SINGLE VEIN RESECTION IN SURGERY FOR PANCREATIC DUCTAL CARCINOMA AS A CRITERION OF RESECTABILITY

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Abstract

Background. Pancreatic ductal carcinoma (PDC) with involvement of the superior mesenteric vein (SMV) or/and portal vein (PV) remains a discussible subject. We have evaluated vein invasion as a criterion of borderline resectability and long-term outcome. Material and Methods. In our center, 68 patients underwent either 65 standard pancreatoduodenal resections or 3 pancreatoduodenectomies for PDC. Resection of SMV/PV was performed in 18 cases (26.5 %). Three patients received neoadjuvant chemotherapy (NACT), and adjuvant chemotherapy (ACT) was assigned to 37 patients (54.4 %). Results. Morbidity (42.0 vs 50.0 %, p=0.590) and mortality rates (4.0 vs 16.7 %, p=0.111) had no significant differences in groups of standard and angioplasty operations respectively. ACT was completed in 10 (16.7 %) patients only. There was true vein invasion in 12 of 18 patients with vein resection. pN+ (p=0.012) and angioplasty by itself (p<0.001) were found out as independent predictors of overall survival (OS). The median OS was 9.4 mo in patients with vein resection. In the group of standard operations, the median OS was 26.9 mo (p<0.001). The median OS in patients with vein resection and complete chemotherapy was 17.7 mo in contrast to 8.9 mo in those who did not receive chemotherapy (p=0.439). Conclusions. PDR with vein resection and incomplete chemotherapy cannot be regarded as a reasonable procedure. PDR with vein resection may be appropriate after efficient NACT.

Key words: carcinoma, pancreatic ductal, portal vein, angioplasty.

ИЗОЛИРОВАННАЯ РЕЗЕКЦИЯ ВЕНЫ В ХИРУРГИЧЕСКОМ ЛЕЧЕНИИ ПРОТОКОВОЙ КАРЦИНОМЫ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ КАК ФАКТОР РЕЗЕКТАБЕЛЬНОСТИ

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Аннотация

Лечение протоковой карциномы поджелудочной железы (ПКПЖ) с вовлечением верхней брыжечной и/или воротной вен — это предмет дискуссий. Мы оценили венозную инвазию как критерий пограничной резектабельности и долгосрочного прогноза заболевания. Материал и методы. В нашем центре 68 пациентов оперированы в объеме стандартной панкреатодуоденальной резекции (n=65) или панкреатодуоденэктомии (n=3) по поводу ПКПЖ. В 18 (26.5 %) наблюдениях выполнена резекция верхней брыжечной и/или воротной вены. Неoadъювантную химиотерапию (НАХТ) получили 3 пациента, адвьюантная химиотерапия (АХТ) начата у 37 (54.4 %) пациентов. Результаты. Частота
Introduction
So far treatment of pancreatic ductal carcinoma (PDC) has been discussible [1, 2]. While the best results have been shown in patients undergoing surgery with chemotherapy, the choice of the adjuvant (ACT) or neoadjuvant (NACT) regime remains unclear. Many investigators demonstrate advantages of NACT such as marginal but significant improvement of the overall survival and increased rate of R0, N0 resections [3–5]. On the other hand, according to several reports these benefits have been achieved in “per protocol” analyses only, whereas there were no significant differences in the frame of the “intention-to-treat” concept. It could be because up to 27% of patients did not enter the surgical protocol due to either tumor progression against the background of chemotherapy or intolerable adverse effects [1, 6, 7]. Nevertheless, the latter evidence cannot be a reason for “up-front” surgery since as few as 55–57% of patients who underwent the “surgery first” protocol obtain complete ACT due to early progression, postsurgical complications, and deaths [8, 9]. Besides, current meta-analyses focused on this problem do not avoid biases most of the time and their authors accentuate high difficulty in retrieving data that strictly meet inclusion criteria [1, 10, 11].

