

ВЕНОЗНЫЕ РЕЗЕКЦИИ И РЕКОНСТРУКЦИИ В ХИРУРГИИ РАКА ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ

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Цель. Оценить результаты венозных резекций при опухолевой инфильтрации венозной стенки при раке поджелудочной железы (РПЖ).

Материал и методы. В исследование включены 74 пациента с РПЖ и опухолевой инвазией стенки мезентерико-портальной системы (T3 N0-1 M0). Сравнение проводили с группой больных (n=53), получающих паллиативную химиотерапию. Средний возраст больных в группе хирургического лечения $61,8 \pm 9,8$ лет, в группе контроля – $63,2 \pm 10,1$ года ($p > 0,05$), средний диаметр опухоли составил 39 мм и 43 мм соответственно ($p > 0,05$). В группе с хирургическим лечением в 62 случаях опухоль локализовалась в головке поджелудочной железы (ПЖ), пациентам выполнена панкреатодуоденальная резекция с венозной резекцией. В остальных случаях (n=12) опухоль располагалась в теле ПЖ, выполнена корпорокреомическая резекция ПЖ с венозной резекцией.

Результаты. В раннем послеоперационном периоде тромбоз зоны реконструкции развился у 2,7% больных, кровотечение – 1,4%. 30-дневная послеоперационная летальность составила 4,1%. Медиана выживаемости при хирургическом лечении РПЖ с венозной резекцией была выше по сравнению с паллиативной химиотерапией: 19 мес. vs 13 мес., $p < 0,05$. В группе с венозной резекцией наиболее низкая годовая выживаемость (46,2%) выявлена у больных с краевой резекцией вены. При прямом венозном анастомозе и венозном протезировании не выявлено значимых различий в показателях выживаемости (66,7% vs 63,2%, $p > 0,05$).

Выводы. Ангиопластические вмешательства, позволяющие достичь микроскопически полной резекцией опухоли при РПЖ с опухолевой инфильтрацией мезентерико-портальной системы, позволяют улучшить выживаемость пациентов по сравнению с паллиативной химиотерапией.

Ключевые слова: рак поджелудочной железы; инфильтрация вены; венозная резекция.

VENOUS RESECTIONS AND RECONSTRUCTIONS IN SURGERY OF PANCREATIC CANCER

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Aim. To evaluate results of venous resections in tumor infiltration of venous wall in pancreatic cancer (PC).

Materials and Methods. The study included 74 patients with PC and tumor invasion of the wall of the mesenteric-portal system (T3 N0-1 M0). The control group included patients (n=53), receiving palliative chemotherapy. The average age of patients in the group of surgical treatment was 61.8 ± 9.8 years, in the control group – 63.2 ± 10.1 years ($p > 0.05$), the average diameter of the tumor was 39 mm and 43 mm, respectively ($p > 0.05$). In 62 cases of the group of surgical treat-



ment the tumor was located in the head of pancreas (P), the patients were conducted pancreaticoduodenal resection with venous resection. In the rest of cases (n=12) the tumor was located in the body of P, corporocaudal resection of P was conducted with venous resection.

Results. In the early postoperative period 2.7% of patients developed thrombosis of the reconstruction zone, 1.4% developed bleeding. 30-Day postoperative lethality was 4.1%. Median survival in surgical treatment of PC with venous resection was higher in comparison with palliative chemotherapy: 19 months vs 13 months, $p < 0.05$. In the group of venous resection the lowest annual survival (46.2%) was noted in patients with marginal resection of the vein. No significant differences were found in the parameters of survival with use of direct venous anastomose and venous prosthetics (66.7% vs 63.2%, $p > 0.05$).

Conclusions. Angioplastic interventions permitting to achieve microscopically complete resection of the tumor in PC with tumor infiltration of mesenteric-portal system, permit to improve survival of patients in comparison with palliative chemotherapy.

