

Duodenopancreatectomy for pancreatic tumors — PROS AND CONS

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ABSTRACT

Objective. To optimize surgical treatment of multiple and advanced pancreatic tumors.

Material and methods. There were 852 patients with various pancreatic tumors for the period 2011 — September 2019. Duodenopancreatectomy (DPE) was performed in 18 patients. Locally advanced ductal adenocarcinoma was diagnosed in 10 patients, acinar cell carcinoma — in 1 patient, multiple neuroendocrine tumors — in 4 cases, intraductal papillary mucinous tumor — in 2 patients, multiple metastases of renal cell carcinoma — in 1 patient. This procedure was avoided in 9 patients who underwent alternative operations: pancreatoduodenectomy (PDE) with pancreatic body resection for intraductal papillary mucinous tumor — 5 cases, two-stage (2) and one-stage (1) distal pancreatectomy and PDE for multiple neuroendocrine tumors — 2 patients, simultaneous pancreatic head resection and distal pancreatectomy for multiple metastases of renal cell carcinoma — 1 patient.

Results. Postoperative complications occurred in 14 patients after DPE (77.8%) and in 5 patients after alternative operations (55.5%). Alternative procedures in patients with neuroendocrine tumors, intraductal papillary mucinous tumors and metastases of renal cell carcinoma ensured radical surgical treatment. These patients did not need for insulin replacement therapy and enzyme drugs.

Conclusion. Strict adherence to oncological canons and differentiated approach in patients with multiple neuroendocrine tumors, metastases of renal cell carcinoma and intraductal papillary mucinous tumors are essential to avoid DPE in some cases in favor of alternative operations.

Keywords: duodenopancreatectomy, total duodenopancreatectomy, pancreatoduodenectomy, pancreas.

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Introduction

Pancreaticoduodenectomy (PDE) is predominantly performed for pancreatic tumors. Surgical feasibility and severity of inevitable postoperative disability associated with this procedure are still discussed. The lifelong need for insulin therapy and enzymatic replacement of pancreatic excretory function significantly impair the quality of life of patients. There are severe disorders of carbohydrate metabolism after PDE. In the English-language literature, diabetes after PDE is called “brittle” due to impaired endogenous regulation of glycemia and reduced insulin resistance. As a result, insulin replacement therapy becomes more difficult [1, 2].

Indications for PDE are strictly determined. This procedure is recommended for intraductal papillary mucinous neoplasm (IPMN) types 1 or 3 with total damage to pancreatic duct including those tumors associated with carcinoma, multiple neuroendocrine tumors (NET), locally advanced ductal adenocarcinoma, multiple metastases of renal cell carcinoma [1, 3, 4]. In some clinics, PDE is considered in case of mellow pancreas and high risk of anastomotic leakage after pancreatoduodenostomy [3,4].

PDE is absolutely indicated for ductal adenocarcinoma with subtotal pancreatic lesion, multiple NETs, multiple metastases of renal cell cancer. R0-resection should be mandatory ensured in these cases. There are clinical situations when unequivocal opinion on the justification

Table 1. Summarized data (diagnosis/PDE, resections, follow-up) 2011-2019

Diagnosis	Number of patients	Surgery			
		PE	PDE with pancreatic body resection	Two-stage approach (PDE/PE*)	PDE + PE
Ductal adenocarcinoma	10	10	—	—	—
Acinar cell carcinoma	1	1	—	—	—
NET	6	4	—	2	—
IPMN	8	2	5	—	1**
Metastases of renal cell cancer	2	1	—	—	1 (pancreatic head resection + PE)
In all	27	18	5	2	2

Note: * — distal pancreatectomy; ** — synchronous solid pseudopapillary tumor of tail and IPMN of pancreatic head associated with ductal adenocarcinoma.

of PDE is absent. Alternative approach ensuring the same surgical quality is discussed in this case.

We report a single-center experience of surgical treatment of pancreatic neoplasms and chronic pancreatitis. All procedures were performed at the Department of Abdominal Surgery of the Vishnevsky Research Center for Surgery.

