Original Article

Impact of preoperative chemotherapy on surgical results in 139 patients with locally advanced pancreatic cancer

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Background: The establishment of preoperative chemotherapy (PCT) with FOLFIRINOX and gemcitabine/nab-paclitaxel in recent years has enabled resectability in many patients with initially locally advanced pancreatic cancer (LAPC). Nevertheless, information about the impact of PCT on surgical results is scarce.

Methods: All patients with initial LAPC who received surgery after chemotherapy at the high-volume centre for pancreatic surgery of St. Josef-Hospital Bochum between 2015 and 2022 were included in this retrospective cohort analysis.

Results: A total of 139 patients underwent surgery after pre-treatment with FOLFIRINOX (76.3%), gemcitabine/nab-paclitaxel (11.5%), both (5.8%) and other regimens (6.5%). Eighty-five tumors (61.2%) were resectable after PCT. R0 resection was achieved in 92.9%, R1 in 7.1% and R2 in 0% of cases. Fifty-four tumors were still not resectable at the time of surgery. Surgical results of the patients did not show increased postoperative mortality and morbidity compared to the literature data. Postoperative 30-day mortality was 1.4%. Rates for pancreas-specific complications [postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), postpancreatectomy hemorrhage (PPH), and others] were not increased. POPF occurred in 10.5% and DGE in 26.3% after pancreaticoduodenectomy. After distal pancreatectomy, POPF was detected in 37.5% and DGE in 12.5%. Median postoperative survival (31 *vs.* 13 months) and overall survival after initial diagnosis (40 *vs.* 20 months) were significantly longer in resected patients (P<0.001). Postoperative recurrence-free survival in resected patients amounted to 12 months.

Conclusions: This study underlines that PCT allows resectability of primarily unresectable patients with LAPC without increasing perioperative mortality and morbidity. It may lead to a significant prolongation of recurrence-free and overall survival in resected patients after PCT.

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Introduction

In 2030, pancreatic cancer (pancreatic ductal adenocarcinoma, PDAC) is expected to be the second leading cause of cancer-related deaths in Western countries (1). In spite of optimal surgical therapy, pancreatic cancer is still burdened with a poor long-term outcome (2). According to Siegel *et al.*, the overall 5-year survival rate was approximately 12% in 2023 (3).

Additional chemotherapeutic strategies could improve survival rates compared to surgery alone. In 2011 and 2013, studies described the use of FOLFIRINOX and gemcitabine/nab-paclitaxel in pancreatic cancer for the first time (4,5). Authors expect neoadjuvant regimes could further improve overall survival, but its application is mainly limited to study purposes so far (6). Especially in locally advanced pancreatic cancer (LAPC), preoperative chemotherapy (PCT) is widely accepted aiming for a reduction of the size of the tumor and vessel infiltration (7). Nevertheless, knowledge about surgical outcome and complications after pre-treatment is scarce. Earlier studies reported similar or reduced morbidity after neoadjuvant regimes compared to patients treated with immediate surgery. Especially preoperative radiochemotherapy (PRCT) is described to reduce the risk of postoperative pancreatic fistulas (POPF) (8).

In the light of increasing use of neoadjuvant strategies in LAPC, evaluation of surgical patients after PCT is of major clinical importance. Therefore, the aim of our study was to evaluate the implications of chemotherapy preceding surgery. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-426/rc).

Highlight box

Key findings

- Preoperative chemotherapy (PCT) allows resectability of primarily unresectable patients with locally advanced pancreatic cancer (LAPC) without increasing perioperative mortality and morbidity.
- PCT followed by surgery leads to a significant prolongation of recurrence-free and overall survival in LAPC.

What is known and what is new?

- In spite of optimal surgical therapy, pancreatic cancer is still burdened with a poor long-term outcome, chemotherapy can prolong survival.
- Surgery after PCT is not associated with an increase of postoperative mortality and morbidity.

What is the implication, and what should change now?

- PCT can be administered in patients with LAPC without fear of impaired surgical results.

