

## Surgical treatment of resectable and borderline resectable pancreatic cancer in tertiary cancer center: the 6-year experience

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### ABSTRACT

**Objective:** The aim of the study is to analyze the short and long-term results of surgical treatment of resectable and borderline-resectable patients during 2015-2017 (1st period) and 2018-2021 (2nd period).

**Material and Methods:** A retrospective analysis of patients treated with pancreatic resection with (VR) and without portal or mesenteric vein resection (standard resection, SR) for exocrine pancreatic carcinoma in National Cancer Institute, Kyiv, Ukraine in 2015-2021.

**Results:** 188 patients underwent surgical treatment, among which 67 received concomitant portal/mesenteric vein resection. Postoperative mortality was 10.04% (14.93% and 6.61% in VR and SR group, respectively,  $p=0.11$ ). Textbook outcome rate was 67.3% vs 72.7% in VR and SR groups, respectively ( $p=0.57$ ). Comparing 2015-2017 and 2018-2021 time periods, TO rate did not change for VR – 67.9% vs 66.8% ( $p>0.99$ ), but tended to increase in SR group – 62.2% vs 80.4% ( $p=0.089$ ). Median overall survival was 17.03 month and did not differ between VR and SR. OS of all patients differed significantly between 2015-2017 and 2018-2021 – 13.8 vs 22.5 month ( $p=0.013$ ). In multivariate analysis pancreatic head resection and lower tumor grade were positive prognostic factors, while age  $>65$  and first study period – negative for OS.

**Conclusion:** Extended due to venous resection pancreatectomies lead to comparable with standard procedures short-term and long-term results. The tumor grade G1-2, patient age less than 65, pancreaticoduodenal resection, and treatment period 2018-2021 were independent factors for better prognosis. Further prospective data is necessary to obtain representative results.

**Keywords:** pancreatic cancer, borderline resectable pancreatic cancer, portal vein resection.

### INTRODUCTION

Pancreatic cancer is the 7th leading cause of death among oncologic diseases (1). Surgical treatment is potentially the only method of achieving long-term survival, and the best results are achieved in patients who received a combination of surgery and chemotherapy, which was demonstrated in studies in the early 2000s (2) and formed the basis of the current treatment concept. However, no more than 20% of patients have a non-metastatic resectable process at the time of diagnosis (3). About 25% of patients will present with non-metastatic locally unresectable cancer, mainly due to the invasion to the major visceral vessels (4). Some of these patients still remain surgical candidates and the removal of the tumor in this case requires extended pancreatic resection with vascular plasty. To unify approaches to treatment and to analyze data, the classifications of resectability were proposed, most of which divides the tumor on resectable, borderline resectable and locally advanced. One of the most widely used classifications is the classification proposed by NCCN (5). Resectable tumors include non-metastatic tumors without vascular invasion, or contact with a superior mesenteric (SMV)/ portal vein (PV) less than 180°. This definition implies the minimum possibility of true invasion into the wall of the vein, although it does not exclude the intraoperative need for the venous resection: among cases of radiological tumor venous contact less than 180° up to 22% demonstrate true invasions, and up to 36% requires venous resection (6). In these cases, unplanned venous resection is associated with an increased frequency of R1-margin (7).

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The borderline resectable tumors include tumors with radiological contact with SMV/ PV more than 180° or the presence of irregular venous contour or vein thrombosis; contact with the inferior vena cava; contact with the common hepatic artery with technical possibility for reconstruction; contact with the superior mesenteric artery (SMA) less than 180°; contact with aberrant liver arteries when variant vascular anatomy is present; and the invasion of the celiac artery for the pancreatic body and tail tumors with intact gastroduodenal artery.

The resection of the arteries (with the exception of SMA and aorta) in the treatment of pancreatic cancer became standard procedures that lead to acceptable long-term results in thoroughly selected patients, but are associated with high postoperative mortality (8, 9). The tumors with a contact with SMA of more than 180°, invasion of the aorta, non-reconstructable portal vein invasion belong to the locally advanced and such patients are mostly not surgical candidates, although in some cases surgical exploration after neoadjuvant therapy may be successful (10).

Early publications of Asian and Western centers demonstrated comparable short-term results of pancreatectomies extended due to venous resection compared with standard procedures (11, 12), but very scarce long-term results - median survival of 13 months, showed in 2006 in a systematic review (13).

After twenty years of accumulation of experience and with the advent of effective systemic therapy regimens, some centers demonstrate median survival up to 35 months (14, 15).

