

Case report

RESECTION OF THE LATE RECCURENCE OF PANCREATIC HEAD CARCINOMA AFTER WHIPPLE PROCEDURE IS SAFE, FEASIBLE AND OFFERS LONG-TERM PROGNOSIS IMPROVEMENT

РЕСЕКЦИЈАТА НА КАСНИОТ РЕЦИДИВ НА ПАНКРЕАТИЧЕН ЦЕФАЛИЧЕН КАРЦИНОМ ПОСЛЕ ВИПЛОВА ПРОЦЕДУРА Е БЕЗБЕДНА, ВОЗМОЖНА И НУДИ ПОДОБРУВАЊЕ НА ДОЛГОРОЧНАТА ПРОГНОЗА

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Abstract

Pancreatic cancer is a severe disease with poor prognosis, the seventh most common cancer cause for death in the world, and the third in the USA. Despite advanced procedures for diagnosis and management, 80% of patients develop recurrence, lethal in the first 2-5 years. One small subgroup with isolated recurrence was the objective of this study, in order to improve the prognosis.

In our practice, of a total of 223 patients who underwent duodenopancreatectomy, we staged 3 patients with resectable recurrent pancreatic carcinoma. Inclusion criteria for selection were: US, CECT scan, PET scan, CEA, CA 19-9, VEGF level. One patient had recurrence on the pancreatic stump, and 2 in the surrounding lymph nodes. They underwent surgery and re-resection of the specimen. The redo was a subtotal pancreatectomy and Roux-en-Y procedure.

There was no perioperative mortality, and morbidity in all 3 patients appeared to be a pancreatic fistula, grade A. Intrahospital stay was 12, 15, 17 days, median 15. Median overall survival was 32 months (14, 22, 61). In comparison with other studies, we had a better postoperative survival, but significantly lower rate of re-operated patients, 1.34% vs. 6.4%, due to late diagnosis. The median overall survival was significantly longer compared to patients treated with radio-and chemotherapy only. Having in mind the available data and our results obtained from the small number of patients treated surgically so far, we can conclude that surgery in these patients with isolated recurrence of the pancreatic carcinoma is feasible, promising a significant improvement of the prognosis. To confirm this active attitude, a multicenter study is required for finding an evidence-based protocol for these patients.

Keywords: pancreatic cancer, recurrence, re-resection, morbidity, survival

Апстракт

Панкреатичниот карцином е тешка болест со лоша прогноза, седма најчеста причина за смрт во светот, а трета во САД. И покрај напреднатите процедури и технологија за дијагноза и третман, 80 % од пациентите развиваат рецидив, летален во првите 2-5 години. Една мала група на пациенти со изолиран локален рецидив е предмет на оваа студија, со желба да ја подобриме прогнозата.

Во нашата праксам од вкупно 223 пациенти кои беа подложени на дуоденопанкреатектомија, ние одвоивме 3 пациенти со ресектабилен рецидивен панкреатичен карцином. Инклузивните критериуми за селекција беа: УС, КЕЦТ, ПЕТ скен, ЦЕА, ЦА 19-9, ВЕГФ маркери. Еден пациент имаше рецидив на панкреатичниот остаток, а 2 на околните лимфни јазли. Тие беа подложени на рересеција на рецидивот. Реооперацијата се состоеше од субтотална панкреатектомија и Ру ен У процедура.

Немаше перооперативна смртност, а морбидитетот кај сите 3 пациенти се експонираше како панкреатична фистула, тип А. Интрахоспиталниот престој беше 12, 15, 17 дена средна вредност 15. Средно вкупно преживување беше 32 месеци (14, 22, 61). Во споредба со други студии, ние имавме подобро постоперативно преживување, но значајно понизок процент на реоперирани пациенти, 1,34 % спрема 6,4%, пред и се поради доцната дијагноза. Средното вкупно преживување беше значајно подолго во споредба со пациентите третирани само со радио-хемотерапија. Имајќи ги предвид достапните податоци и нашите резултати добиени од мала група на пациенти кои досега ги третиравме хируршки, можеме да заклучиме дека хируршкиот третман на овие пациенти со изолиран ресектибилен рецидив на панкреатич-

ниот карцином евозможен и ветувачки за значајно подобрување на прогнозата. За да се потврди ваквиот активен став потребна е мултицентрична клиничка студија, за да се пронајде протокол базиран на доказ за овие пациенти.