Methods

All patients were diagnosed with LAPC and underwent surgery between January 1st 2015 and April 1st 2022. Every procedure was performed at the high-volume centre for pancreatic surgery of St. Josef-Hospital, Ruhr-University Bochum, Germany. After PCT, pancreaticoduodenectomy (PD), distal pancreatectomy (DP), total pancreatectomy (TP) or palliative surgery was performed. All procedures were carried out by the same certified pancreatic surgeons who perform more than 100 resections per year and have performed more than 6,000 pancreatic operations in total. All patients received octreotide (100 µg) perioperatively. In high-risk cases for POPF, octreotide was additionally administered for seven postoperative days.

The study was approved by the ethics committee of the Ruhr-University Bochum (Reg. No. 22-7610 and 20-7140-bio) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent of each patient was given for the analysis and data was gathered prospectively. Retrospectively, the hospital inhouse database was analysed and information about demographics, laboratory values, surgical and oncological outcome was gathered. Only patients capable of a surgical treatment were included. POPF has been assessed according to the International Study Group of Pancreatic Surgery (ISGPS) (9). All other complications were assessed according to the Clavien-Dindo classification (10). Resectability was assessed

initially and after chemotherapy in an interdisciplinary tumor board by certified surgeons and radiologists. Decisions were based on National Comprehensive Cancer Network (NCCN) and International Association of Pancreatology (IAP) guidelines (11,12). Tumor response to PCT was classified according to RECIST criteria (13). Regression grading was reported according to Le Scodan (14). Follow-up examinations were performed for in- and outpatients at recurring intervals.

Primary endpoints of the study were postoperative complications and 30-day mortality. Secondary endpoints included overall survival, postoperative survival and recurrence-free survival, R0-resection rate, duration of surgery, tumor response to PCT, and lengths of stay in hospital and in intensive care unit (ICU).

Statistical analysis

Statistical analysis was performed using SPSS V29.0 (IBM Corp., IBM Statistics for Windows, Armonk, NY, USA; RRID: SCR_002865**)**. Data is displayed as medians with interquartile ranges as well as percentages. Statistical comparisons were performed using Fisher's *t*-test, Kruskal-Wallis test, Mann-Whitney *U* test or using two-tailed chi-squared tests when appropriate. Survivals are expressed using Kaplan-Meier curves. P values <0.05 were considered as statistically significant.

Results

Patient baseline characteristics

A total of 139 patients were analysed in our study. Patient baseline characteristics are shown in *Table 1*. All patients suffered from PDAC, which was located in the pancreatic head in 44.6% (n=62), processus uncinatus in 15.8% (n=22), pancreatic corpus in 24.5% (n=34) and pancreatic tail in 15.1% (n=21). At the time of diagnosis, 30 patients (21.6%) had undergone palliative surgery and 41 patients (29.5%) had received bile duct stenting due to jaundice. In all patients, tumorous tissue had been gathered either via surgery or fine needle aspiration. All tumors were initially staged as locally advanced PDAC, classified as unresectable according to NCCN and IAP criteria at diagnosis and therefore pre-treated with chemotherapy (11).

Among 139 pre-treated patients, 106 patients (76.3%) received FOLFIRINOX, 16 patients (11.5%) received gemcitabine/nab-paclitaxel, 8 patients (5.8%) received both regimens (due to a change in the course) and 9 patients (6.5%) received other regimens (e.g., gemcitabine alone, combined radiochemotherapy or capecitabine).

Of 139 tumors that were preoperatively assessed as resectable after chemotherapy, PDAC could be resected in 85 patients (61.2%). A PD was performed in 38 patients (27.3%), DP in 24 patients (17.3%) and TP in 23 patients (16.6%). In case of irresectability (38.8%, n=54), patients underwent palliative double bypass surgery (gastroenterostomy and hepatojejunostomy) or solely surgical exploration, depending on tumor site. *Table 2* presents the frequency of surgical procedures. Venous resections were performed in 5.8% (n=8) and arterial resections in 2.2% (n=3) of all cases. A transfusion of two packed red blood cells (PRBCs) each was administered to two patients, not because of relevant blood loss, but because of low initial hemoglobin levels. In the resected patients, pancreatic cancer was R0-resected in 92.9% (79 patients) and R1-resected in 7.1% (6 patients). There were no R2 resections.

Out of 139 patients, 84 patients died (60.4%) and 55 patients were alive by the end of the observation period (39.6%), which had a mean length of 19.4 months (minimum 0 months, maximum 86 months). In resected patients, the proportion of patients alive was significantly higher (51.8% *vs.* 20.4%, P<0.001) and the proportion of deceased patients was significantly lower than in non-resected patients (48.2% *vs.* 79.6%, P<0.001).

