UNIVERSITY OF VERONA

Department of Medicine
Department of Engineering for Precision Medicine

DOCTORAL PROGRAM IN
INFLAMMATION, IMMUNITY AND CANCER

Cycle XXXVII/ 2021

Post-operative and oncological outcomes of surgical management options for localized pancreatic ductal adenocarcinoma.

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Summary

Abstract

Abstract

The present document presents a comprehensive analysis of postoperative and long-term survival outcomes for distinct surgical approaches undertaken in the treatment of patients with localized pancreatic ductal adenocarcinoma - a condition associated with the poorest prognosis in gastrointestinal oncology, where tumor resection coupled with systemic treatment nowadays offers the only chance for cure. The research project is articulated in two clinical original studies, which follow one another both chronologically and substantially. The first study was intended to scrutinize predictors and outcomes of resection failure, namely, the dismal scenario where surgery needs to be aborted due to the presence of advanced disease not suitable for resection. Analyzing a contemporary series of some 700 consecutive patients who underwent laparotomy with curative intent, a 10% resection-to-exploration ratio was delineated, with preoperative anatomical staging resulting as the strongest predictor of resection omission when primary chemo(radiation)therapy was undertaken. Thus, the study findings provide relevant information for patient triaging and surgical planning.

Furthermore, patients who were omitted resection not only exhibited an extremely poor life expectancy (slightly surpassing one year) but also displayed a substantial risk of early metastatization, which surprisingly was not dissimilar to that of patients who underwent *extended* surgery to achieve tumor clearance due to a locally advanced disease ascertained intraoperatively. Therefore, the beneficial effect of the latter, technically demanding operations was questioned. On these premises, a more refined project was designed to compare head-to-head patients who did not undergo resection to those who underwent standard and extended procedures. Such a follow-up study including an enriched cohort of 800 patients operated upon over four years, indicated that when extra-pancreatic and peri-vascular tumor spread was confirmed intraoperatively, extended surgery did provide an overall survival advantage compared to non-resectional procedures. However, systemic disease progression was confirmed to occur early regardless of the surgery.

These data are of utmost importance for the pancreatic surgeon. In fact, while being often associated with a significant complication burden, extended pancreatectomy including vascular and multivisceral resections proved to marginally modify the disease trajectory and the risk of systemic dissemination.

Collectively, such data highlight that, once the technical proficiency to perform extended pancreatic resections is achieved at high-volume institutions, decision-making needs to be refined to identify patients who can actually benefit from such procedures. Unfortunately, solid biological data are still eagerly awaited. In this respect, in addition to crude postoperative survival estimates, patient-reported longitudinal quality-of-life metrics can provide important information to evaluate surgical appropriateness and effectiveness, as well as for shared decision-making. On the basis of the data reported herein, a prospective, longitudinal observational study is currently under development at the defendant's institution, aiming to define long-term physical and social deterioration associated with surgery for pancreatic cancer.

Study I

Resection to exploration ratios and associated outcomes in patients with pancreatic ductal adenocarcinoma.

Abstract

Objective: To investigate resection/exploration ratios (RER), reasons for omission of pancreatectomy, and survival outcomes in patients undergoing surgical exploration with resection intent for pancreatic ductal adenocarcinoma (PDAC).

Summary Background Data: While surgical indications for PDAC are expanding, information about intraoperative attrition is lacking.

Methods: The RER was calculated in PDAC patients undergoing exploration from 2018 through 2020. Factors associated with uncompleted resection and survival were identified using multivariable models.

Results: In total, 681 patients were included. Upfront explorations were 296 (43.7%), and post-neoadjuvant explorations were 385 (56.3%). The overall RER was 89.7% (90.5% in the upfront setting and 89.1% post-neoadjuvant treatment). In this latter subgroup, the RER decreased from 96.1% in resectable disease to 86.6% in borderline resectable disease and 61.9% in locally advanced disease. The primary reasons for uncompleted resection were occult metastases in presumed resectable/borderline resectable disease (without difference between upfront and post-neoadjuvant operations) and local unresectability in locally advanced disease. No preoperative variable was associated with uncompleted resection in upfront explorations, while anatomical staging informed the likelihood of surgical attrition following neoadjuvant treatment. Uncompleted resection was invariably associated with a median survival of around one year. The median post-pancreatectomy survival was 36.9 months in the upfront setting and 29.5 months following neoadjuvant treatment. The median survival from diagnosis in patients receiving post-neoadjuvant resection was 34.5 months.

Conclusions: This analysis provided contemporary information about resection rates, reasons for intraoperative attrition, and survival outcomes in the entire spectrum of PDAC patients selected for surgical exploration at an experienced institution.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a dreadful disease, with 5-year overall survival rates only recently surpassing 10% [1]. While a combination of resection and systemic treatment is the only chance for long-term survival, the bulk of patients will never qualify for pancreatectomy because of locally unresectable or metastatic disease.

Current indications for immediate pancreatectomy include absence or minimal solid tumor contact with peri-pancreatic vasculature (so-called anatomically resectable disease) and no concern for occult metastatic disease [2]. Otherwise, a chemo(radio)therapy-first strategy is undertaken, with a stable or responsive localized disease being the minimum requirement for attempting subsequent resection [2,3]. Thanks to effective chemotherapy strategies and improvements in surgical proficiency, the chances for pancreatectomy post-treatment have expanded. This has led to a surge of data supporting improved survival following "radical" extended operations with synchronous venous or arterial resection, even in conjunction with complex multivisceral resections [4-10]. Regardless of the initial treatment strategy, narrowing the denominator to patients who came to resection may overestimate outcomes by overlooking those who experience intraoperative attrition. In this respect, there is little information about the incidence of non-resectional procedures, the reasons for which resection is omitted, and the associated outcomes[11,12].

Because of the evolving landscape of surgical triaging and operative attitudes, we focused on a contemporary series of surgical candidates to investigate the resection-to-exploration ratios (RER) and the characteristics of patients who undergo exploration but do not receive resection. Furthermore, postoperative and survival outcomes of patients receiving pancreatectomy *versus* non-resectional procedures were compared.

Methods

Study design

This registry-based observational analysis was approved by the local Ethical Committee (n.1101CESC). Study reporting complies with the Strengthening the Reporting of Observational Study in Epidemiology (STROBE) guidelines [13]. The institutional electronic system was queried to identify patients evaluated for pathologically proven or suspected localized PDAC. Consecutive patients who underwent exploration with intent of pancreatectomy (either in the upfront setting or post-treatment) between 2018 and 2020 were extracted and considered for inclusion in the analysis. Only patients with conventional PDAC were included in the final analysis.

Patient triaging and Perioperative Management

Institutional practices for baseline evaluation and perioperative management were discussed elsewhere.[14-16] NCCN criteria were used to define tumor resectability.[2] Serum Ca19.9 levels were measured at the time of diagnosis and at re-staging in those receiving primary chemo(radio)therapy. Patients with baseline levels <5 U/mL were considered non-secretors.[17] Patients with radiologically resectable disease and no suspicion of occult metastases were assigned to upfront surgery or neoadjuvant treatment within clinical trials.[18] Further work-up was performed in case of suspicious, undetermined lesions, including MRI and/or CT-PET and/or pathological confirmation of the target lesion.

In patients who received primary chemo(radio)therapy, restaging was performed using CT and MRI as appropriate; tumor response was defined per the Response Evaluation Criteria in Solid Tumor (RECIST) definition v1.1.[19] Ca19.9 response was defined as a decrease >50% relative to the baseline.[16] All cases were discussed in a multidisciplinary meeting; surgical exploration was indicated when a macroscopically radical pancreatectomy was achievable without superior mesenteric artery resection (absence of arterial contour irregularity, lumen

narrowing with “string” sign). The decision to commit to exploration was further discussed and agreed upon during a preoperative surgical meeting.[20] Symptomatic patients who underwent exploration with the intent of a palliative procedure were excluded. All procedures were performed by experienced pancreatic surgeons. Laparoscopic staging was not routinely performed. Determinants of intraoperative resectability were the absence of distant metastases and reconstructible superior mesenteric/portal veins. When periarterial solid tissue was found, biopsies for frozen section analysis were performed. The decision to proceed with pancreatectomy was made based on frozen section analysis results and the presence of a plane for periarterial divestment. Peripancreatic lymph nodes were excised en bloc with the specimen, whereas additional lymph node stations were retrieved separately. All patients underwent postoperative oncological evaluation. Follow-up was carried out on a three-month basis for the first year and at 6-month intervals thereafter and updated until December 31st, 2022.