Клучни зборови: панкреатичен карцином, рецидив, пересекција, морталитет, морбидитет, преживување

Introduction

Pancreatic carcinoma is the seventh most common cancer-related cause for death annually in the world, and the third for cancer-related deaths in the USA. Prognosis of patients suffering from pancreatic ductal adenocarcinoma (PDA) is poor; after diagnosis 24% of patients survive 1 year, and 9% survive 5 years. The incidence is variable, i.e., in Europe it is 7.7/100,000, in North America 7.6/100,000 inhabitants. It is more common in males than in females: 5.5 vs. 4.0/100,000. Because of the obscure, torpid appearance and course of the disease as well as demanding sophisticated means for disclosure, the diagnosis is often made in an advanced stage, decreasing the possibility for cure and worsening the long-term prognosis. The desirable early diagnosis makes feasible the radical curative treatment, improving the overall survival (OS). Namely, 40 years ago, the 5-year OS was 5%; 20 years ago, it was 20%; and nowadays, up to 40%. There are series of treated patients referring a 5-year survival up to 67%. The treatment is variable due to the stage at diagnosis. It consists of neoadjuvant therapy, surgery, adjuvant therapy. The main role in this treatment is indubitably a radical surgical treatment-pancreatectomy. It may be: proximal duodenopancreatectomy -Whipple procedure (DP), distal pancreatectomy, total pancreatectomy, depending on the topographic presentation of the tumor. A certain period of time after surgery and completed adjuvant treatment, majority of patients develop and suffer from a recurrent pancreatic carcinoma (RPC), reported in up to 80%. It is usually disseminated, incurable and a cause for death. In a small group of patients, this recurrence is local and isolated, limited to the operative site. It usually emerges in the local lymph nodes, surrounding tissue, or pancreatic remnant, although R0 resection has been reported on pTNM. Such a localized RPC may offer a slight hope for further surgical treatment and expanding the expected disease-free life.

The aim of this study was to present the treatment of this group of patients with resectable and due to this curable RPC, in order to provide further disease-free period of life, and consequently to improve the prognosis

of the disease. Nevertheless, a small number of patients with RPC are referred and involved in clinical trials to provide evidence-based data and to enable decision for further management and treatment [2].

Material and methods

In a period of 8 years, we had 223 patients suffering from PDAC, with cephalic presentation. They were submitted to DP, Whipple procedure (WP). From the group who underwent an extensive duodenopancreatectomy (EDP), we analyzed 3 male patients with resectable RPC. The inclusion criterion was diagnosed solitary recurrence, confirmed with CE angio-CT, MRI, and elevated level of Lewis tumor marker CA 19-9, VEGF. Concerning the age and topography of the RPC, these 3 patients were:

65 yrs. - patient 1 (P1) with RPC on the pre aortal lymph nodes, and with infiltration-abutment of the efferent jejunal loop, also the superior mesenteric artery (SMA),

69 yrs.- patient 2 (P2) with RPC on the pancreatic remnant, and

73 yrs. - patient 3 (P3), with RPC in peri pancreatic-retro anastomotic lymph nodes and with infiltration-interface of the portal vein (PV) - superior mesenteric vein (SMV).

The implied procedure was re-resection of the RPC, with subtotal pancreatectomy-blind stump, with perioperative frozen section probe, and the reconstruction with Royx-en-Y limb of the digestive tube (Figure 1). In the first patient (P1), the re-resection was also extended with the efferent hepaticojejunal loop, because of the infiltration by the recurrence (Figure 2). In the same patient, a tangential resection and reconstruction of the SMA was imposed at the emerging site of the first jejunal artery.