Pancreatic resections combined with vascular resections have been performed systematically at the National Cancer Institute since 2015. Today, this paper is the first analysis of the results of surgical treatment of patients with resectable and borderline resectable pancreatic cancer at the National Cancer Institute of Ukraine.

## MATERIAL and METHODS

We performed a retrospective analysis of patients with exocrine pancreatic cancer, that received radical surgical treatment at the National Cancer Institute (Kyiv, Ukraine) from January 2015 to July 2021. Inclusion criteria were:

- 1) histologically confirmed pancreatic adenocarcinoma (based on postoperative histological exam);
- 2) absence of arterial invasion (in the common hepatic artery, SMA or the celiac artery);
- 3) absence of radiological or pathological signs of distant metastases at the time of surgical treatment;
- 4) performance of standard or extended (due to resection of adjacent visceral organs, SMV or PV) surgical procedure (pancreaticoduodenectomy, distal pancreatectomy ( or radical antegrade modular pancreatosplenectomy), total pancreatectomy).

We define the type of vein resection in accordance with the ISGPS classification:

- 1) wedge resection;
- 2) wedge resection with a patch insertion;
- 3) segmental resection with end-to-end anastomosis;
- 4) segmental resection with an interposition of a graft.

Patients were divided into two groups - a group of standard pancreatic resections (SR) - 121 patients, and a group of pancreatic resection group combined with resection of SMV/ PV (VR) - 67 patients.

An analysis of subgroups of patients receiving treatment in the first time period (2015-2017 years) and the second period (2018-2021 years) was performed.

Postoperative mortality was defined as mortality during the same hospitalization.

Major postoperative complications were defined as grade 3b and higher according to Clavien-Dindo classification.

The failure-to-rescue rate was defined as the ratio of postoperative mortality to the number of patients with major postoperative complications.

Textbook outcome was defined as the absence of postoperative and 90-day mortality, major postoperative complications and readmission within 90 days after surgery in patients followed-up at least 90 days after index surgery.

The overall survival was counted from the date of operation to the date of death.

Statistical analysis was performed using GraphPad Prism software version 9.2.0 and SPSS version 22.0.

## RESULTS

During a 6-year period, 188 patients underwent surgical treatment for pancreatic adenocarcinoma (men, 83; mean age, 57.7 years). Pancreaticoduodenectomy was performed in 131 cases (48 with venous resection), distal pancreatectomy in 43 patients (10 with venous resection), total pancreatectomy in 14 patients (9 with venous resection). Patients' characteristics are shown in **Table 1**.

In the VR group, the wedge resection of the vein (type 1) was performed in 6 cases (8.96%), segmental resection with end-to-end anastomosis (type 3) in 60 cases (89.6%), interposition of venous autograft (type 4) in 1 case (1.5%).

Postoperative mortality was 10.04% in the general group. In the SR group, postoperative mortality was 6.56%, in the VR group - 14.93% (differences are statistically insignificant,  $p=0.11$ ). 90-day mortality was 13.07% in the general group; 10.74% and 20.9% in the SR and VR groups, respectively ( $p=0.092$ ). (**Table 2**)

Major postoperative complications occurred in 17.02% of patients, 16.53% against 17.91% in SR and VR, respectively ( $p=0.969$ ). Bleeding was the cause of postoperative death at 12.5% and 40% of cases in patients without with venous resection, respectively, although difference is statistically insignificant ( $p=0.31$ ). The failure-to-rescue rate differed significantly: 40.0% and 83.36% in the SR and VR groups, respectively ( $p=0.0276$ ).

The type of pancreatic resection did not affect neither postoperative, nor 90-day mortality: postoperative mortality was 8.4%, 7.1% and 6.97% after pancreaticoduodenectomy, total pancreatectomy and distal pancreatectomy, respectively ( $p=0.958$ ); 90-day mortality - 12.98%, 14.3% and 18.6%, respectively ( $p=0.659$ ).

The length of postoperative hospital stay did not differ significantly between the SR and VR groups - the average length of stay was 15.8 versus 18.16 (p=0.1563).

Among patients who were followed up 90 days or more after resection (140 patients), the textbook outcome was achieved in 70.7%; 72.7% vs. 67.3% in the SR and VR groups, respectively (p=0.57).

When comparing time periods (2015-2017 versus 2018-2021), mortality was significantly different in the general group - 16% versus 5.3%, respectively (p=0.0213). The 90-day mortality also differed for time periods in the general group - 21.3% vs. 9.7% (p=0.0337), and there was a trend in the SR group - 18.2% vs. 6.5% (p=0.0659). The incidence of major complications did not differ between time periods in the general group and subgroups; however, there was a change in the failure-to-rescue rate in the VR group - 100% versus 50% (p=0.0114).