Outcome Measures

This study is intended to define the RER and factors associated with the omission of resection and survival in patients deemed eligible for pancreatectomy. Sub-analyses were performed between patients who underwent upfront versus post-treatment operations. Preoperative data included standard variables (tumor location and resectability status, serum Ca19.9, and tumor response in patients receiving neoadjuvant treatment). The type of surgery and reasons for not performing pancreatectomy were captured. The severity of 90-day postoperative complications was graded using the Clavien-Dindo classification.[21] For patients undergoing pancreatectomy, pathological tumor characteristics included margin status, tumor grading, T-status, N-status, and final stage per the AJCC classification, 8th edition.

Statistical Analysis

Categorical variables were expressed as frequencies with percentages and compared using the Chi-Square or Fisher's exact test. Continuous variables were expressed as medians with interquartile ranges (IQR) and compared using the Mann-Whitney or Kruskall-Wallis test. Multivariable binary logistic regression (backward stepwise elimination, Wald method, $P<0.5$ for entry, $P<0.1$ for removal) was employed to determine independent outcome predictors. Variables for model entry were selected based on clinical and statistical criteria ($P<0.1$ at univariable analysis). Continuous predictors were not categorized for multivariable modeling to minimize information loss.

Overall survival (OS) was calculated from the date of surgery to death or last follow-up. Survival functions were calculated using the Kaplan-Meier method; pairwise comparisons were performed through the log-rank test. Factors associated with survival were identified using Cox regression after confirming model assumptions. All analyses were performed using R 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

General characteristics and operative outcomes

During the study period, 1161 patients with localized PDAC were evaluated at the authors' institution. In total, 681 patients (58.6%) were selected for surgical exploration with resection intent. Of these, 296 (43.7%) were upfront explorations, and 385 (56.3%) were post-treatment explorations. Pancreatectomy was performed in 611/681 patients (RER=89.7%), whereas 70 (10.3%) did not undergo resection due to a locally unresectable disease (n=25, 35.7%) and evidence of distant metastases (n=45, 64.3%). Among these 70 patients, 38 underwent exploration only (54.3%), while cholecystectomy with or without bypass procedures was performed in 32 patients (45.7%). Baseline characteristics stratified by resection versus non-resectional procedures are shown in Table 1. Remarkably, the resection rates and reasons for omission of resection did not differ between patients who were operated in the upfront setting or post-treatment (RER of 90.5% versus 89.1%, p=0.611; metastatic disease 67.9% vs. 61.9%, p=0.799). Pathologic details of patients who underwent resection are displayed in Supplemental Digital Content, Table 1. A margin-free resection was achieved in 380 patients (62.2%), while R1 and R2 resection were reported in 223 (36.5%) and eight patients (1.3%), respectively.

Sub-analysis of upfront surgery cohort

At baseline, 317 patients were evaluated for upfront exploration; 21 (6.6%) were excluded after restaging for disease progression. Nearly all patients undergoing upfront surgical exploration had an anatomically resectable disease (282/296, 95.3%). The 14 patients with borderline resectable disease were evaluated for initial exploration after refusing neoadjuvant therapy or participation in clinical trials. Overall, 268/296 patients received resection (RER=90.5%). The RER was 92.2% (260/282) in anatomically resectable disease and 57.1% (8/14) in borderline resectable disease ($p<0.001$). Other clinical and radiological parameters did not differ between patients who received resection and those who did not (Table 2). Still,

unresected patients were more likely to be heavy alcohol drinkers (17.9 vs. 5.7%, p=0.031). The main reason for not performing pancreatectomy was the finding of unanticipated metastatic disease (19/28, 67.9%; Figure 1A). In the 268 patients receiving pancreatectomy, the rate of synchronous vascular resections was 12.3% (31/33 venous, 2/33 synchronous venous plus arterial). The rate of R0, R1, and R2 resection was 61.6%, 36.9%, and 1.5%, respectively, with no significant difference according to resectability status (resectable vs. borderline resectable, p=0.939). At pathological staging, most patients resulted having pT1/T2 tumors (19.0 and 69.9%, respectively), with N0, N1, and N2 disease being found in 14.9, 35.4 and 49.6% of patients, respectively (Supplemental Digital Content, Table 1). At the adjusted analysis, no preoperative factor was associated with the omission of resection (data not shown). Overall, 69.8% of patients received adjuvant therapy (187/268), and 50.4% (132/262) completed a full 6-month cycle.

Sub-analysis of post-treatment cohort

At baseline, 844 patients were evaluated for neoadjuvant/primary chemotherapy (283 with resectable disease, 281 with borderline resectable disease, and 280 with locally advanced disease). No information on the initial number of patients with metastatic disease could be abstracted. In total, 385/844 patients (45.6%) were selected for surgical exploration post-treatment, 185 (48.1%) following FOLFIRINOX and 140 (36.4%) following Gemcitabine plus Nab-Paclitaxel (Table 3). The median duration of primary chemotherapy was five months (IQR 3-6). Radiation therapy was delivered in 159 patients (41.3%). On restaging, 207/385 patients (53.8%) were anatomically resectable, while 135 (35.1%) were borderline resectable, 42 (10.9%) locally advanced, and one patient (0.2%) was oligometastatic. Overall, 343/385 patients underwent resection (RER=89.1%). The RER was 96.1% in anatomically resectable disease (199/207), 86.6% in borderline resectable disease (117/135), and 61.9% in locally advanced disease (26/42). The oligometastatic patient was excluded from further analyses. The

main reasons for uncompleted resection were unexpected metastatic disease in presumed resectable (6/8, 75.0%) and borderline resectable patients (12/18, 66.7%), whereas the presence of extended vascular infiltration was the primary reason for the omission of resection in half patients with locally advanced disease (8/16, 50%; Figure 1B). In patients receiving pancreatectomy, the rate of vascular resections was 37.9% (31.4% venous, 4.1% arterial, and 2.4% combined). On final pathologic examination, the median tumor size was 25 mm (IQR 18-30). One hundred twenty-three patients (35.9%) had N0 disease, while 36.4% and 27.7% had N1 and N2 disease, respectively (Supplemental Digital Content, Table 1). The rate of R0 resection was 62.7% (215/343), with no difference when stratifying by local extension (67.3% in resectable disease versus 54.7% in borderline resectable versus 61.5% in locally advanced, p=0.131).

At the adjusted analysis, preoperative anatomical staging significantly predicted omission of resection (borderline resectable: OR 3.21, 95%CI 1.83-12.3; and locally advanced: OR 30.6, 95%CI 6.05-154.6 vs. anatomically resectable, p<0.001) while increasing age-adjusted CCI (OR 0.43, 95%CI 0.25-0.73, p<0.001), the presence of symptoms at diagnosis (OR 0.22, 95%CI 0.06-0.77, p=0.018) and administration of radiation therapy (OR 0.21, 95%CI 0.05-0.81, p=0.024) were associated with resection (Supplemental Digital Content, Table 2). Overall, 67.9% of patients (233/343) received six months of chemotherapy (total neoadjuvant therapy=131/233, 56.2%; perioperative treatment =102/233, 43.8%).

Postoperative course

The rate of postoperative complications was 58.9% (401/681), and 128 patients (18.8%) had severe complications. Forty-nine patients underwent reoperation (7.2%), and twenty-one (3.1%) eventually died. The rate of overall complications (63.2% vs. 21.3%), severe complications (20.1% vs. 7.1%), reoperations (7.9% vs. 1.4%), and length of stay (median 9, IQR 7-17 vs. 5, IQR 4-7 days) was greater in patients undergoing pancreatectomy compared to

non-resectional procedures (all p<0.001). Conversely, there was no difference in 90-day mortality (1.4% vs. 3.3%, p=0.713). When stratifying by upfront versus post-treatment operations, patients receiving pancreatectomy were confirmed to have poorer outcomes (Supplemental Digital Content, Table 3).