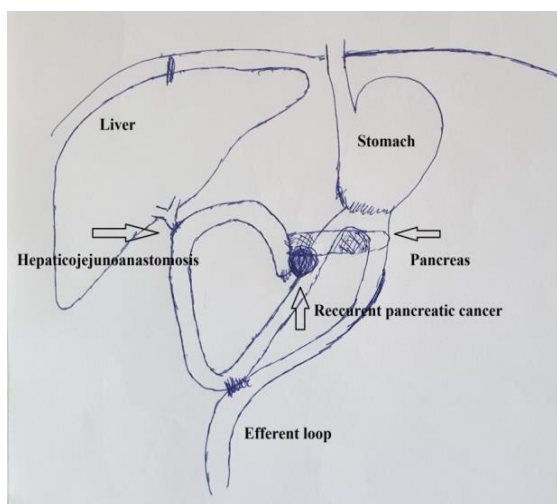


Fig. 1a. Schematic topography of the RPC before surgery

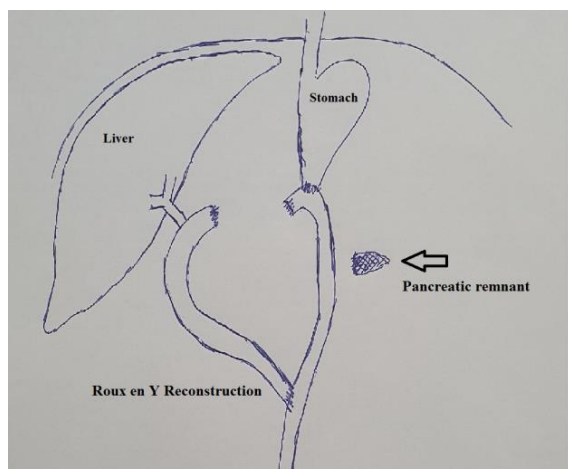


Fig. 1b. Reconstruction of the site after surgery and extirpation of the RPC

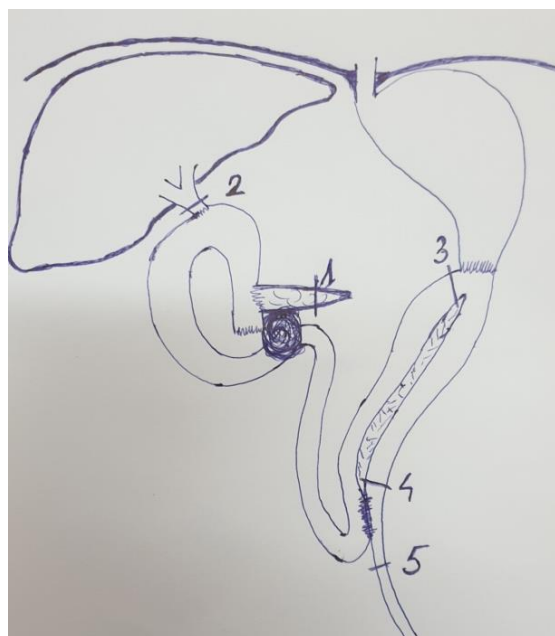


Fig. 2. Specific re-resection procedure in patient P1, with extirpation of the entire previous reconstruction, with 5 re-resection lines: 1. Re-resection line on the pancreatic remnant, 2. Re-resection line on the common hepatic duct, 3. Re-resection line on the afferent hepatogastric loop, 4. Re-resection line on the efferent gastrojejunal loop, which later goes to Y anastomosis, 5. Distal re-resection line on the efferent jejunal loop, which later goes to hepatojejunoanastomosis

Results

In our series of 223 patients with PDA with cephalic presentation, submitted to DP, WP, 120 underwent a standard duodenopancreatectomy (SDP) with D2 lymph node dissection, while 103 underwent extensive duodenopancreatectomy (EDP) with D3 dissection. In the SDP group of patients, there were 61% males (73 of 120), and 39% females (47 of 120). In the EDP group, 65% (67 of 103) were males and 35% (36) were females. The recruitment was done at the Clinic for Gastro-

enterohepatology, after US, CECT scan, PET scan, laboratory findings of CEA, Lewis CA 19-9, and VEGF. Inclusion criterion for surgery was operable-resectable PDA, and/or borderline resectable by the subclassification according to SMV/PV invasion, by the protocol and consensus of the ISGPS, JPS, NCCN. Of the total sample (223), 15 patients had borderline resectable carcinoma (BRC), and all of them received EDP. Eight of these 15 patients were subjected to portal vein resection, either longitudinal resection with direct suture without graft, or transversal resection with direct anastomosis, also without venous graft.