Keywords: *pancreatic cancer; venous infiltration; venous resection.*

Pancreatic cancer (PC) is the leading course of death from malignant neoplasms (MNs) – mortality of patients within a year after the diagnosis is 66.9% [1]. Moreover, in recent 5 years, morbidity with PC shows a tendency to grow (from 10.5 to 13.5 per 100 000 population). Due to late manifestation of symptoms, PC has the highest index of late diagnosis – 58.9%, and of the lowest index of accumulation of patient population with MNs – 1.3. Therefore, only a small part of patients are candidates for radical surgical intervention. With this, in 18.3% of patients the tumor is diagnosed in the stage of a regional (borderline resectable) process with spread to the major vessels and adjacent organs [2,3].

At present, infiltration of venous wall with tumor cell in PC is not considered a non-resectable condition. There are available different technical variants of vein resection and reconstruction depending on location of the tumor and the extent of damage to large vessels [4,5]. Angioplastic interventions are important in PC, since they help maintain perfusion of the liver and venous outflow from the small intestine. Total resection (R0) is the only variant of treatment of patients with PC that improves parameters of survival. Tumor infiltration of the large vessels, a possibility for their resection and reconstruc-

tion is one of the greatest problems in surgery of PC, since it determines the border between a radical and palliative operation.

A golden standard for evaluation of resectability of PC is computed tomography (CT) of the abdominal cavity with contrast enhancement [6]. Here, according to M.R. Porembka, et al. (2011), standard CT is not considered a high-precision method of diagnosis of tumor invasion of the venous wall and has low sensitivity – 60% [7]. Sensitivity of CT with contrast enhancement is much higher. Thus, M. Kim, et al. in their study (2018) evaluated the preoperative CT parameters predicting invasion of the vessel wall. According to the authors, predictors of invasion are size of the tumor and its contact with the vein, here, sensitivity may reach 87%. Contact of the tumor with 0 to 90° of the vein circumference increased the risk for tumor invasion almost 4 times, with 90° to 180° – 20 times, if the tumor encloses most of the vein circumference (more than 180° contact), the risk increases 47 times [8].

According to the clinical recommendations of American oncologists (NCCN, version 1.2020), and the data of the International Study Group of Pancreatic Surgery (ISGPS), *PC is considered resectable in the absence of contact with the main venous or arterial vessels, and borderline resectable –*

in case of suspicion of infiltration of the wall of the superior mesenteric vein (SMV) and/or of portal vein (PV) with a possibility for reconstruction. A limited lesion of the common hepatic artery (CHA) at the site of branching of the gastroduodenal artery with a possibility for angioplasty is also referred to a borderline resectable process [4,9].

On suspicion of the tumor infiltration of the venous wall, most oncologists recommend surgical intervention in the first stage. If limited infiltration of the artery is suspected, treatment should start with neoadjuvant therapy with subsequent evaluation of resectability of the tumor, however, the decision may be taken individually. *An extended lesion with the tumor enclosing the circumference of the superior mesenteric artery or celiac artery by more than 180°, or spread of the process to the wall of the aorta, is considered non-resectable condition.*

Possibilities for venous reconstruction depend on spread of the tumor infiltration of the wall and may be divided to four types, according to the classification of ISGPS [4]:

- type I – spread of the tumor along the semicircumference of the vein permits to perform marginal resection with the primary suturing of the vein;
- type II – spread of the tumor along the semicircumference of the vein with a possibility of closure of the defect with a patch;
- type III – circular enclosure of the vein with the tumor that requires circular resection with application of end-to-end anastomosis;
- type IV – resection of a segment of vein more than 4-5 cm in length requires prosthetics with an autovein or synthetic prosthesis [10].

Thus, at present vein resection is not an obstacle for surgical treatment in PC with suspicion of invasion of the venous wall. The *aim* of the given study was analysis of the immediate and long-term results of vein resections in pancreatic cancer.

Materials and Methods

The study involved 74 patients with PC and tumor invasion of the wall of SMV/PV (T3 N0-1 M0) according to the data of CT with bolus tracking used in the surgical stage of treatment in National Medical Research Institute of Oncology in 2015-2019. The control group (53 patients with PC and tumor invasion of the wall of SMV/PV) was selected retrospectively. Patients of the control group received palliative chemotherapeutic treatment (PCT) (gemcitabine, capecitabine).