Survival analysis – overall cohort

The median postoperative follow-up was 16.7 months (95%CI 9.2-28.4) for the overall cohort. At the time of last contact, 314 patients (46.1%) were still alive, with a median follow-up of 28.7 months (reverse Kaplan-Meier estimator, 95%CI 27.3-30.1 months). The median OS in the overall cohort was 28.6 months (95%CI 26.4-33.1). Patients receiving non-resectional procedures displayed worse survival than those who underwent resection (median OS 11.8 months, 95%CI 9.9-13.6 vs. 31.4 months, 95%CI 27.2-35.6, p<0.001; Figure 2A). The estimated 1 to 3-year survival rates were 47.3%, 21.1%, and 8.1% following non-resectional surgery and 80.1%, 59.4% and 44.1% after pancreatectomy. In a Cox model excluding patients who experienced postoperative mortality, non-resectional surgery was the strongest predictor of decreased survival (HR 3.19, 95%CI 2.14-4.75, p<0.001; Supplemental Digital Content, Table 4). In the subgroup of unresected patients, there was no survival difference between those who had been found with metastatic disease and those with locally advanced disease (median OS 10.8 months, 95%CI 7.6-14.0 vs. 14.4 months, 95%CI 1.5-27.3, respectively, p=0.10; Figure 2B).

Survival analysis - upfront surgery cohort

In the upfront surgery cohort (n=290), the median OS was 32.0 months (95%CI 27.2-39.3). The median OS was 36.9 months (95%CI 31.8-42.1) in patients who underwent pancreatectomy and 11.7 months (95%CI 7.9-15.5) in those who underwent non-resectional procedures (p<0.001). Pairwise comparison of survival outcomes across preoperative variables

is shown in Supplemental Digital Content, Table 5. Intraoperative attrition remained the strongest factor associated with decreased survival at the adjusted analysis (HR 3.59, 95%CI 1.94-6.62, p<0.001), together with the development of severe postoperative complications (HR 1.72, 95%CI 1.05-3.01, p=0.046).

In the subgroup of patients undergoing pancreatectomy (Supplemental Digital Content, Table 6), the estimated 1-year to 3-year survival rates were 86.7%, 64.7%, and 48.3%, respectively. The only preoperative factor associated with survival at multivariable analysis was serum Ca 19.9 (HR 1.00, 95%CI 1.00-1.00, p=0.016). Other variables associated with reduced survival were multi-visceral resection (HR 3.12, 95%CI 1.00-9.74; p=0.05), T-status (T2: HR 2.68, 95%CI 1.41-9.65, p=0.008; and T3: HR 3.39, 95%CI 0.7-8.15, p=0.065) and N-status (N1: HR 2.48, 95%CI 0.81-7.59, p=0.113; and N2: HR 8.60, 95%CI 2.79-26.5, p<0.001). Conversely, the administration of adjuvant chemotherapy was associated with improved survival (HR 0.24, 95%CI 0.12-0.35, p<0.001).

Survival analysis - post-treatment cohort

In the post-treatment cohort (n=370), the median OS from diagnosis was 33 months (95%CI 33.0-37.7). The median OS from diagnosis was 34.5 months (95%CI 32.6-43.2) in patients who underwent resection and 17.5 months (95%CI 16.4-25.9) in those who underwent non-resectional procedures (p<0.001). The median OS from surgery was 27.1 months (95%CI 23.6-32.2). The median post-pancreatectomy OS was 29.5 months (95%CI 24.5-34.5) and 11.4 months (95%CI 7.9-15.5) following non-resectional procedures (p<0.001). Pairwise comparison of survival outcomes across preoperative variables is shown in Supplemental Digital Content, Table 7. Patients receiving primary Gemcitabine plus Nab-Paclitaxel displayed decreased survival (median OS 21.0 months, 95%CI 13.4-28.7) compared to those who received FOLFIRINOX (median OS 26.4 months, 95%CI 22.3-30.4) or other regimens (median OS 40.4 months, 95%CI 24.2-56.6, p=0.004). Yet, at the adjusted analysis, neither

primary chemotherapy regimen nor radiation therapy delivery or post-treatment radiological response per RECIST criteria were associated with survival. Conversely, more advanced disease status per NCCN criteria at pre-operative imaging (borderline resectable: HR 1.74, 95%CI 1.20-2.53, p=0.001, and locally advanced: HR 1.12, 95%CI 0.63-1.99, p=0.085) and higher Ca19.9 (HR 1.01, 95%CI 1.00-1.01, p=0.01) resulted independently associated with reduced survival, with non-resectional surgery being the strongest predictor of a poorer prognosis (HR 2.33, 95%CI 1.33-4.07, p=0.003).

In the subgroup of patients receiving pancreatectomy, the estimated 1 to 3-year survival rates were 78.9%, 57.4%, and 41.7%. Patients with more advanced disease at preoperative imaging, those with unresponsive disease per RECIST criteria, and those with greater tumor size and higher Ca19.9 displayed decreased survival compared to their counterparts (Supplemental Digital Content, Table 8). After multivariable adjustment, only preoperative Ca19.9 (HR 1.00, 95%CI 1.00-1.01, p=0.01), radiologic tumor response per RECIST criteria (stable disease: HR 0.79, 95%CI 0.52-1.22, p=0.055, and progressive disease: HR 2.06, 95%CI 0.94-4.54, p=0.065), as well as N-status (N1: HR 1.75, 95%CI 1.02-2.98, p=0.039; and N2: HR 1.77, 95%CI 0.96-3.26, p=0.066), R-status (R1: HR 1.59, 95%CI 1.05-2.44, p=0.012; and R2: HR 6.45, 95%CI 1.09-37.9, p=0.04) and receipt of adjuvant treatment (HR 0.61, 95%CI 0.39-0.95, p=0.030) remained associated with survival.

Discussion

This observational analysis of 681 consecutive PDAC patients undergoing exploration with resection intent recapitulates the recent practice of a tertiary-care center. The overall RER was 89.7%, indicating that 1/10 patients amenable to resection on preoperative staging failed to receive pancreatectomy. While the overall rate of uncompleted resections was similar in the upfront setting and following primary chemo(radio)therapy, the reasons for intraoperative attrition and factors associated with survival were nuanced. In the 296 patients undergoing upfront operations, unanticipated metastatic disease was the leading cause of non-resectional procedures and was not associated with any preoperative variable in the adjusted analysis. These were almost invariably patients with anatomically resectable disease (282/296) and no concern for biologic or conditional borderline status [22]. Indeed, in this select subgroup, the RER was 92.2%. Previous studies of patients undergoing upfront exploration showed lower resection rates, ranging from 66% to 80% [11,23]. Instead, in a recent analysis from the Dutch Pancreatic Cancer Audit, the rate of unexpected metastases was comparable to the present data (10%). A preoperative prediction model for occult metastatic disease, applied in an external set of patients from the author's institution, performed poorly, [24] confirming how difficult it is to spare an unnecessary upfront laparotomy using conventional clinical and radiologic features. In the 14 patients with borderline resectable disease undergoing upfront exploration, the RER was only 57.1%. It is well-accepted that the primary treatment for initially borderline resectable PDAC is neoadjuvant chemotherapy [2]. These few patients came to surgical exploration with the presumption of a localized disease with reconstructible venous anatomy as they refused neoadjuvant chemotherapy or failed to enroll in clinical trials.

There was a substantial survival difference between patients who underwent upfront pancreatectomy and those who underwent non-resectional procedures (36.9 months versus 11.7 months), with resection being the primary determinant of improved outcomes, along with the absence of postoperative complications. The negative impact of major complications on

survival, primarily mediated by the omission of adjuvant therapy, has already been suggested by a nationwide study from the Dutch Pancreatic Cancer Group [25]. Of note, the median OS in patients who underwent pancreatectomy and received adjuvant therapy in the present series was 41 months.