Assessment of the tumor extent is another important aspect that affects the choice of treatment. While either primary resectable or locally advanced tumors are believed to be quite determined groups, the so-called borderline resectable malignancies cannot be defined properly. Anderson’s criteria proposed in 2009 are based on radiological findings only. Some authors mention the uncertainty of borderline resectability which can depend not only on anatomical but also on subjective and technical predictors (surgical modality, experience, equipment, etc.) [12, 13]. All this provides “migration” of potentially resectable tumors to the group of unresectable locally advanced ones, thus surgical exploration as a final diagnostic procedure becomes warranted [13, 14].

Nowadays “up-front” surgery is regarded as an acceptable procedure in case of isolated involvement of the vein [2, 15]. Necessity and availability of arterial resection are expected to be utterly rare in pancreatic surgery [16]. On the other hand, we believe that isolated vein involvement should not be a contraindica-

Material and Methods
In our department, 120 patients underwent pancreateoduodenal resection (PDR) or pancreateoduodenectomy (PDE) within a period from 2014 to 2021. According to inclusion criteria we picked up patients with PDC only who underwent PDR or PDE with/without resection of the superior mesenteric or/and portal vein. All arterial resections were excluded. Finally, the total investigated group included 68 patients, 34 males and 34 females (50.0%). The age range was 43–79 years with an average of 63.3 ± 8.1 years. pT1 tumor was observed in 5 patients (7.4%), pT2 – in 2 (2.9%) and pT3 – in 61 (89.7%). Regional lymph node metastases (pN+) were found in 29 cases (42.6%), all of them were N1. There was the following stage distribution: IA – 5 (7.4%), IB – 1 (1.5%), IIA – 33 (48.5%), IIB – 23 (33.8%), III – 1 (1.5%), IV – 5 (7.4%). Stage IV was determined by paraaortic metastases in 3 patients and by the solitary liver metastasis – in 2 ones.

PDR and PDE were performed as a standard procedure with lymph node dissection including groups 3b, 4d, 5, 6, 8, 9, 12V, 12P, 12D, 13, 14V, 14A, 17 according to the modified classification of Japanese Research Society for Gastric Cancer (1962). Paraaortic lymph nodes (group 16) were excised in case of proven metastases only (3 patients). The restoring stage of the surgery was executed by pancreaticojejunoscopy, hepaticojejunoscopy, and gastrojejunostomy in this sequence using the single intestinal loop.

In the case of the dilated pancreatic duct, we performed two-layer anastomosis by sewing the duct up separately with interrupted sutures (polypropylene 6–0 or 7–0). Such a technique was employed in 55 patients (89.9%). In the case of the non-dilated pancreatic duct, we performed sleeve-like pancreaticojejunoscopy without a separate connection of the duct (14.7% of patients). There were three PDEs. Hepaticojejunoscopy was accomplished by running suture (polypropylene 5–0 or 6–0). One metastasectomy and one S2,3-liver
resection were concomitants in two patients with stage IV, respectively.

Patients with superior mesenteric (SMV) or/and portal (PV) vein involvement were considered to be candidates for vein resection if it did not require multiple vascular anastomoses of SMV confluents. PV resection was performable most of the time. Lateral SMV/PV resection with closing the defect by running suture (polypropylene 6–0) was made in 4 patients. Sleeve SMV/PV resection (Fig. 1) with direct suturing of vein cuffs was made in 7 patients and with prosthesis replacement (Fig. 2) in 6 cases. Closure of the vein defect with a patch (Fig. 3) was performed in one patient. There were 18 (26.5 %) vascular resections altogether. In all cases, we used polytetrafluoroethylene prostheses and the running suture (polypropylene 6–0).

The performance status of patients was assessed according to the ECOG scale. Postoperative pancreatic fistulas were defined in accordance with International Study Group for Pancreatic Surgery (ISGPS) classification, 2016. Data were processed and calculated with the statistical package SPSS Statistics v. 17.0. Descriptive statistics, cross-tabulation, two-tailed Fisher's exact test, Cox regression analysis, Kaplan-Meier analysis were employed.

Results

Post-surgical complications were observed in 30 (44.1 %) patients. There were 19 (27.9 %) complications in grade II, 5 (7.4 %) – in grade IIIb, 1 IV (1.5 %) – in grade, and 5 – in grade V (7.4 %) according to the Clavien–Dindo classification (Table 1). Causes of death were as diverse as the myocardial infarction (1), the pancreonecrosis (2), the pancreatic fistula type C (1), intestinal anastomosis leakage with the consequent peritonitis (1).