Surgical results

The perioperative mortality was low—two patients (one resected patient and one non-resected patient) died, corresponding to an overall 30-day mortality of 1.4%. Major complications (complications ≥ grade 3B of the Clavien-Dindo classification) occurred in 8.6% of patients (n=12). Revisional surgery was necessary in 4.3% of patients (n=6). The ICU readmission rate during hospital stay was 5.8% (n=8). The 30-day hospital readmission rate was 5.0% (n=7). 90-day mortality was 2.9% (n=4). There were no significant differences in postoperative complication rates in resected and non-resected patients (except POPF). Details are presented in *Table 3*.

POPF was seen in four patients after PD (10.5%) and in nine patients after DP (37.5%). In total, POPF grade A was measured in five patients (3.6%) and grade B in nine of all patients (6.5%). POPF grade C never occurred. Delayed gastric emptying (DGE) was detected in ten patients with

Table 1 Patient baseline characteristics and comparison of data from resected and non-resected patients

Characteristics	All patients (n=139)	Resected (n=85)	Non-resected (n=54)	P value
Gender				
Female	62 (44.6)	37 (43.5)	25 (46.3)	0.861
Male	77 (55.4)	48 (56.5)	29 (53.7)	0.861
Age at diagnosis (years)	61 [55.5–68]	60 [56–68]	62 [54.25–68]	0.645
BMI (kg/m^2)	23.9 [21.5–27.2]	23.9 [21.5–26.4]	23.95 [21.625–28]	0.243
ASA	3 [2–3]	2 [2–3]	3 [2–3]	0.202
Preoperative chemotherapy regimens				
FOLFIRINOX	106 (76.3)	64 (75.3)	42 (77.8)	0.839
Gemcitabine/nab-paclitaxel	16 (11.5)	12 (14.1)	4 (7.4)	0.283
Both regimens	8 (5.8)	5 (5.9)	3 (5.6)	>0.99
Other regimens	9 (6.5)	4 (4.7)	5 (9.3)	0.310
Preoperative chemotherapy				
Cycles	11 [6–12]	11 [6–12]	12 [6.25–12]	0.391
Months	6 [4–6]	6 [3–6]	6 [4–6]	0.705
Time between diagnosis and surgery (months)	7 [5–9]	7 [5–9]	7 [5–9]	0.466
Duration of surgery (min)	318 [223.5–393]	376 [314–425]	215.5 [169–295]	<0.001
Length of stay in hospital (days)	16 [13–23]	19 [15–26]	13 [9.25–16]	<0.001
Length of stay in ICU (days)	1 [1–2]	1 [1–3]	1 [0–1]	<0.001
30-day mortality	2 (1.4)	1 (1.2)	1 (1.9)	>0.99
90-day mortality	4 (2.9)	1 (1.2)	3 (5.6)	0.299
Postoperative survival (months)	24 [10–53]	31 [18–59]	13 [5–20]	<0.001
Overall survival (months)	31 [19–51]	40 [27–73]	20 [13–31]	<0.001
Recurrence-/progression-free survival (months)	9 [3–17]	12 [4–21]	4 [2–7]	<0.001
5-year survival rate	23.0%	34.1%	6.3%	<0.001
Patient status				
Deceased	84 (60.4)	41 (48.2)	43 (79.6)	<0.001
Alive	55 (39.6)	44 (51.8)	11 (20.4)	<0.001

Data are presented as n (%) or median [interquartile range], unless otherwise indicated. BMI, body mass index; ASA, American Society of Anesthesiologists; ICU, intensive care unit.

PD (26.3%) and in three patients with DP (12.5%). In total, DGE grade A was reported in 11 (7.9%), grade B in 9 (6.5%) and grade C in 2 of all patients (1.4%). A detailed overview of all postoperative complications can be found in *Table 4*.

The median duration of surgery was significantly shorter in non-resected patients than in resected patients (376 *vs.* 215.5 minutes, P<0.001). Furthermore, the median length of stay in the hospital (19 *vs.* 13 days, P<0.001) and in the ICU (1 *vs.* 1 day, P<0.001) was significantly shorter in non-resected patients.