Patients from the post-treatment cohort (385, 57% of the study sample) were more heterogeneous in that 207 (53.8%) had a radiologically resectable disease, and 178 (46.2%) had a more advanced disease. As already pointed out, the former subgroup received neoadjuvant chemotherapy because of high-risk features or were enrolled in clinical trials.[18] The latter subset had an initially borderline resectable or locally advanced disease and received primary chemo(radio)therapy followed by exploration because of responsive or stable disease with associated serum Ca19.9 drop and adequate conditional status. The RER post-treatment declined from 96% in initially radiologically resectable disease to 87% in borderline resectable disease to 62% in locally advanced disease, with preoperative resectability status being the strongest predictor of subsequent pancreatectomy at the adjusted analysis. While the primary reason for uncompleted resection in resectable disease was the presence of unanticipated metastases, the finding of a locally unresectable disease increased in borderline resectable and locally advanced patients. This is consistent with recent large multi-institutional series [26] and with a recent meta-analysis including high-quality observational studies and prospective trials (i.e., the SWOG1505 and the PREOPANC-1 trials), showing pooled RER from 77.4% in resectable disease to 60.6% in borderline resectable and 22.2% in locally advanced disease [27]. Not only do the resection rates herein described compare favorably to pooled data from external institutions, but also to internal historical data. In a prospective analysis examining the trajectory of an unselected cohort of patients with borderline resectable and locally advanced disease (2013-2015), we showed a RER of 63.3% in the overall cohort, 76.9% in initially borderline resectable, and 47.8% in initially locally advanced patients.[14] The improvement in resection rates relative to historical data (+9.7% in borderline resectable and +14.1% in locally

advanced disease) could depend on increasing experience, a deeper understanding of the underlying disease processes, better preoperative triaging, and technical prowess.

Even in the post-treatment cohort, there was a sharp survival difference between patients who underwent resection and those who did not (29.5 months versus 11.4 months), as already shown by previous studies [14,28-31]. Anatomical staging as per NCCN guidelines was strongly associated with OS in the whole post-treatment cohort but not in the subgroup of resected patients.

The relationship between anatomical staging, likelihood of resection, and post-operative survival has been very controversial, especially in non-progressive locally advanced disease, where the attitude towards arterial divestment or resection drives the decision to proceed with pancreatectomy. Because superior mesenteric artery resection is not practiced at our institution and omission of pancreatectomy was associated with dismal outcomes, some would interpret this as a justification for aggressive surgical conduct. In this respect, it has been suggested that arterial involvement is more a question of tumor geography and that pancreatectomy with arterial resection can be safely performed in non-progressive PDAC to improve prognosis [6-10,32]. Conversely, others consider the degree of vascular involvement as a marker of aggressive biology, the natural history of which extended pancreatectomy is unlikely to alter [33]. On this line of reasoning, observational data of patients with stable disease receiving ablative radiation showed a locoregional disease control comparable to resection, with encouraging survival outcomes [34]. In the absence of randomized trials, it is impossible to control the selection bias associated with operative decisions, and whether differences in surgical attitude translate into different oncologic outcomes remains unclear [35]. While we acknowledge that a subset of patients may benefit from “radical” surgery even in case of arterial involvement, prognostic models trying to overcome anatomic features are hardly applicable because the population at risk was limited to the pool of resected patients, neglecting those who experienced intraoperative attrition [36].

This study has limitations. Both patients undergoing upfront and post-neoadjuvant exploration were included under a real-world practice perspective. Although resectable patients were assigned to upfront surgery or neoadjuvant therapy based on anatomic, biochemical, conditional factors [22] or availability of clinical trials [18], a direct comparison between the two approaches is not necessarily appropriate and was beyond the scope of this analysis. Second, this study was not designed to track patients who started chemotherapy but never came to surgical exploration. Although the crude number of patients evaluated at baseline is provided from our registries, in most cases chemotherapy was delivered at spoke institutions. Because of that, there was no systematic information about the reasons for pre-surgical attrition (toxicity, disease progression, clinical deterioration) and the outcomes of patients not re-referred to our center. This makes it impossible to capture details about the selection point for surgical exploration. Third, it was impossible to dissect the specific radiologic parameters associated with local unresectability (i.e., arterial lumen narrowing, length of vascular encasement, perivascular tissue attenuation, radiomic signatures), as this will be the focus of future efforts.

Last, as already mentioned, the reported resection rates reflect the characteristics of our practice and might not be universally generalizable.

With these limitations in mind, the present study provides contemporary information about resection rates, reasons for intraoperative attrition, and survival outcomes across the entire spectrum of PDAC patients selected for surgical exploration. The resection rates were high in resectable disease (with or without neoadjuvant therapy) and progressively decreased in borderline resectable and locally advanced disease post-treatment. Survival outcomes of patients who did not come to resection for unanticipated metastatic disease or local unresectability were poor at around one year. While metastatic disease was unpredictable preoperatively, operative decisions and prognostic implications in locally advanced tumors are dictated by anatomic features and remain debatable in the lack of clinically applicable biologic tools able to anticipate the disease course.

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Figures

Figure 1. Reasons for intraoperative attrition in patients who underwent (a) upfront and (b) post-treatment exploration stratified by pre-operative resectability status.