In the group of surgical treatment in 62 cases the tumor was located in the head of pancreas (P), patients were performed pancreaticoduodenal resection with resection of vein. In the rest of cases (n=12) the tumor was located in the body of pancreas; corporocaudal resection of pancreas with resection of vein was performed. Clinical and demographic characteristics of the study cohort of patients are given in Table 1.

The most common condition was moderately differentiated ductal adenocarcinoma of pancreas; in 25.6% of patients draining of biliary ducts was conducted in the preoperative period. None of the patients received neoadjuvant chemotherapy.

According to TNM classification (8th edition, 2015, [11]), 26.8% of patients were diagnosed with IIA stage (25.7% in the group of surgical treatment and 28.3% in the group of PCT, $p>0.05$) and 73.2% – with IIB stage (74.3% and 71.7%, respectively, $p>0.05$).

Vein resection included resection of the PV, SMV and SMV/PV confluence. The zone of tumor infiltration most commonly spread to SMV and SMV/PV confluence (68 patients, 91.9%). In case of lesion of SMV/PV confluence and location of the tumor in the head of pancreas, ligation of splenic vein without restoration of the blood flow was not performed in a single case. The blood flow through splenic vein was restored through splenorenal shunting (application of end-to-side anastomosis). In prosthe-

Table 1

Characteristics of Patients with Infiltration of Venous Wall with PC

Parameter	Surgical Treatment	Palliative Chemotherapeutic Treatment	p
n	74	53	-
Age of patients, years	61.8±9.8	63.2±10.1	0.4
Men, abs. (% of n)	43 (58.1%)	31 (58.5%)	1
Localization of tumor:			
head, abs. (% of n)	62 (83.8%)	42 (79.2%)	0.8
body, abs. (% of n)	12 (16.2%)	11 (20.8%)	
Size of tumor*, mm	39 (24-53)	43 (31-57)	0.3
Differentiation of tumor:			
high, abs. (% of n)	18 (24.3%)	10 (18.9%)	0.5
moderate, abs. (% of n)	41 (55.4%)	27 (50.9%)	
low, abs. (% of n)	15 (20.3%)	16 (30.2%)	
Lesion of regional lymph nodes:			
N0, abs. (% of n)	19 (25.7%)	15 (28.3%)	0.8
N1, abs. (% of n)	55 (74.3%)	38 (71.7%)	
Preoperative draining of bile ducts, abs. (% of n)	19 (25.7%)	-	-

Note: * – the data are presented in the form of median, minimal and maximal values

tics of the venous segment, a polytetrafluoroethylene prosthesis with braiding was used. In most surgical interventions (61 operations, 82.4%) venous reconstruction was planned in the preoperative period.

Before the vascular stage, unfractionated heparin (UFH) was introduced intraoperatively at a dose 5000 UN. In the postoperative period introduction of anticoagulants was continued for prophylaxis of venous thrombosis. The dose of UFH and later of low-molecular heparins was selected on the basis of the data of coagulogram (activated partial thromboplastin time, fibrinogen, soluble fibrin-monomer complexes, D-dimers, antithrombin).

Prosthetics of mesenteric-portal segment was conducted in 20 patients (27.0%). Resection of SMV/PV confluence with prosthetics was required in 8 cases (10.8%), of SMV – in 12 cases (16.2%). The most common type of reconstruction of the venous segment was direct end-to-end anastomosis – 55.4%. Circular resection of SMV with anastomosis was conducted in 36 patients (48.6%), in two cases ligation of the vein of jejunum was required. In 5 cases (6.8%)

it was necessary to perform circular resection of the PV with application of anastomosis. Marginal (tangential) resection of the venous wall was rather rare – in 13 cases (17.6%), it was mostly performed in the period of introduction of vein resection in PC in our clinics. In recent time we practically do not use this type of vein resection in PC due to high frequency of a positive margin of resection.

In the postoperative period, adjuvant chemotherapy was conducted (gemcitabine, capecitabine). A possibility of observation and survival data for all the patients were available. In the postoperative period the patency of the angioplasty zone and postoperative complications were evaluated.

In postmortem examination, the margins of resection of the preparation were evaluated. The margins of resection of the preparation were preliminary marked with dye. R0 resection was considered the distance ≥ 1 mm from the tumor cell to the margin of resection, R1 – < 1 mm. Macroscopically positive margins of resection were referred to R2.