Survival

Regarding the oncological results, in patients who underwent resection after PCT, median postoperative survival, overall survival and recurrence-/progression-free

survival were significantly longer than in unresected patients (P<0.001). Details are shown in *Table 5* and *Figure 1*.

Oncological results

Pre-treatment led to a downsizing of 90.6% of the tumors (n=126) after chemotherapy. For patients with good chemotherapy tolerability, a statistically significant longer overall survival was reported than for patients with poor tolerability (37 *vs.* 27 months, P=0.013). Most patients (n=82, 59.0%) showed partial response (PR) on computed tomography (CT) scan after chemotherapy according to RECIST criteria, corresponding to a shrinkage of at least 30% of size. The resected patients had a higher proportion of patients with PR than the non-resected patients (65.9% *vs.* 48.1%, P=0.051). In some patients, despite progressive disease on re-staging CT scan, exploration after PCT was performed due to clinical improvement, tumor marker decline and regressive vascular involvement. According to Le Scodan, following regression grades were reported: grade 1 in 26 patients (30.6%), grade 2 in 36 patients (42.4%), grade 3 in 11 patients (12.9%) and grade 4 in 9 patients (10.6%). Grading was not specified in three patients (3.5%). The tumors of the resected patients had significantly smaller diameters and volumes both before and after chemotherapy than the tumors of the unresected patients (P<0.001). Additional information is found in *Table 6*.

The analysis showed that patients pre-treated with FOLFIRINOX were significantly younger (60 *vs.* 65 years, P=0.017) and had a significantly longer time between diagnosis and surgery due to longer chemotherapy than patients pre-treated with gemcitabine/nab-paclitaxel (7 *vs.* 3.5 months, P<0.001). FOLFIRINOX was associated with a higher proportion of patients with a PR (66.0% *vs.* 37.5%, P=0.05). In addition, there was a non-significant longer median overall survival in patients pre-treated with gemcitabine/nab-paclitaxel of 40 to 31 months (P=0.314).

Table 2 Frequency of surgical procedures

Procedure	Frequency	Percentage
Resections	85	61.2
Pancreaticoduodenectomy	38	27.3
PPPD	21	15.1
PRPD	17	12.2
Distal pancreatectomy	24	17.3
Total pancreatectomy	23	16.6
Palliative surgery	54	38.8
Double bypass surgery	28	20.1
Exploration	26	18.7

PPPD, pylorus-preserving pancreaticoduodenectomy; PRPD, pylorus-resecting pancreaticoduodenectomy.

Table 3 Comparison of postoperative complications in resected and non-resected patients

	All patients (n=139)	Resected (n=85)	Non-resected (n=54)	P value
Mortality	2 (1.4)	1 (1.2)	1 (1.9)	>0.99
Major complications*	12 (8.6)	9 (10.6)	3 (5.6)	0.368
Re-operations	6 (4.3)	4 (4.7)	2 (3.7)	>0.99
30-day hospital readmission rate	7 (5.0)	5 (5.9)	2 (3.7)	0.706
POPF	14 (10.1)	13 (15.3)	1 (1.9)	0.009
DGE	22 (15.8)	14 (16.5)	8 (14.8)	>0.99
PPH	4 (2.9)	3 (3.5)	1 (1.9)	>0.99
Surgical site infection	9 (6.5)	4 (4.7)	5 (9.3)	0.310
Bile leak	3 (2.2)	3 (3.5)	0	0.282
Chyle leak	9 (6.5)	4 (4.7)	5 (9.3)	0.310
Cholangitis	2 (1.4)	2 (2.4)	0	0.521

Data are presented as n (%). *, complications ≥ grade 3B of the Clavien-Dindo classification. POPF, postoperative pancreatic fistula; DGE, delayed gastric emptying; PPH, postpancreatectomy hemorrhage.