Material and methods

There were 852 various pancreatic resections for the period from 2011 to September 2019 performed at the Department of Abdominal Surgery of the Vishnevsky Research Center for Surgery. PDE was required only in 18 (2.1%) cases. This analysis enrolled 27 patients. PDE was made in 18 patients. Nine patients formally had indications for PDE, but they underwent various alternative procedures (Table 1).

All patients underwent comprehensive examination within 2 — 4 weeks prior to surgery including abdominal ultrasound and endoscopic ultrasound, contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) with MR-cholangiopancreatography (MRCP). Arterial stimulation and venous sampling was made in patients with multiple NET (insulinoma) to accurately localize endocrine-active tumor.

Concomitant and comorbid diseases were observed in 19 patients (cardiovascular diseases — 12, pulmonary diseases — 4, chronic pyelonephritis — 1, diabetes mellitus — 10, impaired fasting glycemia — 2, organic hyperinsulinism — 3).

Unified perioperative management involved prevention of infectious and thrombotic complications, postoperative pancreatitis in patients after pancreatectomy and correction of carbohydrate metabolism [5].

Synthetic analogues of somatostatin (octreotide, 200 µg i.v.) was administered 1 hour before surgery. Pancreatectomy was followed by postoperative administration of octreotide 100 µg 3 times a day by subcutaneous injection for consecutive 5 days. Proton pump inhibitors were administered for consecutive 7-10 days after surgery. In-hospital prevention of thrombotic complications was carried out using prophylactic doses of indirect anticoagulants in

patients without vascular reconstructions and therapeutic doses in patients undergoing mesenteric and portal vein surgery. Tabled anticoagulant drugs were prescribed for 6 months after discharge in patients with vascular reconstruction. Anticoagulant therapy was followed by subsequent ultrasound control of vascular patency. Antibiotic prophylaxis was carried out using broad-spectrum drugs for 1 day in standard situations and for 2-3 days in patients after previous bile drainage procedures. In some cases, antibiotic therapy was prescribed in accordance with the results of intra- and postoperative microbiological examination.

Correction of carbohydrate metabolism was carried out in accordance with international guidelines [1, 6]. Intravenous infusion of short-acting insulin at a rate of 0.1 U/kg/h and simultaneous glucose infusion (150 g of carbohydrates per day) were administered on the first postoperative day. Then, the approximate mean daily dose of insulin was calculated (25-34 IU per day (0.3 IU/kg) after PDE). A dose of prolonged insulin was 7-16 IU per day (0.2 IU/kg) that accounted 50-80% of the calculated dose of insulin. Short-acting insulin was prescribed in "sliding" fashion to maintain the target glycemia level of 4-9 mmol/L. Prolonged insulin was injected within 2 hours before cessation of short-acting insulin infusion. Appropriate therapy was determined by fasting glycemia of 3.8 — 7.2 mmol/L. A dose of basal insulin was reduced by 4 IU in case of decrease of fasting glycemia less than 3.8 mmol/L. Glycemia over 7.2 mmol/L required augmentation of basal insulin dose by 2 IU per day.

Blood glucose was measured at least 4 times a day before ingestion and at bedtime.

Exocrine insufficiency was managed using replacement therapy with a daily dose of 80-150 thousand units of enzymatic drugs in terms of lipase [6]. An initial dose of substitution therapy was 72000-75000 units of lipase for main ingestion and 36000-45000 units for intermediate meal.

Urgent intraoperative histological examination of resection margin was performed in all patients. The number of acini was analyzed in resection margin besides tumor tissue in order to objectify the state of pancreatic excretory function. Summarized area of acini in resection margin was determined as a percentage from the overall area [7].