Post-surgical complications were registered in 21 (42.0 %) patients after standard PDR and in 18 (50.0 %) cases after angioplasty PDR/PDE. This difference was not significant (two-tailed Fisher's exact test, p=0.590). The post-surgical mortality rate was 4.0 % (2 of 50) in the standard group and 16.7 % (3 of 18) in the angioplasty group. This difference was not significant either (two-tailed Fisher's exact test, p=0.111). It should be noted we have not observed specific vascular complications which ended up with death.

There were only 12 of 18 cases of true vein invasion according to pathologists' reports. 40 (58.8 %) patients received chemotherapy. NACT was assigned in 3 (4.4 %) patients and ACT in 37 (54.4 %) ones. The following regimes were applied as preoperative or postoperative modalities: FOLFIRINOX, GEMOX, GEM, GEMCAP, XELOX, FOLFOX, FOLFIRI, capecitabine, and 5-fluorouracil as monotherapy.

Twenty-three patients did not receive ACT for the following reasons: early tumor progression (4), post-surgical complications (5), PS ECOG≥3 (4), patient's refusal (10). All patients completed NACT. Only 10 (16.7 %) of the remaining 60 patients received appro-

### Table 1/Таблица 1

<table>
<thead>
<tr>
<th>Complications/Осложнения</th>
<th>Rate/Частота</th>
</tr>
</thead>
<tbody>
<tr>
<td>DGE grade A/Гастростаз степень A*</td>
<td>12 (17.6 %)</td>
</tr>
<tr>
<td>DGE grade C/Гастростаз степень C</td>
<td>1 (1.5 %)</td>
</tr>
<tr>
<td>Stomach bleeding/Желудочное кровотечение</td>
<td>2 (2.9 %)</td>
</tr>
<tr>
<td>Myocardial infarction/Инфаркт миокарда</td>
<td>1 (1.5 %)</td>
</tr>
<tr>
<td>Bile anastomosis leakage/Несостоятельность гепатикоеюноанастомоза</td>
<td>1 (1.5 %)</td>
</tr>
<tr>
<td>Intestinal anastomosis leakage/Несостоятельность колоэнтероанастомоза**</td>
<td>1 (1.5 %)</td>
</tr>
<tr>
<td>Pancreatitis/Панкреатит</td>
<td>1 (1.5 %)</td>
</tr>
<tr>
<td>Pancreonecrosis/Панкреонекроз</td>
<td>2 (2.9 %)</td>
</tr>
<tr>
<td>Liver failure/Печеночная недостаточность</td>
<td>1 (1.5 %)</td>
</tr>
<tr>
<td>Pneumonia/Пневмония</td>
<td>1 (1.5 %)</td>
</tr>
<tr>
<td>Biochemical leak/«Биохимическая несостоятельность»*</td>
<td>1 (1.5 %)</td>
</tr>
<tr>
<td>Pancreatic fistula type В/Панкреатическая фистула тип В*</td>
<td>2 (2.9 %)</td>
</tr>
<tr>
<td>Pancreatic fistula type С/Панкреатическая фистула тип С*</td>
<td>3 (4.4 %)</td>
</tr>
<tr>
<td>Stomach ulcer/Язва желудка</td>
<td>1 (1.5 %)</td>
</tr>
<tr>
<td>Total/Всего</td>
<td>68 (100.0 %)</td>
</tr>
</tbody>
</table>

Note: * – in accordance with the current International Study Group for Pancreatic Surgery (ISGPS) classification. DGE, delayed gastric emptying; ** – the patient has undergone PDE with right-sided hemicolectomy.

Примечание: * – в соответствии с текущей классификацией International Study Group for Pancreatic Surgery (ISGPS); ** – пациенту выполнена ПДЭ с правосторонней гемиколэктомией.
appropriate adjuvant treatment. ACT was terminated in 27 patients due to developed intolerable toxicity (adverse effects) or worsening of PS ECOG ≥ 3.

Long-term results were assessed as standard modalities of disease-free survival (DFS) and overall survival (OS). Among three patients who underwent surgery after NACT, two died in 5.2 and 17.9 months, respectively, due to tumor progression. The third one has been alive for 16.8 months without recurrence of the tumor.