Calculations were performed in R program (version 3.2, R Foundation for Statisti-

cal Computing, Vienna, Austria). Medians in the groups were compared using Mann-Whitney test, frequencies were compared using Fischer exact test. Odds and qualitative values risk ratio was calculated using contingency tables. Statistical significance was evaluated using Fischer exact test. Odds and qualitative values risk ratio was calculated by construction of logic regression. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion

In the early postoperative period two patients (2.7%), developed thrombosis of the reconstruction zone and one patient (1.4%) developed hemorrhage. 30-Day postoperative lethality was 4.1% ($n=3$). The causes of lethal outcome were hemorrhage, mesenteric thrombosis and peritonitis.

Subtotal resection was macroscopically diagnosed in 2 patients (2.7%, Table 2). After

the final post-mortem examination, subtotal resection was found microscopically in 10.8% of examined preparations (with marginal resection of the venous wall – in 5 preparations, with direct anastomosis – in 2 preparations, with prosthetics of SMV – in one). Subtotal resection was performed in 38.5% of patients with marginal resection of the vein and venorrhaphy. Thus, the risk of subtotal resection of the tumor in this kind of venous resection increases 12-fold (OR with 95% confidence interval (CI) 12.19 (1.99-74.30)). With direct anastomosis and prosthetics, the positive margin of resection did not exceed 5% (4.9 and 5.0%, respectively) without any reliable difference depending on the reconstruction method ((OR with 95% CI 1.03 (0.09-12.04)). The highest frequency of R1 resection was found for retroperitoneal margin (6 preparations, 75%).

Table 2

Results of Surgical Treatment

Duration of operation*, min	450 (360-700)
Types of reconstruction:	
- venorrhaphy, n (%)	13 (17.6%)
- end-to-end anastomosis, n (%)	41 (55.4%)
- prosthetics, n (%)	20 (27%)
Duration of reconstruction*, min	19 (11-45)
Intraoperative blood loss*, ml	450 (350-1500)
Length of vein excision*, mm	30 (20-55)
Totality of resection:	
R0, n (%)	63 (85.1%)
R1, n (%)	9 (10.8%)
R2, n (%)	3 (4.1%)
Quantity of removed lymph nodes*	18 (7-36)
Postoperative complications:	
- pancreatic fistula, n (%)	9 (12.2%)
- gastrostasis, n (%)	11 (14.9%)
- hemorrhage n (%)	1 (1.35%)
- thrombosis of reconstruction zone, n (%)	2 (2.7%)
- peritonitis, n (%)	2 (2.7%)

Note: * – the data are presented in the form of median, minimal and maximal values

Median of survival in surgical treatment of PC with resection of vein was higher in comparison with palliative chemotherapy (19 against 13 months, $p < 0.05$). In the group of surgical treatment of PC, the lowest annu-

al survival rate was noted in the group with marginal resection (46.2%). No significant differences were found in the parameter of survival between the direct venous anastomosis and venous prosthetics (66.7% and

63.2%, respectively, $p > 0.05$). Microscopically total R0 resection of the tumor improves survival rate of patients ((risk ratio (RR) 3.66; 95% CI 2.09-6.38)). As compared to

the group of PCT, survival rate in the group of surgical treatment was twice higher (RR 2.16; 95% CI 1.05-4.47, Table 3).

Table 3

Parameters of Survival Rate of Patients Depending on Type of Treatment

Parameter	Surgical Treatment	Palliative Chemotherapeutic Treatment	p
Survival rate:			
In one year, n (%)	44 (62.0%)	26 (49.1%)	<0.05
In two years, n (%)	17 (23.9%)	5 (9.4%)	<0.05

Thus, the given results demonstrate a possibility of venous resection and reconstruction in PC with admissible level of postoperative complications, morbidity and lethality.