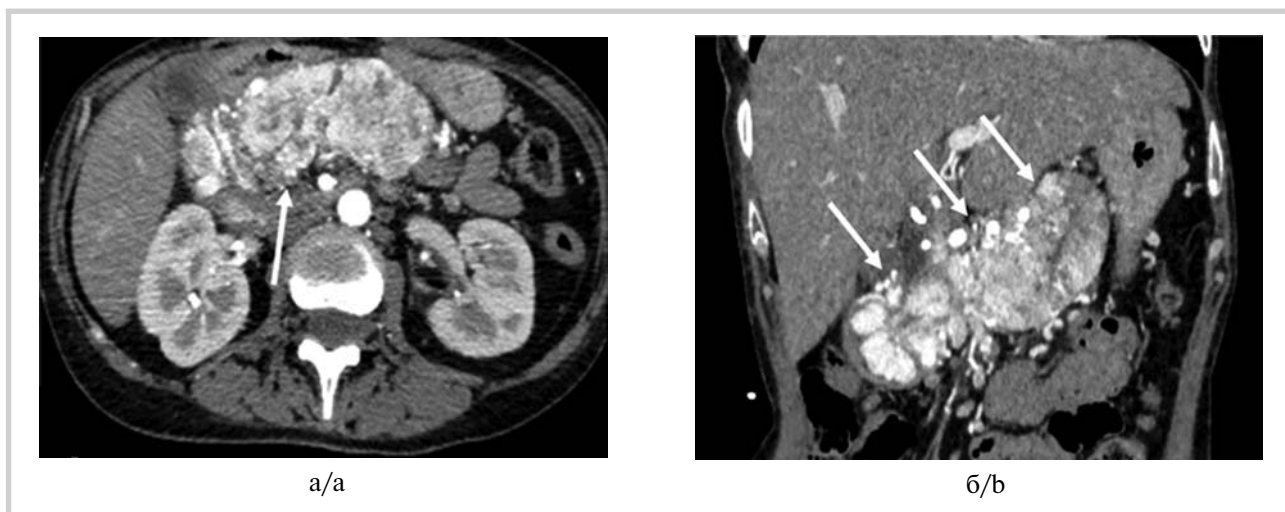


Fig. 1. CT-scan, arterial phase. Acinar cell carcinoma, total lesion of the pancreas: A — axial plane. B — frontal plane.

Table 2. Postoperative complications

Complication	Pancreaticoduodenectomy (18)	Organ-sparing surgery (9)
Pancreatico- or hepatocoejunostomy leakage	4 (22,2%)	2 (22,2%)
Gastrostasis	5 (27,7%)	0
Type B	3 (16,6%)	0
Type C	2 (11,1%)	0
Postoperative bleeding	5 (27,7%)	0
Early	3 (16,6%)	1 (11,1%)
Delayed	2 (11,1%)	0
Wound suppuration	2 (11,1%)	0
Sepsis	1 (5,5%)	0
Eventration	1 (5,5%)	0
Acute liver failure	2 (11,1%)	0
Colon perforation	1 (5,5%)	0
Pancreatic fistula (type B)	-	2 (22,2%)
In all	14 (77,7%)	5 (55,5%)

Scheduled histological examination of specimen was carried out in accordance with the methodology adopted in our center. This protocol is based on the recommendations of the College of American Pathologists (CAP) and included marking the surface of the gland, examination of pancreatic stump sections and pancreatic duct, edges of the bile ducts and proximal margin of the duodenum or stomach [8]. Tumor dimensions, invasion of peripancreatic tissue and adjacent organs were evaluated using axial sections of the gland in analysis of pancreatoduodenal complex and sagittal sections in analysis of specimen after corporeo-caudal pancreatectomy. The final histological conclusion included histological type of the tumor, dimensions, spread with assessment of resection margins, metastases in regional lymph nodes.

Results

PDE for pancreatic tumors was performed in 18 patients. Mesenteric-portal vein resection was required in 8 of these patients. Clear preoperative indications for PDE

were confirmed only in 8 out of 18 patients: advanced malignant lesion of the pancreas (n=3) (Fig. 1), multiple NET (n=4), multiple metastases of renal cell carcinoma (n=1).

In other 10 cases, preoperative examination gave a hope to avoid PDE or this operation was not expected. However, urgent histological examination during PDE revealed the structures of invasive carcinoma within resection margin that required total pancreatectomy. R0-resection was ensured in 12 cases among patients with ductal adenocarcinoma, IPMN associated with carcinoma and NET G2, R1-resection — in 5 cases, R2-resection — in 1 patient. The number of excised lymph nodes ranged from 18 to 66 (median — 30).

