treatment, is to be solved with endoscopic, percutaneous drainage, and interventional angiography. It significantly affects the morbidity, but not the mortality. Finally, POPF C, is associated with multiple organ failure, and requires reoperations, with significant influence on the mortality (4, 5).

There are many studies referring a broad range of onset of POPF, either the mechanism of the development. The novel reviewed knowledge suggests the important role of the postoperative pancreatitis (POP) in adverse to prior theory, based merely on the insufficiency of the suture line-impaired anastomotic wall (6). We also revealed clinical and biochemical signs of POP in all four patients with POPF B. Tender in the upper abdomen, emphasized by deep inhalation, delayed gastric emptying (DGE), paresis to absence of peristalsis, body temperature over 38°C – lead us to suspicion for POP. The elevation of the serum level of alpha amylases, prostration, high levels of inflammatory parameters (Leu, CRP), and finally, the US and CECT scan undauntedly confirmed the diagnosis of POP.

Many studies report high incidence of POPF, up to 25 %, particularly connected with soft gland and narrow MPD, < than 3 mm (7). This status of the pancreatic tissue and diameter of the MPD was associated with all 4 patients acquiring POPF B in our study. Thus, the incidence of POPF B in our study was 16 %, 4 out of 25 total, and 4 out of 11 with soft gland, and 4 out of 12 with narrow MPD. When we have comparable and substantially unified groups of patients like we had, particularly for the influent parameters like

the pancreatic tissue and diameter of the MPD, we can clearly compare the operative technique by which the PJA was created. One Randomized Clinical Trial (RCT) of 197 patients researching this issue exposed a total incidence of 17.8 % of POPF. The distribution between the groups was 24 % in the DA group, and 12 % in the DMA group, $p < 0.05$ (8). Quite opposite results were in another RCT revealing 10 % of POPF B or C in the invagination DA group, while 23 % in the DMA group, $p = 0.077$. Significant difference appeared between the subgroups with soft pancreas: 10 % in the DA group v 42 % in the DMA group ($p = 0.01$) (9). These and other randomized clinical trials (RCT) obtain different, even opposed results between DA and DMA PJA.

Another RCT investigated the impact of the external and internal stenting of the PJA. The PJA was DMA. Patients with external stent group developed clinically relevant POPF in 24.4 %, while the internal stent group 18.9 %. The clarification of the risk factor for such relatively high incidence of clinically significant POPF, B or C, was soft pancreas, BMI (10). Nevertheless, if we objectively observe this results referring to this higher rate of the onset of POPF, compared to the DMA without stenting, the imposed conclusion can be – does the stent contribute to the decubital lesion of the internal layer of the anastomosis, especially when the MPD is less than 3 mm?

On the other hand, many RCT, investigated and compared also pancreaticogastric anastomosis (PGA) versus pancreaticojejunum anastomosis (PJA), affirming the attitude of superiority that this PGA reconstruction may offer, reporting significant difference in the onset of POPF B or C. The appearance of POPF in the PGA group was 0 %, while in the PJA group it was 13 %, $p = 0.014$ (11). This result was not confirmed in one big German RCT, which revealed no difference in the emergence of POPF B or C between these two techniques for reconstruction, 22 % v 20 %. Nevertheless PGA remains as a safe and regular reconstruction procedure (12). Another study compared all three reconstruction techniques, DA, DMA, and PGA. The result concerning clinically relevant POPF was favorable for DMA, also providing longer disease free and all over survival. DA on the other hand, prevailed with shorter operative time and shorter hospital stay. The presence of POPF B or C was 2 of 15 in the PGA group, 2 of 17 in the DA group, and 1 of 9 in the DMA group (13).

When we match the results from our study, they are comparable with the results in other studies where DMA prevails the DA.

Additionally, if we carefully observe and estimate the results in many trials, and also the result in our study, they inevitably offer ambiguous prospect. Not all trials while comparing the DA and DMA concerned other risk factors in the potential subgroups like soft pancreas, narrow MPD less than 3 mm, BMI, prolonged jaundice, liver disease like cirrhosis, chronic cardio vascular or respiratory disease, age, blood loss, etc. The probability to involve and stratify all potential impact risk factors determining all subgroups in one study are practically impossible. For this reason, there are many reviews collecting and analyzing the data, but the results remain diverse and confusing (13, 14, 15). Reasonably, until the consensus is reached, every referent institution with high caseload should undertake its own study based on the observations and experience for the eligibility between these 2 techniques, DA (invagination) and DMA.

CONCLUSION

According to the results we retrieved in our study, DMA is superior over DA affecting the morbidity mainly presented by clinically relevant POPF. Accepting the inverse results revealed in other studies, we believe that further big prospective RCTs would be necessary to clarify this dilemma. These predicted trials would deal with many and fairly stratified groups and subgroups depending on many risk factors as variables, (i.e. soft pancreas, narrow main pancreatic duct, liver disease, cardiovascular diseases, pulmonary diseases, preoperative radiographic stage of the disease, age, etc.) and would firmly contribute to achieve an attitude for the type of PJA eligible and favorable to any group or subgroup of patients suffering PC.