In the study of S. Mohammed, et al. (2018), 51 cases of PC with vein resection were analyzed and it was shown that *the vascular stage does not increase the morbidity, but is often complicated with thrombosis of the reconstruction zone*. Frequency of thromboembolic complications in patients with and without vein resections was comparable (4.0% against 3.2%, $p = 0.678$), and frequency of thrombosis of the reconstruction zone made 8.3%. Although no statistically significant factors influencing development of thrombosis of SMV/PV were found, its higher frequency was noted in prosthetics of vein. On the basis of these data it may be suggested that *SMV/PV thrombosis was associated with technical peculiarities of reconstruction of venous segment rather than with disorders in the system of hemostasis*. It was also shown in the study that subtotal resection leads to 2-fold reduction of the general survival rate.

In our work, similar data were obtained in relation to survival rate of patients with vein resection in PC – *total resection influences the parameter of survival in this category of patients*. However, in our study the frequency of thrombosis of the reconstruction zone was lower.

The data of S. Hoshimoto, et al. (2017) do not show any difference in the general survival rate between patients with and with-

out venous invasion. Authors showed in the multivariant analysis that independent factors influencing survival, include invasion of the arterial wall, metastases to lymph nodes, histologically confirmed invasion of the venous wall and adjuvant chemotherapy. However, the depth of tumor invasion of the venous wall did not influence survival of the patients with vein resection [15].

R. Bell, et al. (2017) in meta-analysis evaluated the influence of the status of resection margin on survival of patients. Patients with R1 vein resection had higher frequency of perineural invasion and larger size of tumor. Nevertheless, postoperative morbidity and 1- and 3-year survival rate did not differ from those in standard interventions [16].

The work of M. Podda, et al. (2017) presents the results of 10-year period of surgical treatment of PC with vascular resections: the rate of postoperative complications and median of survival in the intervention with vein resection and in standard intervention were comparable [17].

In meta-analysis of W. Song, et al. (2017), no differences were found in the frequency of postoperative complications and lethality in comparison with other types of reconstructions. Here, the authors indicate reliably higher frequency of thrombosis of the reconstruction zone with use of autovein [18].

In the study of D. Kleive, et al. (2017), patients with PC with tumor infiltration of the venous wall who underwent end-to-end venous anastomosis and prosthetics with allogenic vein,

were compared. In result, with use of allotransplant, the rate of severe stenoses (more that 70%) reached 61.9%. The main causes of stenosis, in the opinions of the authors, were local recurrence (73.1%) and thrombosis (11.5%) [19]. In our study we did not use an autovein because of technical difficulties of its taking, expansion of the volume of surgical intervention and higher risk of stenosis and thrombosis of the reconstruction zone.

In 2018 the study of X. Zhang, et al. was published presenting the results of vein resections and reconstructions with satisfactory 1-year survival rate reaching 62.9%, and with recurrence-free survival 43.9% [20]. We obtained similar results for 1-year survival after vein resections in PC. The parameter of recurrence-free survival was not evaluated bearing in mind incorrect comparison by this parameter of the group with surgical intervention and the group with palliative chemotherapy.

In the Italian study of Nigri G., et al. (2018), the data of patients with vein resection in PC are given for 25-year period, and the main prognostic factors are shown to be a damage to the regional lymph nodes and histologically confirmed invasion of venous wall [21].

According to the work of O. Kantor, et al. (2018) including 977 venous resections in PC, a significantly higher frequency of postoperative complications (hemorrhages and thrombosis) and lethality takes place in ex-

pansion of the volume of surgical interventions in the vascular stage. The highest frequency of complications was found in prosthetics of venous segment [22]. It can be suggested that this fact is associated with technical complexity of prosthetics in comparison with application of end-to-end anastomosis.

Conclusion

Despite increased frequency of angioplastic interventions in oncology, it needs improvement of techniques of vascular resection, investigation of influence of the extended surgical interventions on survival and of the peculiarities of postoperative management of patients. Vein resection and reconstruction in PC may be performed safely and with satisfactory results.

In our study the frequency of postoperative complications and 30-day lethality after vein resection in pancreatic cancer was comparable with the results of the majority of previous studies. We think that low frequency of thrombosis of the reconstruction zone results from use of the appropriate anticoagulant therapy and techniques of angioplastic reconstructions. Parameters of the general survival rate agree with the results of observations of the majority of researchers.

Surgical treatment of regional pancreatic cancer with spread to the venous wall permits to improve parameters of survival of patients in comparison with palliative therapy.

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