The absolute contraindications for PDE were distant metastases, invasion of superior mesenteric or hepatic arteries, celiac trunk, impossibility to ensure R0-resection, no effect of neoadjuvant chemotherapy in patients with borderline resectable tumors.

Complications after PDE occurred in 14 (78%) out of 18 patients (Table 2). One patient died from early intra-

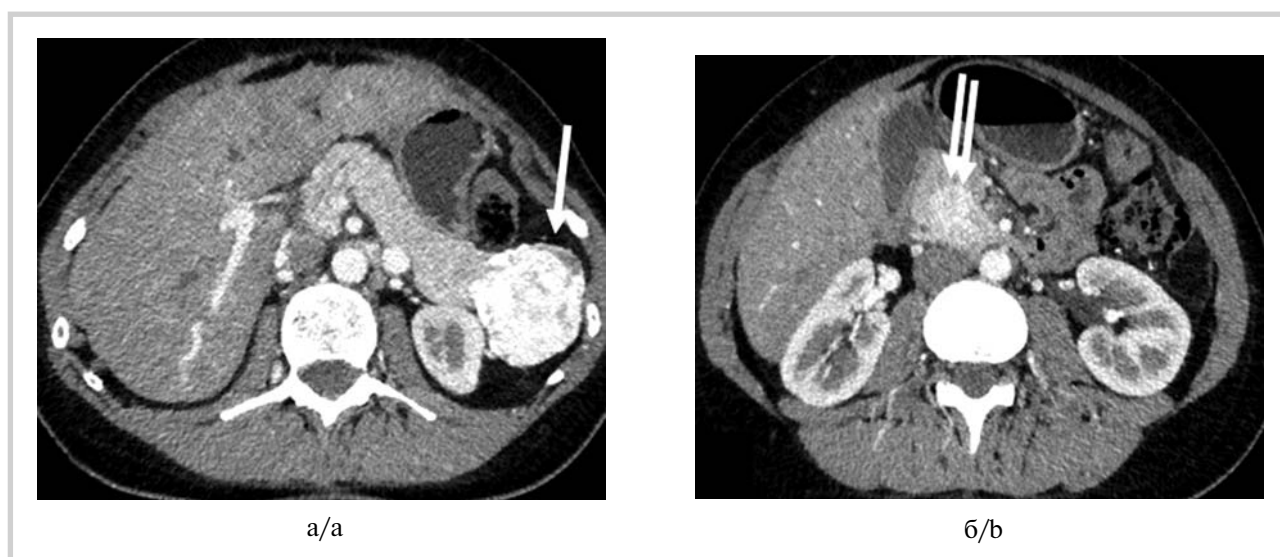


Fig. 2. CT-scan, arterial phase, axial plane. A. NET (Grade 2) of the pancreatic tail 40×50 mm. B. NET (Grade 2) of the pancreatic head 17×21 mm.