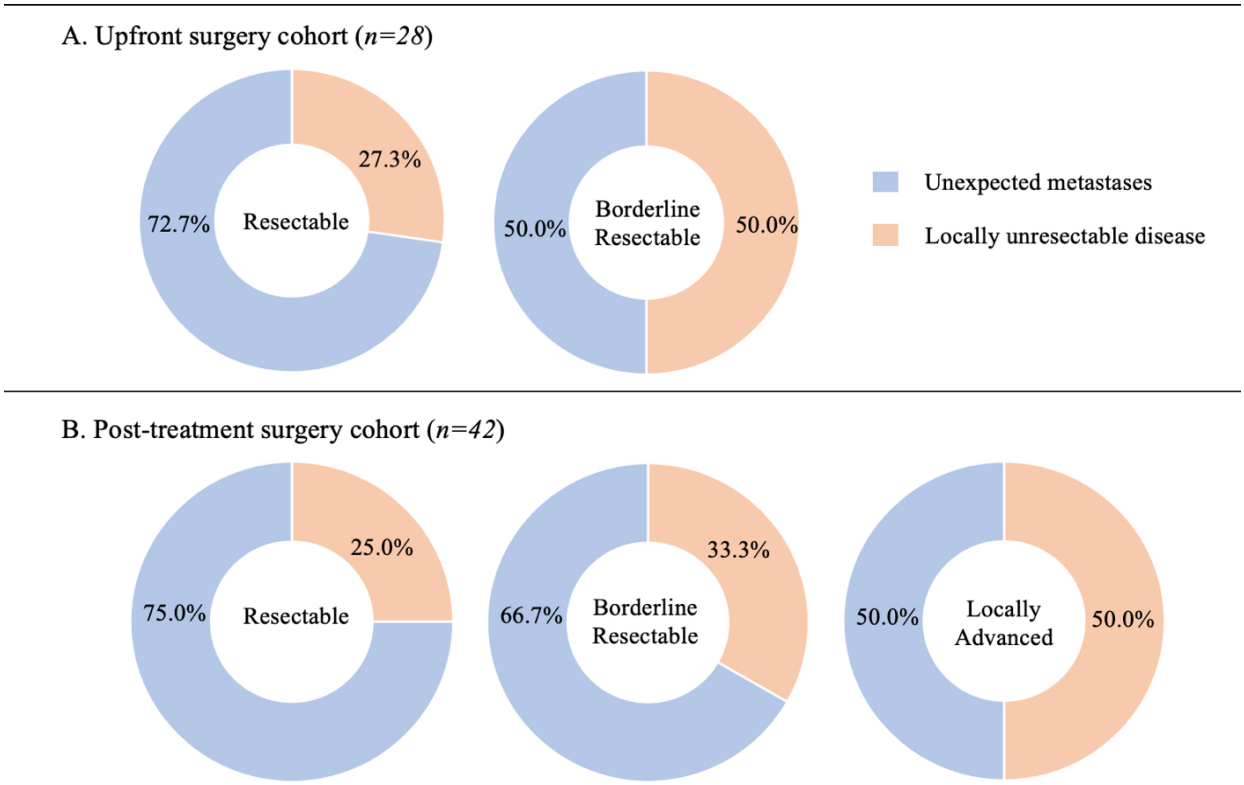
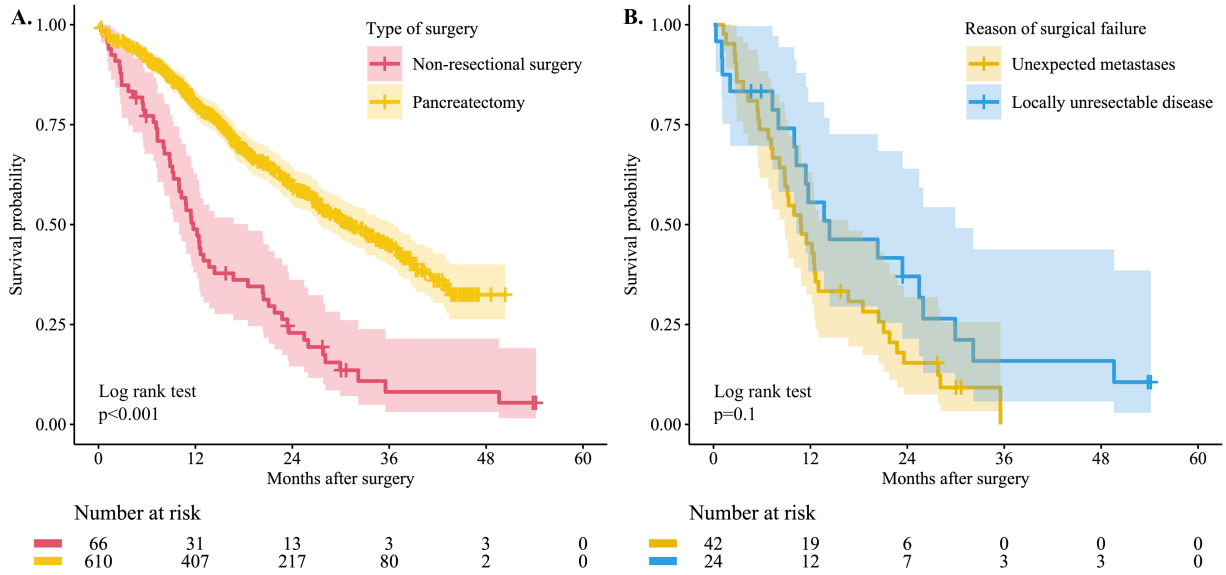


Figure 2. Kaplan-Meier curves of overall survival of (a) overall study population stratified by surgical procedure and (b) patients undergoing non-resectional procedures stratified by reasons of surgical failure.



Tables

Table 1
Baseline features of the study population (n=681).

	Overall population (n=681)	Non-resectional procedures (n=70)	Pancreatectomy (n=611)	P-value*
Gender (female)	329 (48.3)	29 (41.1)	300 (49.1)	0.256
Age, median (IQR)	66 (59-72)	64 (58-73)	66 (59-72)	0.417
BMI	24.1 (21.8-26.7)	24.2 (21.1-25.8)	24.0 (21.8-26.6)	0.585
ASA score				0.479
ASA 1-2	499 (73.3)	54 (77.1)	445 (72.8)	
ASA 3-4	182 (26.7)	16 (22.9)	166 (27.2)	
Age-adjusted CCI	5 (4-6)	2 (2-6)	6 (5-6)	**<0.001**
Cigarette smoking				0.222
No	289 (42.7)	35 (50.0)	254 (41.8)	
Active smoker	162 (23.9)	11 (15.7)	151 (24.9)	
Former smoker (stop >6 months prior to diagnosis)	226 (33.4)	24 (34.3)	202 (33.3)	
Alcohol abuse†	34 (5.0%)	8 (11.4%)	26 (4.3%)	**0.017**
Diabetes	187 (27.5)	17 (24.3)	170 (27.8)	0.575
Jaundice	367 (53.9)	43 (61.4)	324 (53.0)	0.453
Symptoms‡ at diagnosis	537 (79.1)	56 (81.2)	481 (78.9)	0.756
Resectability status (preoperative)				**<0.001**
Anatomically resectable	489 (71.8)	30 (42.9)	459 (75.1)	
Borderline resectable	149 (21.9)	24 (34.3)	125 (20.5)	
Locally advanced	42 (6.2)	16 (22.9)	26 (4.3)	
Oligometastatic	1 (0.1)	0	1 (0.2)	
Tumor size (preoperative), median (IQR)	25 (20-30)	29 (21-38)	25 (20-30)	**0.012**
Preoperative Ca19.9, median (IQR)	44 (15.5-133.8)	56 (24-230)	42 (15-123)	**<0.001**
Preoperative Ca19.9, normal (<37 UI/mL)	286 (45.3)	25 (36.8)	261 (46.3)	0.156
Ca19.9 non secretors (<5 UI/mL)	46 (6.8)	7 (10.0)	39 (6.4)	0.309
Tumor location				
Head	496 (72.9)	54 (77.1)	442 (72.5)	0.478
Body-tail	184 (27.1)	16 (22.9)	168 (27.5)	
Peripancreatic organ involvement	32 (4.7)	4 (5.7)	24 (3.9)	0.519
Primary chemo(radiation) treatment	385 (56.5)	42 (60.0)	343 (56.1)	0.611

*Statistical significance for $p<0.05$.

† Defined as >2 alcohol units/day for men and >1 alcohol unit/day for women according to the WHO classification.

‡ Symptoms at diagnosis include: jaundice, acute pancreatitis, upper abdominal pain, severe weight loss (>10% in six months), gastric outlet obstruction.

Table 2
Clinical and radiological characteristics of patients undergoing upfront surgery (n=296).

	Overall population (n=296)	**Non-resectional procedures (n=28)**	**Pancreatectomy (n=268)**	**P-value***
Gender (female)	145 (49.0)	14 (50.0)	131 (48.9)	0.91
Age, median (IQR)	69 (63-74)	70 (61-74)	69 (63-74)	0.862
BMI	24.1 (21.7-26.9)	24.5 (21.8-26.2)	23.9 (21.6-26.9)	0.762
ASA score				0.509
ASA 1-2	216 (73.0)	19 (67.9)	197 (33.5)	
ASA 3-4	80 (27.0)	9 (32.1)	71 (26.5)	
Age-adjusted CCI	5 (5-7)	5 (2-7)	6 (5-7)	0.05
Cigarette smoking				0.494
No	127 (43.3)	14 (50.0)	113 (42.6)	
Active smoker	80 (27.3)	5 (17.9)	75 (28.3)	
Former smoker (stop >6 months prior to diagnosis)	86 (29.4)	9 (32.1)	77 (29.1)	
Alcohol abuse†	20 (6.8)	5 (17.9)	15 (5.7)	**0.031**
Diabetes	96 (32.4)	10 (35.7)	86 (32.1)	0.677
Jaundice	175 (59.1)	22 (78.6)	153 (57.1)	**0.042**
Symptoms‡ at diagnosis	229 (77.6)	25 (89.3)	204 (76.4)	0.154
Resectability status (preoperative)				**<0.001**
Anatomically resectable	282 (95.3)	22 (78.6)	260 (97.0)	
Borderline resectable	14 (4.7)	6 (21.4)	8 (3.0)	
Tumor size (preoperative), median (IQR)	25 (20-32)	27 (22-34)	25 (20-32)	0.232
Preoperative Ca19.9, median (IQR)	71 (26-212)	89 (28-280)	71 (26-197)	0.386
Preoperative Ca19.9, normal (<37 UI/mL)	90 (33.3)	8 (30.8)	82 (33.6)	0.831
Ca19.9 non secretors (<5 UI/mL)	24 (8.1)	4 (14.3)	20 (7.5)	0.309
Tumor location				
Head	222 (74.3)	23 (82.1)	197 (73.5)	0.263
Body-tail	76 (25.7)	5 (17.9)	71 (26.5)	
Peripancreatic organ involvement	10 (3.4)	2 (7.1)	8 (3.0)	0.242

* Statistical significance for $p<0.05$.