The frequency of the textbook outcome did not change in the VR group (67.9% vs. 66.8%, p>0.99), but tended to increase in the standard resection group (62.2% vs. 80.4%, p=0.089). (Table 3)

The median overall survival for all patients was 17.03 months. 1 year survival accounted for 60.02%, 3-year - 28%. The overall survival was not significantly different between patients with and without venous resection (p=0.41): median 15.1 versus 17.3 months, 1-year survival rate 52.4% versus 64.49%, 3-year 35.19% vs. 23.38%. (Figure 1)

In univariate analysis, overall survival differed between patients who received treatment in 2015-2017 and 2018-2021: median 13.8 versus 22.5 months. (p = 0.013). (Figure 2) The difference remains when analyzing the subgroup of standard resection: 11.4 against 22.5 months. (p = 0.02), but not in the subgroup of venous resection: 15.1 months versus not reached (p = 0.366).

Information about the tumor grade was available in 114 patients: G1-2 in 76, G3 in 38. The frequency G3 was not significantly different between groups of standard and venous resections (29.1% versus 42.9%, p = 0.1965). The tumor grade (G1-2 against G3) did not significantly affect the survival in the general group in univariate analysis: 17.8 versus 9.63 months. (P = 0.08). In the group of venous resection, differences were significant: 36.5 versus 4.33 months. (p = 0.04).

In multivariate analysis (Table 4), the resection of pancreatic head (RR 0.3, CI 0.1-0.87, p=0.027), and tumor grade G1-2 (RR 0.4, CI 0.197-0.83, p=0.014) were factors associated with improved overall survival. Age over 65 years at the time of treatment (RR 3.7, CI 1.47-9.36, p=0.05) and the first (2015-2017) treatment period (RR 2.13, CI 0.97-4.69, p=0.061) were factors associated with decreased survival.

The presence of pathologically confirmed regional lymph node metastases, advanced pT stage (3-4), the performance of venous resection and neoadjuvant chemotherapy did not affect the survival in multivariate analysis.

Table 1. Study groups' characteristics.

	Standard resection 121	Venous resection 67	p
<b>Total number</b>	121	67	
<b>Pancreaticoduodenectomy, n (%)</b>	83 (68.6%)	48 (71.6%)	n.s.
<b>Distal pancreatectomy, n (%)</b>	33 (27.3%)	10 (14.9%)	n.s.
<b>Total pancreatectomy, n (%)</b>	5 (4.1%)	9 (13.4%)	n.s.
<b>Males, n (%)</b>	51 (42.1%)	32 (47.8%)	n.s.
<b>Females, n (%)</b>	70 (57.9%)	35 (52.2%)	n.s.
<b>Age</b>	14-78 yrs, mean 57.39 (CI 95% 55.58-59.16)	39-77 yrs, mean 58.39 (CI 95% 56.29-60.48)	n.s.
<b>pT1*</b>	4	2	n.s.
<b>pT2*</b>	32	7	<b>p=0.0177</b>
<b>pT3*</b>	52	38	<b>p=0.0066</b>
<b>pT4*</b>	6	2	n.s.
<b>pN0*</b>	63	33	n.s.
<b>pN+*</b>	34	16	n.s.
<b>G1**</b>	5 (6.3%)	1 (2.9%)	n.s.
<b>G2**</b>	51 (64.6%)	19 (54.3%)	n.s.
<b>G3**</b>	23 (29.1%)	15 (42.9%)	n.s.

Table 2. Short-term outcomes.