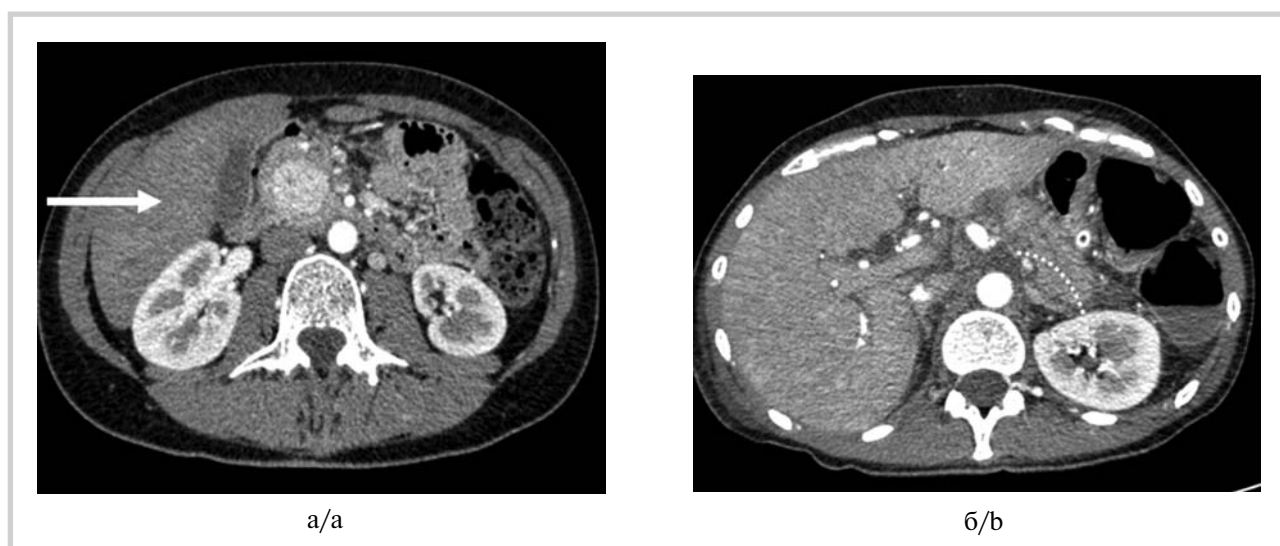


Fig. 3. CT-scan, arterial phase, axial plane. A — control follow-up in 6 months after distal pancreatectomy: NET (Grade 2) of the pancreatic head 26×26 mm. B — residual pancreatic parenchyma after partial pancreateoduodenectomy and distal pancreatectomy.

abdominal bleeding followed by multiple organ failure and sepsis.

PDE was avoided in 9 patients who underwent alternative surgeries. PDE was inevitable in patients with locally advanced ductal adenocarcinoma. Less aggressive tumors made it possible to consider the possibility of abandoning PDE.

Surgical strategy was individual in each case. Two patients with multiple non-functioning NETs type G1 and G2 (pancreatic head and tail) had “feathery” CT-pattern of the pancreas that was typical for mellow gland. Moreover, urgent histological examination revealed that acini accounted about 80—95% of resection margin (indicator

of high excretory pancreatic activity). Therefore, two-stage surgical approach was preferred, since preservation of pancreatic tissue would inevitably result severe postoperative pancreatitis in this situation. The first surgical procedure (robot-assisted distal pancreatectomy, splenectomy) resulted excision of a larger tumor. According to CT-data, its malignancy grade was G2 (**Fig. 2**).

Pylorus-sparing partial PDE was performed 6–8 months later for enlargement of residual NET of pancreatic head. As a result, we avoided severe postoperative pancreatitis and significant part of the pancreas was preserved (**Fig. 3**). Postoperative complications occurred in 1 patient. The first surgery was followed by fluid accumulation that re-