Patients with SDP, after certain months of disease-free life, grossly developed disease relapse, mainly metastases in the liver, peritoneal dissemination, or lung metastases, either or not associated with local recurrence; thus, the malignancy recurrence in these cases after follow-up was inoperable and incurable.

In the EDP group, 3 patients developed localized RPC, 2 cases were in local lymph nodes, while 1 was on the pancreatic remnant. These 3 patients, all males, were 65, 69 and 73 yrs. old, and like all others, were treated with chemotherapy by protocol after primary surgery (Table 1). The onset of the RPC in these three patients, ending disease-free life, was 16 months, 20 months, 23 months after primary surgery (Table 1). Two of them were subclinical, and one patient suffered from jaundice, mild discomfort and tender in the upper abdomen. The jaundice was amid the infiltration of the efferent hepaticojejunal loop with obstruction, by the RPC.

Patients underwent US, CECT scan, and PET scan, verifying the local recurrence without further distal dissemination of the disease, and feasible for surgery.

In all 3 patients, the Lewis CA 19-9 was elevated, in 2 of them VEGF. After the verification of the operability, patients did not undergo another neoadjuvant chemotherapy for the RPC. They were submitted to surgery, and operated. The surgery consisted of massive adhesiolysis, dissection of the RPC-specimen, extirpation, and further reconstruction. The extirpation of the specimen in all three was re-resection of the entire pancreatojejunoanastomosis, proximal resection of the remnant of the pancreas to subtotal pancreatectomy, without pancreatojejunoanastomosis-blind stump. In 2 cases resection of the efferent pancreatojejunal loop was proximally from and with preservation of the hepaticojejunoanastomosis. In patient 1, suffering from obstructive jaundice, a complete efferent hepaticojejunal loop was also resected, altogether with the hepaticojejunoanastomosis. In the same patient, a partial-marginal resection of the superior mesenteric artery (SMA) was imposed due to infiltration of the RPC, exactly at the origin site of the first jejunal artery, with primary reconstruction (Figure 3). The digestive reconstruction was carried out with Roux-en-Y procedure, in all three cases (Figure 1b.). As mentioned before, one

Table 1. Patients' characteristics

Patient	Age	Staging pTNM at the first op	Type of procedure, number of lymph nodes retrieved	Other treatments	Disease free period (months)	Topography of the recurrence	Post-recurrence procedure	Other treatment after re-resection
1.	65	Iib	Extended Whipple procedure, 28 lymph nodes	Chemotherapy postoperatively	16	Preaortocaval lymph nodes	Re-resection of the pancreatojejunal anastomosis+hepaticojejunal anastomosis+resection of the SMA	Chemotherapy postoperatively
2.	69	IIa	Extended Whipple procedure, 26 lymph nodes	Chemotherapy postoperatively	20	Pancreatic stump	Re-resection of the pancreatojejunal anastomosis	Chemotherapy postoperatively
3.	73	Ib	Extended Whipple procedure, 21 lymph nodes	Chemotherapy postoperatively	23	Peripancreatic lymphatic tissue, station 18	Re-resection of the pancreatojejunal anastomosis, portal vein resection	Chemotherapy postoperatively

PRC was on the pancreatic stump (patient 2), one was on the peripancreatic lymphatic tissue (patient 3), 18 station below the inferior edge of the pancreas, with dorsal abutment-shift of the portal vein, leading to a complete dissection and partial portal vein resection with direct reconstruction, and patient 1, with RPC at the preaortocaval lymph nodes, 16 station, with infiltration of the efferent jejunal loop (jaundice), also first jejunal artery leading to a complete dissection and partial SMA resection with direct reconstruction. We avoided total pancreatectomy; the estimation was to facilitate the postoperative course and management, despite so-

me authors who propose a total pancreatectomy, and refer good results thereafter.

All three patients survived; there was not perioperative mortality. In all three, the morbidity was expressed with present postoperative pancreatic fistula (POPF) A. The POPF was pancreatic occlusion failure (POF) type, explaining the expected desirable postoperative course. In 2 patients, there was a wound infection, and one suffered from delayed gastric emptying. There were no other complications or advert events affecting the morbidity.