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ABBREVIATIONS:

Delayed gastric emptying (DGE)	Operative site (OS)
Duct to mucosa anastomosis (DMA)	Pancreatic carcinoma (PC)
Dunking anastomosis (DA)	Pancreticogastric anastomosis (PGA)
Duodenopancreatectomy (DP)	Pancreaticojejunoanastomosis (PJA)
Gastroenteroanastomosis (GEA)	Portal vein superior mesenteric vein (PV/SMV)
Hepaticojejunoanastomosis (HJA)	Postoperative pancreatic fistula (POPF)
Main pancreatic duct (MPD)	Postoperative pancreatitis (POP)
	Randomized clinical trial (RCT)
	Standard duodenopancreatectomy (SDP)

Резиме

СПОРЕДБА МЕЃУ ДАНКИНГ (ИНВАГИНАЦИЈА) ПАНКРЕАТОКОЈЕЈУНОАНАСТОМОЗА И АНАСТОМОЗА „ДАКТ ТУ МУКОЗА“ ВО ДВА СЛОЈА ПО ЦЕФАЛИЧНА ДУОДЕНОПАНКРАТЕКТОМИЈА – ПРОЦЕДУРА WHIPPLE ЗА ПАНКРЕАТИЧЕН ЦЕФАЛИЧЕН КАРЦИНОМ

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Вовед: Панкреатичниот карцином е малигнитет со лоша прогноза и за квалитетот на живот и за вкупното преживување. Инциденцата е различна, 7,7 на 100000 жители во Европа, 7,6 /100000 во САД, 2,2/100000 во Африка. Единственото вистинско лекување е хирургија, дуоденопанкратектомија. Клучни моменти за оваа процедура се радикалноста, нискиот морбидитет, нискиот морталитет, како и следењето и очекуваното вкупно преживување. Најважен дел од процедурата е панкреатокојејуноанастомозата, со нејзината критична стапица, постоперативната панкреатична фистула, од типот Б и Ц. Следствено на ова, начинот на креирање на панкреатикојејуноанастомозата ја дефинира безбедноста, а со тоа и постоперативниот морбидитет и морталитет. Секако, на крајот, ова најмногу зависи од хирургот и од хируршката техника при креирањето на анастомозата. Ние во студијата користевме две техники со поединечни шевови, данкинг-инвагинирачка анастомоза и „дакт ту мукоза“ во два слоја. Предмет на студијата беше споредување на овие две техники на шиене што ги применивме, додека цел беше да го откриеме соодносот меѓу ризикот и бенефитот за обете, данкинг и „дакт ту мукоза“ анастомозата.

Материјал и метода: Во нашата последна серија од 25 пациенти со карцином на главата на панкреасот направивме стандардна дуоденопанкратектомија. По предоперативната подготовка и стејдингот со УС, контрастен ангио цт-скен, ту-маркери, пациентите беа оперирани. Кај 15 пациенти направивме инвагинациска данкинг-анастомоза, додека кај 10 направивме „дакт ту мукоза“ анастомоза во два слоја. Во првата група имавме 6 пациенти со мек панкреас и 8 пациенти со тесен панкреатичен канал, помал од 3 мм. Во групата пациенти со „дакт ту мукоза“ имаше 5 пациенти со мек панкреас и 4 со тесен главен панкреатичен канал. Сите други фази од операцијата беа унифицирани, така што единствената разлика во процедурата остана на типот од панкреатикојејуноанастомозата. Појавата на постоперативната панкреатична фистула беше проценето со откривање на алфа-амилаза во трипати поголема концентрација од серумската, од третиот постоперативен ден во течноста од дренажите.

Резултати: Во групата пациенти со „дакт ту мукоза“ анастомоза немаше клинички релевантна постоперативна панкреатична фистула, додека во групата данкинг-анастомоза имавме 4 постоперативни панкреатични фистули Б, 26 %. Еден од овие 4 пациенти доби интраабдоминална колекција – апсцес, кој конзервативно го менаџиравме со промивање низ дренажот. Во споредба со групите, сепак, немаше значајна разлика во појавувањето на постоперативна панкреатична фистула, $p > 0,05$ $p = 0,125$. Кај 21 пациент од вкупно 25 предоперативно беше инсталиран билијарен стент за разрешување на предоперативната жолтица. Сите 21 страдаа од предоперативен и постоперативен рефлуксен холангитис, кој го продолжи болничкото лекување.

Заклучок: Досега има многу студии што објавуваат спротивни резултати кога ги компарираат овие две техники при креирањето на панкреатикојејуноанастомозата. Во нашата студија, техниката „дакт ту мукоза“ покажа подобри резултати како техника, докажувајќи го подобар соодносот на ризикот и добивката. Сепак, понатамошни големи рандомизирани клинички студии мора да се направат за да се разјасни која од овие процедури би била главен избор на хирургот за креирање на панкреатикојејуноанастомоза.

Клучни зборови: карцином на главата на панкреасот, данкинг анастомоза, дакт ту мукоза анастомоза, стандардна дуоденопанкратектомија, постоперативна панкреатична фистула, постоперативен панкреатитис, морбидитет, морталитет