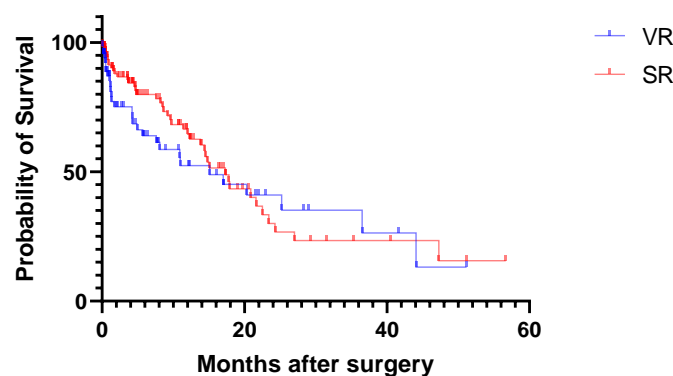
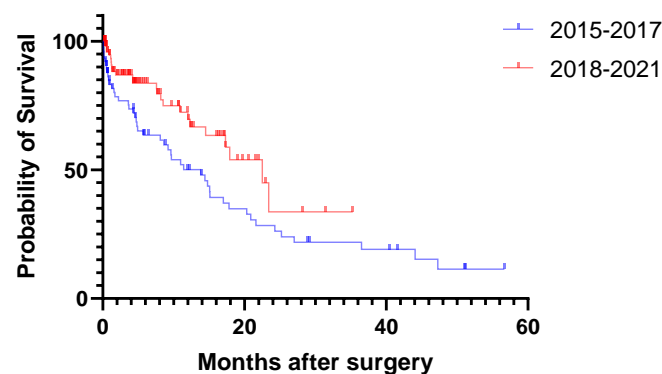
	Standard resection	Venous resection	p
<b>Postoperative mortality, n (%)</b>	8 (6.6%)	10 (14.93%)	p=0.11
<b>90-day mortality, n (%)</b>	21 (10.74%)	14 (20.9%)	p=0.092
<b>Major complications, n (%)</b>	20 (16.53%)	12 (17.91%)	p=0.969
<b>Failure-to-rescue, %</b>	40%	83.36%	<b>p=0.0276</b>
<b>Death due to hemorrhage, n (%)</b>	1 (12.5%)	4 (40%)	p=0.3137
<b>Length of stay, mean (CI 95%)</b>	15.81 (CI 95% 13.79-17.83)	18.16 (CI 95% 15.19-21.14)	p=0.1563
<b>Textbook outcome</b>	72.7%	67.3%	p=0.57

**Table 3.** Comparison of the short-term outcomes in the first (2015-2017) and second (2018-2021) study periods.

	2015-2017	2018-2021	p
<b>Number of patients</b>	75	113	
<b>Standard resection, n (%)</b>	44 (58.7%)	77 (68.1%)	n.s.
<b>Venous resection, n (%)</b>	31 (41.3%)	36 (31.9%)	n.s.
<b>Mortality, n (%)</b>	12 (16%)	6 (5.3%)	<b><i>p=0.0213</i></b>
a) <b>Standard, n (%)</b>	5 (11.4%)	3 (3.9%)	n.s.
a) <b>Venous resection, n (%)</b>	7 (22.6%)	3 (8.3%)	n.s.
<b>90-day mortality, n (%)</b>	16 (21.3%)	11 (9.7%)	<b><i>p=0.0337</i></b>
a) <b>Standard, n (%)</b>	8 (18.2%)	5 (6.5%)	<b><i>p=0.0659</i></b>
a) <b>Venous resection, n (%)</b>	8 (25.8%)	6 (16.7%)	n.s.
<b>Major complications, n (%)</b>	18 (24%)	16 (14.2%)	n.s.
a) <b>Standard, n (%)</b>	11 (25%)	10 (13%)	n.s.
a) <b>Venous resection, n (%)</b>	7 (22.6%)	6 (16.7%)	n.s.
<b>Failure to rescue, %</b>	66.7%	37.5%	n.s.
a) <b>Standard, %</b>	45.5%	30	n.s.
b) <b>Venous resection, %</b>	100%	50%	<b><i>p=0.0114</i></b>
<b>Textbook outcome, %</b>	64.6%	76%	n.s.
a) <b>Standard, %</b>	62.2%	80.4%	<b><i>p=0.089</i></b>
b) <b>Venous resection, %</b>	67.9%	66.8%	n.s.

**Table 4.** Multivariate analysis of risk factors influencing overall survival

Risk factors	p	HR	CI 95,0% for HR
Pancreaticoduodenectomy	<b><i>0,027</i></b>	<b><i>0,302</i></b>	<b><i>0,105-0,873</i></b>
Tumor grade G1-2	<b><i>0,014</i></b>	<b><i>0,406</i></b>	<b><i>0,197-0,834</i></b>
Venous resection	0,663	1,194	0,538-2,648
pN+	0,684	1,172	0,545-2,519
pT1-2	0,831	1,090	0,495-2,400
Neoadjuvant chemotherapy	0,983	226,837	-
Age older than 65 years	<b><i>0,005</i></b>	<b><i>3,713</i></b>	<b><i>1,473-9,359</i></b>
Year of treatment 2015-2017	<b><i>0,061</i></b>	<b><i>2,128</i></b>	<b><i>0,966-4,689</i></b>

**Figure 1.** Overall survival of patients underwent standard (SR) and combined with venous (VR) pancreatic resection.**Figure 2.** Overall survival of patients underwent surgical treatment in 2015-2017 vs 2018-2021 periods.