Two of the patients with low outlet POPF were dismissed on the 15th and 17th postoperative day, after removal of the drains. The third patient had high outlet of the POPF, over 200 ml/24 h, and was released on the 12th postoperative day with remained soft silicon drain in the neighborhood of the pancreatic stump, presenting controlled POPF (POF) type A. After 3 weeks and decreased outlet, the drain was removed. The postoperative pathohistology findings were R0 in 2 patients, and R1 in patient 2, although perioperative frozen section probes were R0 in all three.

Concerning the survival, the patient with R1 at the reoperation, 11 months after this re-surgery presented with advanced stage of the disease, liver metastases, and died 14 months after surgery. The second one, had 15 months of disease-free period, overall survival of 22 months, and perished with peritoneal dissemination, while the third is still alive, disease-free, 110 months after surgery. The average, medial postoperative overall survival is approximately 48 months.

Discussion

Pancreatic cancer is a severe disease, leading to unsatisfactory outcome after all efforts and improvement of

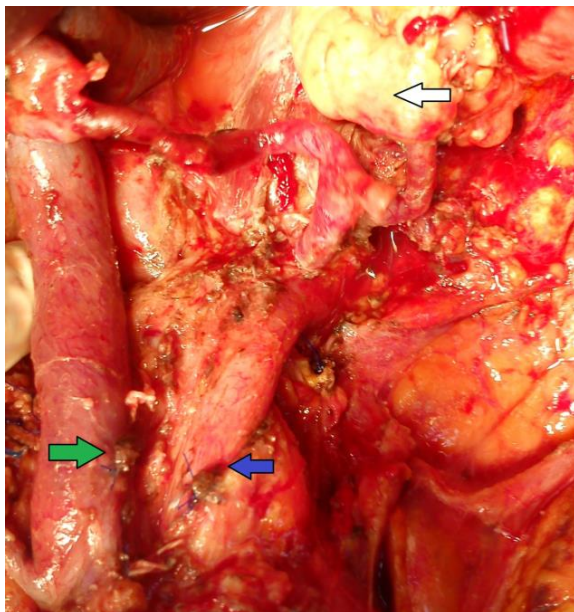


Fig. 3. Partial-tangential resection of the SMA, with primary reconstruction-suture Pancreatic remnant-blind stump after subtotal pancreatectomy, white arrow, Resected and reconstructed SMA, blue arrow, Resected and ligated splenic vein, green arrow

the management so far. Pertinent data refer 24% survival for 1 year, below 10% for 5 years overall [1]. Disappointing data suggest 80% of the radically operated patients who develop RPC, which is even worst for cure, management, and prognosis [1-3]. The treatment of these patients with RPC is still interfered with bias, ambiguity, and insufficient confidence affecting the decision for further treatment. Also, one major group of patients after DP, with high potent malignancy of the PDA, express RPC in the first 6 months, during the adjuvant chemotherapy, defined as local-pancreatic stamp, lymph node, or distant metastases, which is very common for R1 resection [3]. When the relapse of the disease is disseminated with distal metastases, the option is clear, chemotherapy and radiotherapy [4], **but the big dilemma is what is to be done with patients with localized-isolated RPC?** A highly demanding surgical procedure and technique on one hand, and uncertain perioperative and postoperative outcome and benefit on the other hand, lead most of the clinicians to negative attitude concerning surgery of RPC. Therefore, so far, a multimodal radiochemotherapy has been proposed [4]. The lack of data and clinical trials involving these particular patients devoid us from a clear protocol for further management, i.e., surgical treatment. The main ambiguity concerning surgery of RPC is: Does surgery contribute to be of benefit for patients' quality of life, or does it improve OS? One retrospective analysis from 2009, (PRISMA-Preferred Reporting Items for Systematic reviews and Meta-Analysis), revealed the extension of the OS after surgical treatment of the isolated local RPC to 26 months, disease-free period 14 months on average, comparing to multimodal radio and chemotherapy treatment only, where median survival was 14 months [5]. In our study, patients had an average 48 month-postoperative median survival after surgical removal of the RPC (14, 22, 110 months). On the other hand, we had only 3 resectable RPC from 223 cases, which is 1.34%, while in other studies there were 6.4%, 82 from 1281 cases [5]. This outcome for the postoperative OS in our small series is likely to be better comparing to other centers and studies (48 vs. 26), and particularly may be amid early diagnosis of the RPC in these three patients, which was at the time of asymptomatic onset of the recurrence (with an exception of one patient, suffering from jaundice because of the efferent loop obstruction), based on increased level of tumor markers (CA 19-9, VEGF), PET scan and CECT, without gross infiltration of the surrounding tissues. Also is inevitable good quality control of the radicality of the re-do procedure, maintained in one single attending surgeon. On the other hand, a significantly smaller rate of resectability reveals late diagnosis generally, when surgery is no more applicable and beneficial. Another study was conducted on 17 patients re-operated for suspected or proven RPC. Of 17, re-resection was possible in only 5