Table 4 Postoperative complications regarding the surgical procedure

	PD (n=38)	DP (n=24)	TP (n=23)	DB (n=28)	Expl (n=26)	Total (n=139)
Mortality	0	0	1 (4.3)	1 (3.6)	0	2 (1.4)
Major complications*	2 (5.3)	2 (8.3)	5 (21.7)	3 (10.7)	0	12 (8.6)
Re-operations	2 (5.3)	2 (8.3)	0	2 (7.1)	0	6 (4.3)
30-day hospital readmission rate	3 (7.9)	1 (4.2)	1 (4.3)	2 (7.1)	0	7 (5.0)
POPF	4 (10.5)	9 (37.5)	NA	1 (3.6)	0	14 (10.1)
DGE	10 (26.3)	3 (12.5)	1 (4.3)	5 (17.9)	3 (11.5)	22 (15.8)
PPH	0	3 (12.5)	0	1 (3.6)	0	4 (2.9)
Surgical site infection	0	2 (8.3)	2 (8.7)	3 (10.7)	2 (7.7)	9 (6.5)
Bile leak	2 (5.3)	0	1 (4.3)	0	0	3 (2.2)
Chyle leak	1 (2.6)	2 (8.3)	1 (4.3)	3 (10.7)	2 (7.7)	9 (6.5)
Cholangitis	2 (5.3)	0	0	0	0	2 (1.4)

*, complications ≥ grade 3B of the Clavien-Dindo classification. PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; DB, double bypass surgery; Expl, exploration; POPF, postoperative pancreatic fistula; NA, not applicable; DGE, delayed gastric emptying; PPH, postpancreatectomy hemorrhage.

Table 5 Survival data of resected and non-resected patients

	All patients (n=139)	Resected (n=85)	Non-resected (n=54)	P value
Postoperative survival (months)	24	31	13	<0.001
Overall survival after diagnosis (months)	31	40	20	<0.001
5-year survival rate	23.0%	34.1%	6.3%	<0.001
Recurrence-/progression-free survival (months)	9	12	4	<0.001

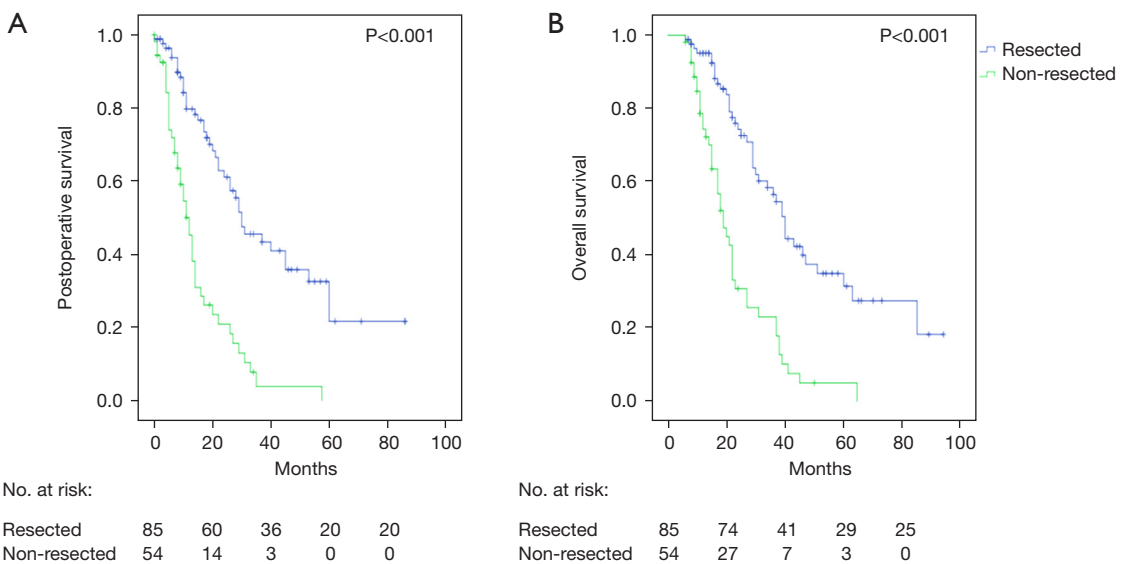

Figure 1 Kaplan-Meier curves with postoperative survival (A) and overall survival (B) in resected and non-resected patients.