## DISCUSSION

This work is the first analysis of the results of surgical treatment of patients with pancreatic cancer in the National Cancer Institute of Ukraine.

The first attempts of resection of a portal vein during surgery for tumors of the pancreatic head belong to Child, who published two cases of two-stage obstructive resection of PV in 1952 (16). In the same year, McDermott proposed a technique for simultaneous pancreaticoduodenectomy with resection of the portal vein and application of the mesocaval anastomosis (17). This was followed by certain reports on successful cases, but the systematization of experience began only in the 1990s.

In the earliest series of pancreatic resections extended due to vascular plasty in the 1990s, Fortner and Sindelal demonstrate 26% and 20% postoperative mortality and median survival of 13 months (18-21). In the 2006 systematic review, which includes 52 series of observations from 1966 to 2005, the experience of 1646 extended pancreatic resections was summarized, while 919 of them belong to Asian authors, and only 338 - European (13). Despite the improvement in short-term results compared to the Fortner's historical cohort (mortality in the general group 5.9%), the overall survival remained at the same level (the median 13 months).

In 2006, the NCCN first introduced the concept of "borderline resectable pancreatic cancer", which was based solely on anatomical criteria. In 2008, it was first proposed to add biological and conditional criteria of borderline resectability (22). In 2016, international consensus clearly defined the criteria of biological borderline resectability as a CA-19-9 level above 500 U/mL or regional lymph node metastases confirmed by biopsy or PET/CT (23) and highlighted the importance of neoadjuvant therapy in this categories of patients.

The accumulation of experience and the use of modern chemotherapy regimens led to a meaningful improvement in long-term results in the publications of recent years. Barnes demonstrates median survival at 31 months in patients with borderline resectable cancer who received neoadjuvant chemotherapy and surgery, compared with 13 months in those received only chemotherapy (24). Similar results were demonstrated by MagGino (25), Javed (26), Byun (27), Kishi (28). Multicenter series, that are the most relevant representers of the "real-world data", declare more modest, but still acceptable results: the median overall survival is 18-24 months (29-31).

Our results are consistent with the literature data. In the first period (2015-2017), short-term and long-term results were significantly worse than in the second period, and were similar to the results of early European and Asian publications. The median survival of 22.5 months in the general cohort in the 2018-2021 period is in line with the global trend.

We associate an unsatisfactory high mortality rate in the first period with an extremely high rate of failure-to-rescue in the treatment of major postoperative complications in patients undergone venous resections. These trends are typical for pancreatic surgery: with a constant rate of postoperative complications, the rate of treatment failure (and therefore

mortality) decreases over time and with an increase in the number of annually performed procedures (32-34). A similar trend is observed in the textbook outcome rate (35), although we found its increase only in the subgroup of standard, but not venous resections.

In our cohort, vein resection was not a risk factor overall survival. The fact of resection of SMV/ PV did not affect the survival in the Kishi's 2019 work (36), while the presence of true invasion into the vein wall did. Previously, similar results were reported by Nakao in 2012 (37), and confirmed in meta analyzes in 2016 and 2017 (36, 38).

The status of regional lymph nodes and the pT-stage of the tumor did not affect the survival in our analysis. These data contradict most literature data (38-40). We associate these results with the absence of routine adherence to the standardized pathological protocol in the clinic. For the same reason, we have not analyzed the influence of R-status, lymphovascular and perineural invasion for survival. We plan to conduct a separate analysis of cases where the standardized pathological protocol was performed.

We noted the extremely low frequency of use of neoadjuvant therapy in our series. Despite the trend of the treatment paradigm change towards the wider use of neoadjuvant chemo or chemoradiotherapy in resectable cancer, and established principles for its use in borderline resectable cancer, the "real-world data" from Australia, New Zealand and Singapore published in 2020, demonstrate that the neoadjuvant is used in only 16% cases (41). Also, we cannot exclude the possibility of data loss during the primary documentation registration in our cohort. Initiated in 2021 in our clinic, a prospective data collection will allow us to perform appropriate analyses in the future.

We did not analyze the impact of the CA-19-9 level on long-term results, because information about it is almost uniformly absent in the primary documentation in the first study period (2015-2017). We are planning an appropriate analysis of patients who have this information in the future.

## CONCLUSION

Extended pancreatic resections with venous plasty make it possible to achieve short- and long-term results comparable with standard procedures. The tumor grade G1-2, the patient's age less than 65, the pancreatic head resection and the period of treatment 2018-2021 were independent factors of the improved survival. Further prospective studies are necessary to obtain representative data.

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**Ethical approval:** All procedures performed in this study were in accordance with the ethical standards of the institutional research committee.

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