† Defined as >2 alcohol units/day for men and >1 alcohol unit/day for women according to the WHO classification.

‡ Symptoms at diagnosis include: jaundice, acute pancreatitis, upper abdominal pain, severe weight loss (>10% in six months), gastric outlet obstruction.

Table 3
Clinical and pathological characteristics of patients undergoing surgery following primary chemo(radiation)therapy (n=385).

	Overall population (n=385)	Non-resectional procedures (n=42)	Pancreatectomy (n=343)	P-value*
Gender (female)	184 (47.8)	15 (35.7)	169 (49.3)	0.104
Age, median (IQR)	64 (56-70)	62 (56-69)	64 (56-71)	0.52
BMI	23.8 (20.8-26.5)	23.8 (20.8-25.8)	24.1 (21.9-26.6)	0.355
ASA score				0.142
ASA 1-2	283 (73.5)	35 (83.3)	248 (72.3)	
ASA 3-4	102 (26.5)	7 (16.7)	95 (27.7)	
Age-adjusted CCI	5 (4-6)	2 (2-5)	5 (4-6)	**<0.001**
Cigarette smoking				0.408
No	162 (42.2)	21 (50.0)	141 (41.2)	
Active smoker	82 (21.4)	6 (14.3)	76 (22.2)	
Former smoker (stop >6 months prior to diagnosis)	140 (36.5)	15 (35.7)	125 (36.5)	
Alcohol abuse†	14 (3.6)	3 (7.1)	11 (3.2)	0.189
Diabetes	91 (23.6)	7 (16.7)	84 (24.5)	0.337
Jaundice	192 (49.9)	21 (50.0)	171 (49.9)	1.000
Symptoms‡ at diagnosis	380 (80.2)	31 (75.6)	277 (80.8)	0.413
Resectability status (baseline)				**<0.001**
Anatomically resectable	152 (39.5)	5 (11.9)	147 (42.9)	
Borderline resectable	140 (36.4)	15 (35.7)	125 (36.4)	
Locally advanced	84 (21.8)	21 (50.0)	63 (18.4)	
Oligometastatic	9 (2.3)	1 (2.4)	8 (2.3)	
Primary chemotherapy regimen				0.592
(m)FOLFIRINOX	185 (48.1)	20 (47.6)	165 (48.1)	
Gemcitabine and Nab-Paclitaxel	140 (36.4)	18 (42.9)	122 (35.6)	
Other	55 (14.3)	4 (9.5)	51 (14.9)	
Radiation only	5 (1.3)	0	5 (1.5)	
Primary chemotherapy duration (months), median (IQR)	5 (3-6)	5 (4-6)	3 (4-6)	0.637
Preoperative radiation type				**<0.001**
None	226 (58.7)	24 (57.1)	202 (58.9)	
SBRT	132 (34.3)	11 (26.2)	121 (35.3)	
External beam radiation	16 (4.1)	7 (16.7)	9 (2.6)	
Other	11 (2.9)	0	11 (3.2)	
Resectability status (preoperative)				**<0.001**
Anatomically resectable	207 (53.8)	8 (19.0)	199 (58.0)	
Borderline resectable	135 (35.1)	18 (42.9)	117 (34.1)	
Locally advanced	42 (10.9)	16 (38.1)	26 (7.6)	
Oligometastatic	1 (0.3)	0 (0.0)	1 (0.3)	
Tumor size (preoperative), median (IQR)	24 (20-30)	30 (20-40)	23 (20-30)	**0.022**
RECIST response				**0.027**
Partial/Complete response	150 (40.7)	16 (43.2)	134 (40.4)	
Stable disease	195 (52.8)	15 (40.5)	180 (54.2)	
Progressive disease	24 (6.5)	6 (16.2)	18 (5.4)	
Preoperative Ca19.9, median (IQR)	33 (13-83)	52 (18-107)	31 (13-81)	0.228
Preoperative Ca19.9, normal (<37 UI/mL)	196 (54.1)	17 (40.5)	179 (55.9)	0.070
Ca19.9 non secretors (<5 UI/mL)	22 (5.7)	3 (7.1)	19 (5.5)	0.721
Ca19.9 responders (≥50% decrease)	213 (62.8)	22 (59.5)	191 (63.2)	0.719
Tumor location				
Head	276 (71.9)	31 (73.8)	245 (71.6)	0.857
Body-tail	108 (28.1)	11 (26.2)	97 (28.4)	
Peripancreatic organ involvement	18 (4.7)	2 (4.8)	16 (4.7)	1.000

* Statistical significance for $p<0.05$.

† Defined as >2 alcohol units/day for men and >1 alcohol unit/day for women according to the WHO classification.

‡ Symptoms at diagnosis include jaundice, acute pancreatitis, upper abdominal pain, severe weight loss (>10% in six months), gastric outlet obstruction.

Supplementary Tables

Supplementary Table 1.
Surgical and pathological characteristics of patients who underwent pancreatectomy.

	Overall (n=611)	Upfront pancreatectomy (n=268)	Post-treatment pancreatectomy (n=343)
Type of pancreatectomy			
Pancreatoduodenectomy	393 (64.3)	182 (67.9)	211 (61.5)
Distal pancreatectomy	147 (24.1)*	65 (24.3)	82 (23.9)
Total pancreatectomy	71 (11.6)	21 (7.8)	50 (14.6)
Vascular resection	161 (26.4)	33 (12.3)	128 (37.3)
Vascular resection type			
Venous†	137 (22.4)	31 (11.6)	106 (31.4)
Arterial	14 (2.3)	0	14 (4.1)
Combined (arterial plus venous)†	10 (1.6)	2 (0.7)	8 (2.4)
No	450 (73.6)	235 (87.7)	215 (62.1)
Multivisceral resection	29 (4.7)	12 (4.5)	17 (5.0)
Tumor size (mm), median (IQR)	25 (20-33)	28 (23-35)	25 (18-30)
T-status			
TX	25 (4.1)	3 (1.1)	22 (6.4)
T0	8 (1.3)	0 (0.0)	8 (2.3)
T1	163 (26.7)	51 (19.0)	112 (32.7)
T2	339 (55.5)	185 (69.9)	154 (44.9)
T3	62 (10.1)	28 (10.4)	34 (9.9)
T4	14 (2.3)	1 (0.4)	13 (3.8)
N-status			
N0	163 (26.7)	40 (14.9)	123 (35.9)
N1	220 (36.0)	95 (35.4)	125 (36.4)
N2	228 (37.3)	133 (49.6)	95 (27.7)
M-status			
M0	598 (97.9)	262 (97.8)	336 (98.0)
M1	13 (2.1)	6 (2.2)	7 (2.0)
AJCC stage			
0	8 (1.3)	0	8 (2.4)
I	139 (22.7)	39 (14.6)	100 (29.7)
II	219 (35.8)	96 (35.8)	123 (36.5)
III	226 (37.0)	127 (47.4)	99 (29.4)
IV	13 (2.1)	6 (2.2)	7 (2.1)
R-status			
R0	380 (62.2)	165 (61.6)	215 (62.7)
R1	223 (36.5)	99 (36.9)	124 (36.2)
R2	8 (1.3)	4 (1.5)	4 (1.2)
Perineural invasion	545 (89.2)	260 (97.0)	285 (83.1)
Lymph-vascular invasion	539 (88.2)	260 (97.0)	279 (81.3)
Peripancreatic fat invasion	491 (80.4)	244 (91.0)	247 (72.0)
Grading			
G1	12 (2.1)	12 (4.5)	0 (0.0)
G2	211 (36.9)	169 (63.3)	42 (13.8)
G3	77 (13.5)	69 (25.8)	8 (2.6)
Anaplastic	6 (1.0)	5 (1.9)	1 (0.3)
Not assessed	266 (46.5)	12 (4.5)	254 (83.3)

* Including 11 patients undergoing modified Appleby procedure (distal pancreatectomy with en-bloc celiac trunk resection).