Table 6 Oncological results

Characteristics	All patients (n=139)	Resected (n=85)	Non-resected (n=54)	P value
Tolerability of chemotherapy				
Good tolerability	58 (41.7)	39 (45.9)	19 (35.2)	0.223
Moderate tolerability	31 (22.3)	20 (23.5)	11 (20.4)	0.835
Poor tolerability	41 (29.5)	20 (23.5)	21 (38.9)	0.059
Unknown	9 (6.5)	6 (7.1)	3 (5.6)	>0.99
Response to chemotherapy				
Partial response	82 (59.0)	56 (65.9)	26 (48.1)	0.051
Stable disease	50 (36.0)	27 (31.8)	23 (42.6)	0.209
Progressive disease	7 (5.0)	2 (2.4)	5 (9.3)	0.109
CT scan comparison				
Sum of diameter (before PCT) (mm)	82 [64.5–99]	74 [56.5–95.5]	91.5 [79.75–104.25]	<0.001
Sum of diameter (after PCT) (mm)	53 [37–70.5]	45 [32–63.5]	63 [52.75–93.25]	<0.001
Sum of diameter (Δ)	–32.6%	–34.6%	–29.6%	0.100
Largest diameter (Δ)	–34.0%	–36.4%	–25.4%	0.159
Tumor volume (Δ)	–70.5%	–71.3%	–65.7%	0.149
Postoperative chemotherapy regimens				
FOLFIRINOX	68 (48.9)	48 (56.5)	20 (37.0)	0.036
Gemcitabine/nab-paclitaxel	17 (12.2)	11 (12.9)	6 (11.1)	0.798
Other regimens	22 (15.8)	17 (20.0)	5 (9.3)	0.101
Combined radiochemotherapy	15 (10.8)	0	15 (27.8)	<0.001
No chemotherapy	13 (9.4)	7 (8.2)	6 (11.1)	0.566
Unknown	4 (2.9)	2 (2.4)	2 (3.7)	0.642

Data are presented as n (%) or median [interquartile range], unless otherwise indicated. Δ = difference (before & after preoperative chemotherapy was administered). CT, computed tomography; PCT, preoperative chemotherapy.

Details can be found in *Table* 7.

Median values of CA19-9 and CEA decreased significantly under chemotherapy until the time of surgery (CA19-9: P<0.001; CEA: P=0.039). There was a significant difference in the decrease of CA19-9 in resected and non-resected patients (–81.5% *vs.* –74.1%, P=0.048). Resected patients expressed lower median values of CA19-9 and CEA at the time of surgery than non-resected patients (CA19-9: 21.9 *vs.* 36.8 U/mL, P=0.109; CEA: 2.4 *vs.* 3.0 µg/L, P=0.107). Furthermore, tumor markers increased earlier and more strongly in non-resected patients than in resected patients from the time of surgery to the follow-up examinations.

Postoperatively, adjuvant treatment was mostly administered about six weeks after surgery. The majority of patients received FOLFIRINOX (48.9%) or gemcitabine/nab-paclitaxel (12.2%). Thirteen patients did not receive postoperative chemotherapy due to their physical condition (9.4%). Median recurrence-free survival was 12 months in resected patients. Distant metastases occurred in 83 patients (59.7%), 35 patients were recurrence-free by the end of the observation period (25.2%) and status was unknown in 21 patients (15.1%). The most common types of metastases were liver metastases (n=34, 24.5%), peritoneal carcinomatosis (n=21, 15.1%), lung metastases (n=14, 10.1%) and lymph node metastases (n=7, 5.0%). Other metastases (to bone, brain, colon and abdominal wall) occurred in seven patients (5.0%). Local recurrence

Table 7 Comparison of data from patients pre-treated with FOLFIRINOX and gemcitabine/nab-paclitaxel