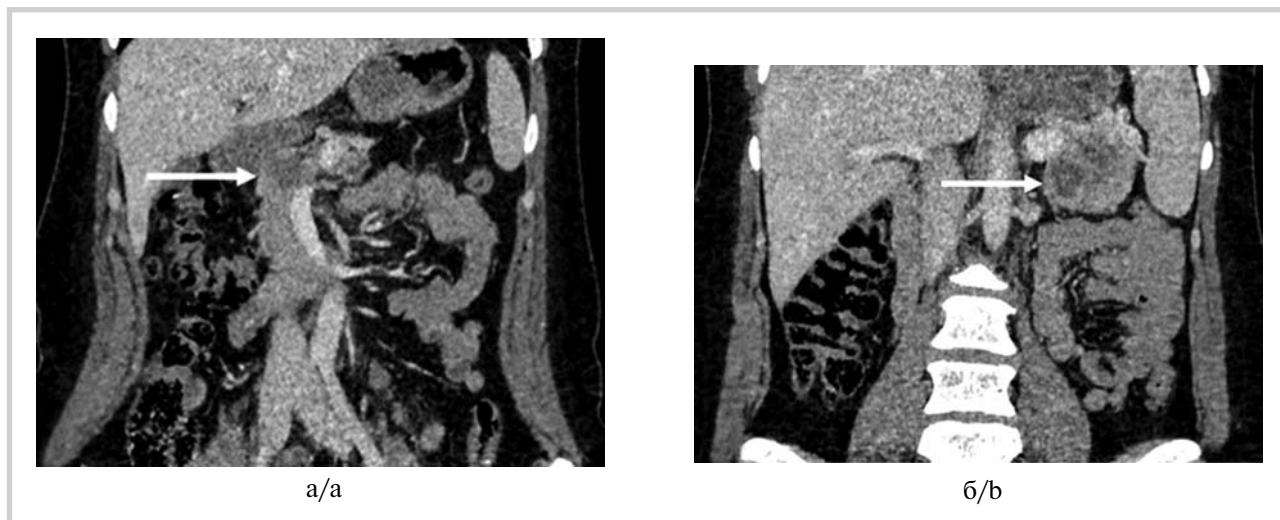


Fig. 4. CT-scan, venous phase, frontal plane: A. IPMN of the pancreatic head associated with ductal adenocarcinoma. B. solid pseudo-papillary tumor of the pancreatic tail.

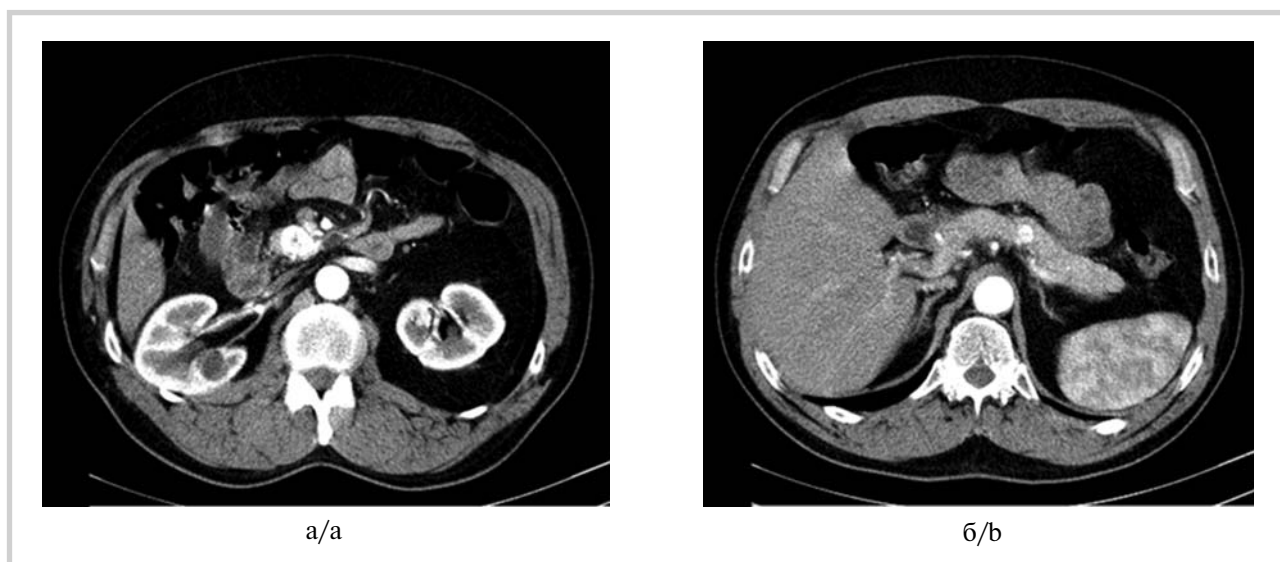


Fig. 5. CT-scan, arterial phase, axial planes. Renal cell cancer metastases in the pancreas: metastasis in uncinus process (A) and pancreatic body.

quired US-assisted drainage. The second operation was associated with arrosive bleeding ISGPS type B with subsequent endovascular hemostasis. The follow-up examination after 6 and 12 months revealed no recurrent tumors and diabetes mellitus. Excretory pancreatic insufficiency was also absent.