We have assessed independent predictors of DFS and OS based on the Cox regression analysis. The following variables were regarded as potential predictors: 1) age, 2) gender, 3) TNM-T, 4) pN+ (yes, no), 5) true invasion of the vein (yes, no), 6) complete NACT or ≥ 6 courses of ACT (yes, no), 7) postsurgical complications (yes, no), 8) tumor stage, 9) vein resection (yes, no).

The tumor stage IB (HR=80.5; 95 % CI, 2.9–2207.4; p=0.009), stage IIA (HR=10.5; 95 % CI, 1.3–87.3; p=0.030), stage IIB (HR=18.8; 95 % CI, 2.1–164.1; p=0.008), stage IV (HR=125.7; 95 % CI, 10.1–1571.7; p<0.001) and the presence of postsurgical complications (HR=0.3; 95 % CI, 0.1–0.8; p=0.010) were significant predictors of DF (the model $\chi^2=29.4$; p<0.001). pN+ (HR=2.4; 95 % CI, 1.2–4.9; p=0.012) and vein resection performed (HR=6.9; 95 % CI, 2.7–17.4; p<0.001) were the only predictors of OS (the model $\chi^2=24.5$; p<0.001).

In the group of vein resection, the median of OS was 9.4 mo (95 % CI, 5.3–13.5). Even 2-year survival has not been obtained and the maximum follow-up period was 17.9 mo. In the group of standard operations, the median of OS was 26.9 mo (95 % CI, 17.2–36.6), the 5-year survival was 29.4 ± 10.1 % . This difference was significant (Log Rank test, $\chi^2=18.7$, p<0.001). Plots of OS are given in Fig. 4.

Although NACT/ACT has not been revealed as an independent predictor of survival we evaluated OS of patients who underwent vein resection combined or not combined with complete NACT or 6 or more courses of ACT (NACT/6ACT). We limited ACT with 6 or more courses because our patients were assigned different regimes of chemotherapy due to diverse objectives, thus stratification of patients in accordance with particular anticancer agents was thought to be inappropriate statistically. Among patients without vein resection, the median of OS was 26.9 vs 29.9 mo in the group of NACT/6ACT and no chemotherapy, respectively (Log Rank test, $\chi^2=0.36$, p=0.546). Among patients with vein resection, analogous figures were 17.7 vs. 8.9 mo, respectively (Log Rank test, $\chi^2=0.60$, p=0.439) (Fig. 5).

Discussion
In the present investigation, we attempted to answer the question of whether vein invasion and, consequent
Vein resection can be regarded as a reliable and essential criterion of borderline resectability. On the one hand, some authors [2, 3, 11, 15] believe that vein resection has become a safe standard procedure and survival in this group is similar to that in the group of standard operations. On the other hand, after successful vein resection, the tumor is considered to be resectable as well as it becomes unresectable locally advanced in the case of failed angioplasty. The problem of borderline resectability is of interest nowadays [17]. Nevertheless, vein invasion can affect survival, this fact has not been reflected in the 8th edition of the TNM classification yet. Thereafter we analyzed only complete vein resections taking into account two aspects: 1) immediate results (safety of the procedure) and 2) survival in the group of accomplished angioplasty PDR/PDE compared to standard ones. In addition, we intended to make our investigation as close to “intention-to-treat” principles as possible but in the group of patients who can undergo complete surgery combined with NACT and/or ACT.

In a technical sense our conception of resectability, variants of angioplasty are determined perfectly well and in general, coincide with current classifications proposed [18].

While the relatively high rate of post-surgical complications is evident in our series, vein resection did not increase this rate significantly. Specific complications consequent to angioplasty were not registered at all. Besides, 2/3 of all complications were controlled and not life-threatening according to the Clavien–Dindo classification. M. Park et al. report analogous results with the rate of morbidity from 28.6 % to 38.6 % [19]. Postsurgical mortality rate was 7.4 % but non-significantly higher (p=0.111) in the group of vein resections. All three cases of death in this group have not been connected with vein resection, in our opinion. Therefore, we believe that vein resection may be regarded as a safe enough procedure which does not worsen a surgical outcome.