† Among the 147 patients undergoing venous resection, 111 (75.5%) had resection followed by direct closure (ISGPS type 1), 3 patients (2.1%) had partial excision with patch reconstruction using either a peritoneal or splenic vein patch (ISGPS type 2), and 33 patients (22.4%) a segmental vein resection followed by end-to-end anastomosis reconstruction (ISGPS type 3).

Supplementary Table 2
Multivariable analysis of factors associated with the omission of resection in the post-neoadjuvant setting.

	OR	95%CI	P-value*
Gender (female)	0.52	(0.68-1.56)	0.238
Age	1.07	(0.98-1.16)	0.122
ASA score			
ASA 1-2	Ref		
ASA 3-4	1.32	(0.35-4.98)	0.680
Age-adjusted CCI	0.43	(0.25-0.73)	**<0.001**
Diabetes	1.97	(0.41-9.34)	0.394
Symptoms† at diagnosis	0.22	(0.06-0.77)	**0.018**
Resectability status (baseline)			
Anatomically resectable	Ref		
Borderline resectable	3.53	(1.24-9.98)	**0.017**
Locally advanced	9.8	(3.53-27.2)	**<0.001**
Oligometastatic	3.67	(0.38-35.2)	0.258
Primary chemotherapy regimen			
Gemcitabine and Nab-Paclitaxel	Ref		
(m)FOLFIRINOX	0.45	(0.11-1.82)	0.265
Other	0.10	(0.01-1.99)	0.133
Primary chemotherapy duration	0.86	(0.65-1.13)	0.268
Preoperative radiation	0.21	(0.05-0.81)	**0.024**
Resectability status (preoperative)‡			
Anatomically resectable	Ref		
Borderline resectable	3.21	(1.83-12.3)	**0.048**
Locally advanced	30.6	(6.05-154.6)	**<0.001**
Tumor size (preoperative)	1.04	(0.99-1.09)	0.220
RECIST response			
Partial/Complete response	Ref		
Stable disease	1.17	(0.33-4.21)	0.806
Progressive disease	1.76	(0.28-11.01)	0.547
Preoperative Ca19.9, normal (<37 UI/mL)	1.61	(0.52-5.03)	0.406
Ca19.9 responders (≥50% decrease)	1.27	(0.42-3.85)	0.666
Tumor location			
Head	Ref		
Body-tail	0.49	(0.14-1.72)	0.264
Peripancreatic organ involvement	0.25	(0.01-10.1)	0.465

* Statistical significance for $p<0.05$.

† Symptoms at diagnosis include jaundice, acute pancreatitis, upper abdominal pain, severe weight loss (>10% in six months), and gastric outlet obstruction.

‡ One patient with oligometastatic disease was excluded from the analysis.

Supplementary Table 3
Comparison of postoperative outcomes of patients receiving pancreatectomy versus non-resectional procedures, stratified by upfront versus post-neoadjuvant operations.

Variable	Overall population (n=681)			Upfront operations (n=296)			Post-treatment operations (n=385)		
	Non-resectional procedures (n=70)	Pancreatectomy (n=611)	P-value*	Non-resectional procedures (n=28)	Pancreatectomy (n=268)	p-value	Non-resectional procedures (n=42)	Pancreatectomy (n=343)	P-value*
Postoperative complications	15 (21.3)	386 (63.2)	**<0.001**	2 (7.1)	156 (58.2)	**<0.001**	13 (31.0)	230 (67.1)	**<0.001**
Severe Complications	5 (7.1)	123 (20.1)	**0.006**	0	50 (18.7)	**0.007**	5 (11.9)	73 (21.3)	0.221
Abdominal collections	3 (4.3)	133 (21.8)	**<0.001**	0	53 (19.8)	**0.004**	3 (7.1)	80 (23.5)	**0.016**
Reoperation	1 (1.4)	48 (7.9)	**0.049**	0	24 (9.0)	0.145	1 (2.4)	24 (7.0)	0.501
Length of stay (days), median (IQR)	5 (4-7)	9 (7-17)	**<0.001**	5 (4-7)	8 (7-15)	**<0.001**	5 (4-7)	9 (7-18)	**<0.001**
Readmission	0	45 (7.5)	**0.01**	0	12 (4.5)	0.613	0	33 (9.9)	**0.036**
90-day mortality	1 (1.4)	20 (3.3)	0.713	0	6 (2.2)	1.000	1 (2.4)	14 (4.1)	1.000

*Statistical significance for $p<0.05$.

Supplementary Table 4
Univariable and multivariable analysis of factors associated with survival in the overall cohort.

		Univariable analysis			Multivariable analysis		
	OS (months, median with 95%CI)	**HR**	**95% CI**	**P-value***	**HR**	**95% CI**	**P-value***
Gender							
Male	26.8 (23.2-30.4)	Ref			Ref		
Female	29.9 (25.3-34.6)	0.87	(0.69-1.09)	0.227	1.17	(0.89-1.54)	0.256
Age	NA	1.01	(0.99-1.02)	0.186	1.01	(0.98-1.02)	0.926
BMI	NA	0.99	(0.96-1.02)	0.406			
ASA score							
ASA 1-2	30.1 (25.7-34.5)	Ref			Ref		
ASA 3-4	22.7 (16.9-28.4)	1.46	(1.15-1.85)	**0.002**	1.39	(0.99-1.82)	0.062
Age-adjusted CCI	NA	1.05	(0.98-1.13)	0.137	1.08	(0.98-1.93)	0.104
Cigarette smoking							
No	27.1 (23.2-31.1)	Ref					
Active smoker	30.1 (23.4-36.8)	1.03	(0.77-1.38)	0.651			
Former smoker	33.1 (26.4-39.8)	0.92	(0.70-1.97)	0.706			
Alcohol abuse[†]							
No	29.5 (25.6-33.4)	Ref					
Yes	26.8 (22.8-30.8)	1.43	(0.91-2.26)	0.12			
Diabetes							
No	30.1 (26.1-34.1)	Ref					
Yes	26.4 (22.6-30.2)	1.21	(0.94-1.56)	0.132			
Jaundice							
No	29.9 (23.3-36.7)	Ref					
Yes	27.3 (23.0-31.5)	1.19	(0.95-1.51)	0.125			
Symptoms[‡] **at diagnosis**	36.5 (23.9-49.1)	Ref					
No	27.6 (24.6-30.6)	1.25	(0.93-1.70)	0.144			
Yes							
Primary treatment							
No	31.5 (26.2-36.4)	Ref			Ref		
Yes	26.4 (22.9.29.8)	1.27	(1.01-1.59)	**0.041**	1.24	(0.91-1.68)	0.254
Resectability status (preoperative)[§]							
Anatomically resectable	33.1 (28.1-38.1)						
Borderline resectable	19.1 (15.3-22.8)	Ref			Ref		
Locally advanced	21.6 (14.6-28.7)	1.85	(1.44-2.37)	**0.001**	1.58	(1.15-2.18)	**0.01**
Oligometastatic	29.9 (NC)	1.88	(1.25-2.81)	**0.005**	1.01	(0.65-1.86)	**0.03**
Tumor size (preoperative)	NA	1.02	(1.01-1.03)	**<0.001**	1.02	(1.00-1.03)	**0.006**
Preoperative Ca19.9[¶]	NA	1.00	(1.00-1.01)	**<0.001**	1.00	(1.00-1.01)	**0.004**
Preoperative Ca19.9, normal (<37 UI/mL)[¶]	29.9 (26.4-33.5)	Ref					
Normal	25.9 (22.9-29.1)	1.16	(0.92-1.46)	0.223			
Elevated							
Ca19.9 nonsecretors (<5 UI/mL)[¶]	22.5 (14.2-30.8)	Ref					
Nonsecretors	28.6 (25.3-32.0)	0.72	(0.49-1.06)	0.222			
Normal expression							
Tumor location							
Head	27.3 (23.5-31.1)	Ref			Ref		
Body-tail	27.8 (19.5-36.1)	0.87	(0.67-1.12)	0.266	0.91	(0.67-1.23)	0.53
Peripancreatic organ involvement	27.8 (24.2-31.1)	Ref			Ref		
No	27.6 (22.9-32.3)	0.94	(0.54-1.64)	0.942	0.54	(0.26-1.11)	0.094
Yes							
Surgery							
Pancreatectomy	31.4 (27.2-35.6)	Ref			Ref		
Non-resectional	11.8 (9.9-13.6)	2.83	(2.12-3.79)	**<0.001**	3.19	(2.14-4.75)	**<0.001**
Postoperative course							
No/mild complications	30.4 (26.2-34.5)	Ref			Ref		
(CD I-II)	23.7 (15.8-31.5)	1.48	(1.11-1.98)	**0.007**	1.45	(1.05-2.01)	**<0.001**

Severe complication (CD ≥3)							

* Statistical significance for $p<0.05$. CD, Clavien-Dindo.