Characteristics	FOLFIRINOX (n=106)	Gemcitabine/nab-paclitaxel (n=16)	P value
Gender			
Female	44 (41.5)	7 (43.75)	>0.99
Male	62 (58.5)	9 (56.25)	>0.99
Age at diagnosis (year)	60 [54.25–67]	65 [60–70.75]	0.017
BMI (kg/m^2)	23.9 [21.6–27.25]	23.8 [20.55–25.7]	0.610
ASA	3 [2–3]	3 [2–3]	0.505
Preoperative chemotherapy			
Cycles	12 [8–12]	2 [2–2.5]	<0.001
Months	6 [4–6]	2 [2–2.5]	<0.001
Tolerability of chemotherapy			
Good tolerability	44 (41.5)	5 (31.25)	0.586
Moderate tolerability	29 (27.4)	1 (6.25)	0.115
Poor tolerability	30 (28.3)	8 (50.0)	0.091
Unknown	3 (2.8)	2 (12.5)	0.128
Response to chemotherapy			
Partial response	70 (66.0)	6 (37.5)	0.05
Stable disease	32 (30.2)	8 (50.0)	0.153
Progressive disease	4 (3.8)	2 (12.5)	0.177
Time between diagnosis and surgery (months)	7 [6–9]	3.5 [3–4.25]	<0.001
Duration of surgery (min)	317.5 [231.25–393.75]	330 [237.75–384.25]	0.955
Resection status			
Resected	64 (60.4)	12 (75.0)	0.407
Non-resected	42 (39.6)	4 (25.0)	0.407
R0 rate	59 (92.2)	12 (100.0)	0.587
Length of stay in hospital (days)	16 [13–22]	22 [14–32.5]	0.184
Length of stay in ICU (days)	1 [1–2]	1 [1–1.25]	0.973
30-day mortality	2 (1.9)	0	>0.99
Postoperative survival (months)	22 [11–40]	30 [10–60]	0.205
Overall survival (months)	31 [19–50]	40 [21–63]	0.314
Recurrence-/progression-free survival (months)	9 [3–15]	11 [2–39]	0.122
5-year survival rate	21.2%	46.2%	0.059
Patient status			
Deceased	61 (57.5)	9 (56.25)	>0.99
Alive	45 (42.5)	7 (43.75)	>0.99

Data are presented as n (%) or median [interquartile range], unless otherwise indicated. BMI, body mass index; ASA, American Society of Anesthesiologists; ICU, intensive care unit.

occurred in 18 of all resected patients (21.2%).

Discussion

Since FOLFIRINOX and gemcitabine/nab-paclitaxel were reported to improve the survival of patients diagnosed with pancreatic cancer, PCT gains in importance (4,5). For resectable PDAC, a surgical approach is primarily recommended, whereas patients in locally advanced tumor stages are often pre-treated with chemotherapeutical regimes (7).

Still, knowledge about surgical results after chemotherapy is mainly based on small study populations and meta-analyses of inhomogeneous studies (15). Others focus on PRCT, but not chemotherapy alone (16). However, PRCT for LAPC is rather uncommon in Germany (17). In multicentre studies, there are clinic-dependent differences in the application of chemotherapy, the performance of surgery and the experience of different surgeons. In addition, there are often exclusion criteria in studies for patients of certain age or pre-existing illness. A positive selection of fit patients with Eastern Cooperative Oncology Group (ECOG) 0–1 to receive chemotherapy is the most common and well-known bias of studies on PDAC, irrespective of prospective or retrospective character (18). Finally, various chemotherapeutical regimens are used in international studies, which might impair comparability.

This study presents both surgical and oncological data gathered at a high-volume centre for pancreatic surgery. The aim of our study was to collect real-world data from an unselected patient population from the daily clinical routine. There were no exclusion criteria. The monocentric design of the study is associated with advantages as high comparability within the enrolled patients and less influencing factors due to the standardised implementation of PCT (regarding regimens, cycles, examiners, and follow-up examinations) and standardised surgical techniques performed by the same certified pancreatic surgeons. An analysis of quality of life (QoL) data was not carried out.

Tumor size is known to be predictor of local recurrence and as a prognostic marker (19). After pre-treatment, radiological evaluation showed a PR and a reduction of the tumor volume in many cases, especially in patients whose tumors could be resected. In 2020, Kunzmann *et al.* reported no statistically significant radiographic response rate after administering gemcitabine/nab-paclitaxel ± FOLFIRINOX (20). In our study, the majority of the patients was exclusively treated with FOLFIRINOX. Furthermore and in contrast to Kunzmann's study, only patients capable of a surgical exploration were analysed. Patients with a poor response to PCT were rarely included.

During chemotherapy, many patients showed a reduction of CA19-9 levels. The strongest decrease was found in patients who could be resected after pre-treatment. The magnitude of reduction of CA19-9 during PCT is known as a strong prognostic factor in PDAC (21).

Surgical outcome of the patients did not show increased postoperative morbidity compared to the literature data (22). Furthermore, there was no significant difference in comparison to patients who underwent primary surgery, even if the patients in our analysis were immunosuppressed for months by PCT and had a high tumor load and advanced malignant disease. The mortality rate of 1.4% in our collective was significantly lower than the average mortality rate of 3.8% of the certified pancreatic cancer centres in Germany (17).