Some authors [20] consider true vein invasion to be a negative predictor of long-term outcomes. We have found out true vein invasion only in 12 of 18 patients with vein resection. In our series, true vein invasion did not affect DFS whereas the procedure of vein resection by itself appeared as a significant unfavorable predictor of OS. Thereafter vein resection may be approved as a technical demand only. According to current meta-analyses, NACT increases OS significantly but marginally in patients with PDC [4]. This was a reason for recommending it as a preferable treatment in many clinical guidelines. Unfortunately, in our series only 4.4 % of patients received NACT. Such a small amount of cases can be explained by the insufficiency of preoperative biopsies and our reserved attitude due to some controversial reports [7, 10]. M. Assifi et al. [6], S. Gillen et al. [7] informed on lack of significant efficacy of NACT, intolerable adverse effects, and failed tumor response, hence they lost over 20 % of patients.

In our investigation ACT was assigned to only 54.4 % of patients, which cannot be a satisfactory indicator. Approximately 65 % or more of patients end up ACT according to current reports. Besides, the majority of patients in our series could not undergo a complete course of ACT for reasons beyond
control. Only 10 (16.7%) patients have received six or more courses of ACT. We consider the treatment protocol to be complete in 13 of 68 (19.1%) patients. Such outcome cannot be satisfactory and reveals no advantages of ACT.

A tumor stage, postoperative complications, pN+, vein resection were independent significant predictors of DFS and OS, respectively, in the frame of the Cox regression analysis. Conclusions concerning a stage, post-surgical complications, and regional metastases are trivial and do not need to be discussed, in our opinion.

The negative influence of vein resection and angio-plastony on OS may be explained by a higher rate of occult metastases consequent to true vein invasion and bulky tumor extent [11]. This suspicion is thought to be a reason for providing further prospective investigations to change TNM-T similar to arterial invasion. We heard controversial reports on how vein involvement affects OS [15]. Although vein resection seems to be as safe as the standard PDR procedure, it should not be excluded from the criteria of borderline resectability because it discriminates PDC into different groups with diverse survival. Nevertheless, OS in the group of vein resections is expected to be much higher if NACN/ACT is complete. Although there was no significant difference of OS curvatures in our series (p=0.439), in the vein resection group with/without chemotherapy the effect size in patients with complete NACT/ACT was approximately twice as high (the median of OS 17.7 mo vs. 8.9 mo). We believe that the absence of statistical significance may be consequent to lack of cases and different efficacy of chemotherapy regimes. The median of OS after R0 PDR with vein resection and concomitant complete chemotherapy is expected to be as high as the median in the group of standard resections. This tendency has appeared.

Conclusion

Borderline resectable tumors are a fictitious heterogeneous group of PDCs. In a pure surgical sense resection and plastic of a vein have become a safe and common procedure, hence PDC with vein involvement may be regarded as a resectable tumor. On the other hand, vein involvement decreases survival significantly, i.e. it is an oncologic but not surgical criterion which cannot be ignored despite the advances in surgical technique. This question requires further studying with possible consequent changes in the TNM-T classification and the PDC stratification.

PDR with vein resection and failed chemotherapy cannot be regarded as a reasonable procedure because its long-term outcomes are comparable to the situation with no surgery at all. Whereas a lot of patients do not receive complete ACT, PDR with vein resection may be appropriate only after efficient NACT. Finally, in the oncology sense, borderline resectable tumors are as challenging as locally advanced ones, that should determine a treatment strategy.


Funding
This study required no funding.

Conflict of interests
The authors declare that they have no conflict of interest.

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AUTHOR CONTRIBUTION

Dmitry A. Chichevatov: the conception and design of the study, acquisition of data, analysis and interpretation of data, final approval of the version to be submitted.

Vyacheslav V. Kalentjev: drafting the article and revising it critically for important intellectual content, final approval of the version to be submitted.

Artem E. Glukhov: drafting the article and revising it critically for important intellectual content, final approval of the version to be submitted.

Финансирование
Это исследование не потребовало дополнительного финансирования.

Конфликт интересов
Авторы заявляют об отсутствии конфликта интересов.