A rare variant of synchronous multiple pancreatic lesion (solid-pseudopapillary tumor of the tail and IPMN associated with ductal adenocarcinoma of the head) was observed in 1 patient. There were no CT and MRI signs of mellow intact pancreatic body. The duct was enlarged (Fig. 4). The patient underwent a single-stage organ-sparing procedure — pylorus-sparing partial PDE with resection and replacement of the portal vein, distal pancreatectomy with splenectomy (80 lymph nodes were resected,

invasion was found in 1 node). An essential aspect of successful simultaneous intervention was the low excretory activity of residual pancreatic segment (acini accounted for 10% of resection margin area). There were no postoperative disturbances of carbohydrate metabolism, despite small volume of residual pancreas. Postoperative complications were absent. The patient receives chemotherapy.

Renal cell carcinoma metastases in uncinus process and pancreatic body were observed in 1 patient who underwent resection of uncinus process and spleen-sparing distal pancreatectomy (acini accounted for 95% of resection margin) (Fig. 5). Postoperative period was complicated by pancreatic fistula ISGPS type B. Closure of this fistula was achieved after US-assisted drainage of fluid accumulation.

In 5 patients with IPMN (types 1 and 3 associated with invasive carcinoma — 4; IPMN type 3 — 1), there were no structures of invasive carcinoma and high-grade dysplasia in resection margin. Therefore, total PDE was abandoned in favor of partial PDE with resection of the body and partially tail of the pancreas. According to histological data, R0-resection was achieved in 3 patients, R1 — in 2 cases (the presence of atypical cells in peripancreatic tissue). The number of excised lymph nodes ranged from 18 to 50 (median — 29). Postoperative period was complicated by biliary fistula in 1 patient. Long-term results were followed-up in 2 patients. Tumor recurrence within the pancreatic stump was not detected.

Discussion

The history of PDE introduction in pancreatic surgery was dramatic and sometimes sad. The first successful pancreatectomy for pancreatic neuroendocrine tumor was performed by Russell Wilder at the Mayo Clinic in 1942 [9]. Reconstructive stage implied gastroentero- and cholecystoenterostomy. Histological examination revealed a “benign islet cell adenoma” 8 x 5 x 5 mm. The patient lived for 29 years after surgery. The cause of death was gallstone disease, cholangitis, multiple liver abscesses.

In our country, the first successful PDE for pancreatic cancer was made by V.A. Vishnevsky in 1975 at the Vishnevsky Institute of Surgery. There were 23 patients who underwent surgery over the next 13 years until 1988. In those years, indications for PDE were determined intraoperatively after palpation of tumor and analysis of its dimensions. Nine patients died in early postoperative period and quality of life of survivors was extremely low due to the absence of adequate replacement therapy. As a result, PDE was recognized as inappropriate. In 2009, our institute returned to this intervention. However, surgical indications are currently based on comprehensive preoperative examination and imaging [10]. Over the past 2 years, we aspire to avoid PDE in patients with NET, IPMN and metastases of renal cell carcinoma in favor of alternative operations. However, we absolutely follow the necessary oncological canons. In our opinion, PDE is inappropriate for chronic pancreatitis.

PDE significantly impairs quality of life. Therefore, responsibility of the clinic determining the necessity and expediency of this intervention is extremely high. Treatment strategy is predominantly determined by radiological diagnosis [10,11].

Current CT, MRI and ultrasound diagnosis gives detailed information about not only dimensions and localization of pancreatic tumor, but also its histological type [10]. In particular, CT is valuable for differential diagnosis between ductal adenocarcinoma and pancreatic NET, to analyze malignancy grade of NET and suspect associated invasive carcinoma in patients with IPMN [12, 13]. Moreover, preoperative imaging can precisely visualize mellow pancreatic parenchyma that should be considered

prior to surgery. A comprehensive radiation examination is useful to choose optimal treatment strategy and surgical approach (conventional, laparoscopic or robot-assisted) [12, 14].