Gleeson *et al.* described major complications in 26.9% of patients after PD in an international dataset (23). In our analysis, 5.8% of patients developed major complications after pancreatoduodenectomy. Regarding the pancreas-related complications [POPF, DGE, postpancreatectomy hemorrhage (PPH), and others], complication rates were not increased compared to literature data of patients not pre-treated with chemotherapy. In patients undergoing primary surgery, the rate of POPF after PD amounts to 20% (24). In our study, we reported a frequency of POPF of 10.5% after PD. Following DP, rates up to 50% have been reported (25). We indicated POPF in 37.5% of cases. Van Dongen *et al.* and Mangieri *et al.* even proposed a protective effect of preoperative chemoradiotherapy, reducing the occurrence of POPF (2,26). Octreotide was regularly administered to all patients, which might also lead to a reduction of POPF (27,28). Histological evaluation of pancreatic tissue after radiotherapy reports atrophy, decreased volume of acinar cells and changes in the lobular structure (29). The resulting fibrosis is supposed to be associated with a firm pancreatic texture, that could prevent parenchymal tearing at the anastomosis (30). A reduced rate of POPF after PRCT could not be supported by our analysis, albeit chemoradiotherapy was rarely applied in our study group.

POPF is associated with DGE (31). It was found in 26.3% after PD and in 12.5% after DP. This corresponds to the results of analyses of German registry data (22,32). Another cause for severe morbidity and high mortality rates is PPH, caused by an erosion of vessels by pancreatic

fluids (33). We reported similar rates of PPH in comparison to data in the literature (32). In conclusion, surgery after PCT was not associated with increased postoperative morbidity.

Resections were performed in 61.2% of patients, leading to a statistically significant better outcome. In terms of median survival, the resected patients showed significantly longer postoperative survival (31 *vs.* 13 months) and significantly longer overall survival (40 *vs.* 20 months) compared to the non-resected patients. There were also significant differences in recurrence-/progression-free survival (12 *vs.* 4 months) in favour of the resected patients. After PCT and resection of the tumor, a 5-year survival rate of 34.1% was calculated, whereas unresectability was associated with a 5-year survival rate of 6.3%. Our data resemble reports in the literature (34,35).

Various chemotherapeutical regimes have been used for patients with PDAC throughout the last decades. The greatest experience was gathered with the use of gemcitabine, but in 2018, Conroy *et al.* stated a longer survival of patients with resected PDAC after the treatment with FOLFIRINOX (36,37). According to these findings, the most common drug regime in our study was FOLFIRINOX. Klein-Brill *et al.* showed a longer median survival after FOLFIRINOX compared to gemcitabine/nab-paclitaxel in metastatic PDAC (38). These findings could not be supported by our results, as there was no significant difference in survival times between FOLFIRINOX and gemcitabine/nab-paclitaxel. As the vast majority of our patients was treated with FOLFIRINOX, the statistical validity regarding the effect of gemcitabine/nab-paclitaxel might be impaired. Furthermore, none of the patients in this study was diagnosed with metastatic disease, which could also impact the results of the chemotherapeutical treatment. Most recently, the ESPAC5-trial reported a beneficial association of PCT preceding surgery (FOLFIRINOX or gemcitabine/nab-paclitaxel) and survival compared to immediate surgery in patients with borderline resectable PDAC (39). Our data suggest that in LAPC, pre-treatment with FOLFIRINOX is also conducive. Adverse effects regarding the surgical results are not to be expected. Future research should focus on randomized controlled trials to improve knowledge about this emerging aspect of the treatment of pancreatic cancer.

Conclusions

This study underlines that PCT allows resectability of primarily unresectable patients with locally advanced pancreatic adenocarcinoma in many cases. Surgery after primary chemotherapy is not associated with an increase of postoperative mortality and morbidity. Furthermore, the combination of PCT followed by surgery leads to a significant prolongation of recurrence-free and overall survival in patients diagnosed with LAPC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-426/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-426/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the Ruhr-University Bochum (Reg. No. 22-7610 and 20-7140-bio) and written informed consent of each patient was given for the analysis.

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