patients, while others underwent a palliative procedure. Of these 5, 3 were proven chronic pancreatitis post-operatively, while only 2 RPC. Only 2 of 14 patients with malignancy were operable and feasible for re-resection and re-anastomosis [6]. Because of the high perioperative mortality (6 %) in this series, this study would suggest a higher level of selection of patients undergoing surgery for RPC. Improved selection and more strict inclusion criteria may be achieved by EUS guided biopsy, PET Scan, tumor markers, etc., thus avoiding re-do surgery for benign reasons.

One German study revealed encouraging data. Patients with re-resection of the isolated RPC, had a significantly longer median survival after resection, 26.0 months, in comparison with non-resected patients, 10.8 months, ($p=0.0104$). This outcome favors the decision of aggressive approach if isolated RPC is diagnosed, as a feasible and curative procedure with low perioperative morbidity (25%) and mortality (1.8%) [7].

Moreover, probably the most beneficial and promising subgroup of these patients are those with RPC of the pancreatic stamp. In this series, six patients with isolated RPC of the stump were submitted to total pancreatectomy. There was no morbidity or mortality in the series. The median survival after reoperation was 27.5 months, also significantly higher than in non-operated patients [8].

Another similar retrospective study was conducted on 11 patients, suffering from RPC of the pancreatic stump. After the completion of the pancreatectomy, the result of the median survival was even better and more encouraging, up to 44 months [9-11]. It is also important to mention that there was no significant difference in the mortality between the results in the studies, (Fisher's Exact Test = 1.622), $p>0.05$ ($p=0.540$).

These promising results, although from a small series and various centers, motivated the clinicians to observe and much more freely and easily to adopt the aggressive and beneficial attitude to RPC [10,11]. In order to improve the management and prognosis in these patients, surgeons have made a further step, an aggressive approach in patients with solitary lung and liver metastases, which would be an issue for discussion in the future [12]. The only absolute contraindication remains peritoneal carcinosis.

Comparing the results from our series to those referred by other studies, we support and adopt the aggressive attitude to radical surgical treatment for isolated RPC. The main goal should be the improvement of OS, and particularly disease-free period. Moreover, the firm suggestion for surgery is low morbidity and mortality, despite the demanding and challenging procedure (in our series none).

Conclusion

The results regarding the active surgical attitude to

isolated RPC overwhelm the conservative approach with radio-and chemotherapy only. The meticulous dissection, extirpation of the RPC with R0, malignancy-free margin, is the aim which imposes to be reached. It is a safe and feasible procedure and treatment in specialized institutions with experienced surgical teams. The mainstream favoring this approach are the obtained data-results for median and overall survival after radical re-operation.

However, the number of patients treated in this manner is still small, and further high volume clinical multi-center trials would have to be conducted in order to achieve consensus concerning this management.

Finally, the additional issue we observed, supplementing this ensemble of topics of RPC is the extension of the primary done DP. In our series, all three patients with resectable RPC were recruited from the extensive duodenopancreatectomy group with extended lymph node dissection, D3. This fact, despite the small series, may suggest the extensive duodenopancreatectomy leads to a higher frequency of resectable RPC, an observation also deserving further high clinical trials.

Conflict of interest statement. None declared.

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