At the same time, resolution capabilities of modern methods of radiological diagnosis are not unlimited. The extent of pancreatic tissue invasion, involvement of adjacent veins and arteries cannot always be accurately established. For example, we were not able to determine distal spread of ductal adenocarcinoma of the pancreatic head prior to surgery in 5 out of 10 patients. The diagnosis was clarified intraoperatively after urgent histological examination and the patient underwent PDE. Diagnosis of vascular invasion is also far from ideal. Preoperative diagnosis of invasion of mesentericoportal venous segment in 7 patients was intraoperatively confirmed in 4 cases and rejected in 3 patients. Moreover, intraoperative diagnosis of vein invasion in 4 cases was not preoperatively suspected.

PDE is rarely advisable in patients with advanced ductal adenocarcinoma of the pancreas because large tumors are usually associated with distant metastases or invasion of celiac trunk and superior mesenteric artery [15, 16]. Therefore, reliable information confirming radical procedure should be ensured prior to PDE for ductal adenocarcinoma [10, 11].

In our opinion, organ-sparing procedures may be considered in patients with less aggressive pancreatic neoplasms. There are 2 types of alternative interventions — 1) preservation of a small fragment of the pancreatic tail; 2) proximal and distal pancreatectomy with preservation of the middle part of the pancreas. Unfavorable factor of these interventions is postoperative pancreatitis. This complication is inevitable in patients with mellow pancreatic parenchyma and preservation of more than 60 — 70% of acini due to persistent excretory activity of the pancreas. This situation is common in the cases of NET and metastases of renal cell carcinoma. We prefer two-staged surgical approach with an interval of about six months in patients with NET G1 in order to reduce the risk of this complication.

Above-mentioned surgical strategy is unacceptable in patients with multiple metastases of renal cell carcinoma because simultaneous resection is required in these cases [17, 18]. Excretory pancreatic activity remains intact in case of metastatic lesion. Therefore, simultaneous proximal and distal pancreatectomy with partial preservation of pancreatic body will be obviously followed by postoperative pancreatitis and pancreatic fistula. Surgeon should be ready to extirpate the remnant pancreatic fragment after organ-sparing surgery in case of severe postoperative pancreatitis.

However, you can count on a successful result after simultaneous resection of 2 pancreatic fragments in the cases of small number of acini within resection margin and low excretory pancreatic activity.

IPMNs types 1 and 3 localized in proximal part of the pancreas result distal enlargement. It should be remem-

bered that even significant dilatation of the duct may be due to impaired drainage rather malignant lesion. Therefore, there is no need for resection of the entire gland if papillary growths and solid component are absent in distal part of the pancreatic duct. In such cases, we are convinced that the gland should be intersected away from the proposed edge of the tumor. Subsequent urgent histological examination should be performed to determine severity of epithelial dysplasia or structures of invasive carcinoma. Partial resection may be performed if severe dysplasia and malignant structures are absent (5 patients in our sample). Preservation of even small part of pancreatic tail prevents post-pancreatectomy syndrome.

Metabolic disorders associated with PDE are caused by not only insulin deficiency, but also the absence of secretion of glucagon and pancreatic polypeptide. The absence of glucagon secretion impairs glycogenolysis and gluconeogenesis. Pancreatogenic peptide causes the resistance of liver receptors to insulin and slowdown of insulin-induced gluconeogenesis in liver. Impaired secretion of these agents results hypoglycemia. Pancreatogenic diabetes is ac-

companied by increased peripheral tissue sensitivity to insulin unlike diabetes mellitus type 2. Increased sensitivity is caused by changed regulation of peripheral insulin receptors as a result of permanent insulin deficiency. These features of glucose metabolism complicate control of glycemia and increase the risk of hypoglycemia during insulin therapy in patients after total pancreatectomy [19].

Conclusion

PDE performed in accordance with indications improves life expectancy in patients with pancreatic neoplasms. The negative consequence of this surgery is inevitable lifelong need for replacement enzyme and insulin therapy that significantly impairs quality of life. Strict critical individual assessment of the pancreas using preoperative CT and MRI, intraoperative histological examination of resection margin in patients with multiple NETs, metastases of renal cell carcinoma and IPMN are valuable to perform alternative operations and avoid negative consequences in some cases.

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