† Defined as >2 alcohol units/day for men and >1 alcohol unit/day for women according to the WHO classification.

‡ Symptoms at diagnosis include jaundice, acute pancreatitis, upper abdominal pain, severe weight loss (>10% in six months), and gastric outlet obstruction.

§ One patient with oligometastatic disease was excluded from the analysis.

¶ Only the continuous Ca 19.9 value was used for multivariable modeling in secretors.

NA = not applicable.

NC = not computable.

Supplementary Table 5
Univariable and multivariable analysis of factors associated with survival in patients who underwent upfront operations.

		Univariable analysis			Multivariable analysis		
	OS (months, median with 95%CI)	**HR**	**95% CI**	**-value***	**HR**	**95% CI**	**P-value***
Gender							
Male	31.5 (23.4-39.6)	Ref			Ref		
Female	33.0 (25.9-40.1)	0.98	(0.68-1.40)	0.892	1.12	(0.68-1.83)	0.665
Age	NA	1.01	(0.97-1.07)	0.206	1.02	(0.98-1.05)	0.341
BMI	NA	1.02	(0.96-1.02)	0.535			
ASA score							
ASA 1-2	36.9 (29.8-44.1)	Ref			Ref		
ASA 3-4	27.1 (19.9-34.3)	1.54	(1.05-2.28)	**0.026**	1.49	(0.89-2.52)	0.126
Age-adjusted CCI	NA	1.11	(0.99-1.23)	0.069	0.97	(0.88-1.13)	0.700
Cigarette smoking							
No	34.9 (23.5-46.3)	Ref					
Active smoker	30.4 (23.5-37.3)	1.12	(0.72-1.73)	0.608			
Former smoker	35.5 (23.6-47.4)	0.94	(0.60-1.46)	0.778			
Alcohol abuse†							
No	34.9 (29.9-38.9)	Ref			Ref		
Yes	25.0 (19.9-30.2)	1.67	(0.94-2.97)	0.079	1.21	(0.59-2.49)	0.602
Diabetes							
No	35.5 (28.4-42.6)	Ref			Ref		
Yes	27.1 (20.4-33.9)	1.55	(1.07-2.25)	**0.021**	1.53	(0.95-2.45)	0.08
Jaundice							
No	41.1 (35.1-47.6)	Ref			Ref		
Yes	27.9 (22.5-32.3)	1.64	(1.22-2.40)	**0.01**	1.34	(0.78-2.28)	0.291
Symptoms‡ **at diagnosis**							
No	41.4 (NC)	Ref			Ref		
Yes	30.0 (25.2-35.0)	1.95	(1.17-3.33)	**0.009**	1.34	(0.69-2.59)	0.385
Resectability status (preoperative)	33.0 (27.9-38.0)	Ref					
Anatomically resectable	25.5 (17.3-33.7)	1.53	(0.74-3.14)	0.245			
Borderline resectable							
Tumor size (preoperative)	NA	1.03	(1.01-1.05)	**0.001**	1.02	(0.99-1.04)	0.087
Preoperative Ca19.9§	NA	1.00	(1.00-1.01)	**0.014**	1.00	(1.00-1.01)	0.454
Preoperative Ca19.9, normal (<37 UI/mL) §	37.7 (32.5-42.9)	Ref					
Normal	30.7 (23.8-37.6)	1.19	(0.79-1.78)	0.402			
Elevated							
Ca19.9 nonsecretors (<5 UI/mL) §	23.7 (NC)	Ref					
Nonsecretors	32.0 (26.4-37.7)	0.72	(0.49-1.06)	0.7			
Normal expression							
Tumor location							
Head	31.5 (25.8-37.1)	Ref					
Body-tail	37.7 (27.5-47.9)	0.79	(0.52-1.21)	0.278			
Peripancreatic organ involvement	33.3 (26.9-39.0)	Ref					
No	27.6 (11.6-43.6)	1.27	(0.52-3.11)	0.604			
Yes							
Surgery							
Pancreatectomy	36.9 (31.8-42.1)	Ref			Ref		
Non-resectional	11.7 (7.9-15.5)	3.31	(2.11-5.19)	**<0.001**	3.59	(1.94-6.62)	**<0.001**
Postoperative course							
No/mild complications (CD I-II)	35.5 (28.9-42.1)	Ref			Ref		
Severe complication (CD ≥3)	27.6 (20.7-34.6)	1.48	(0.94-2.34)	0.092	1.72	(1.05-3.01)	**0.046**

* Statistical significance for p<0.05. CD, Clavien-Dindo.
† Defined as >2 alcohol units/day for men and >1 alcohol unit/day for women according to the WHO classification.

‡ Symptoms at diagnosis include jaundice, acute pancreatitis, upper abdominal pain, severe weight loss (>10% in six months), and gastric outlet obstruction.

§ Only the continuous Ca 19.9 value was used for multivariable modeling in secretors.

NA = not applicable.

NC = not computable.

Supplementary Table 6

Univariable and multivariable analysis of factors associated with survival in patients who underwent upfront pancreatectomy.

		Univariable analysis			Multivariable analysis		
	OS (months, median with 95%CI)	**HR**	**95% CI**	**P-value***	**HR**	**95% CI**	**P-value***
Gender							
Male	37.7 (30.5-44.8)	Ref			Ref		
Female	34.9 (29.0-40.8)	0.99	(0.66-1.49)	0.983	1.19	(0.69-2.05)	0.53
Age	NA	1.02	(0.99-1.04)	0.136	1.04	(0.99-1.10)	0.096
BMI	NA	1.01	(0.96-1.06)	0.768			
ASA score							
ASA 1-2	39.3 (32.7-45.9)	Ref			Ref		
ASA 3-4	30.4 (22.7-38.1)	1.58	(1.02-2.43)	**0.04**	1.68	(0.88-3.23)	0.116
Age-adjusted CCI	NA	1.22	(1.04-1.43)	**0.016**	0.82	(0.57-1.18)	0.291
Cigarette smoking							
No	36.9 (30.7-43.2)	Ref					
Active smoker	30.7 (27.6-33.8)	1.14	(0.71-1.85)	0.585			
Former smoker	41.4 (35.6-46.2)	0.89	(0.54-1.48)	0.664			
Alcohol abuse[†]							
No	37.2 (31.3-43.0)	Ref					
Yes	26.8 (22.9-30.7)	1.58	(0.79-3.15)	0.189			
Diabetes							
No	39.3 (NC)	Ref			Ref		
Yes	30.4 (29.4-35.9)	1.54	(1.01-2.35)	**0.042**	1.32	(0.72-2.42)	0.369
Jaundice							
No	41.4 (36.7-49.2)	Ref					
Yes	32.0 (25.9-38.1)	1.43	(0.94-2.18)	0.092			
Symptoms[‡] **at diagnosis**							
No	41.4 (NC)	Ref			Ref		
Yes	32.0 (27.9-36.2)	1.69	(0.98-2.88)	0.056	1.05	(0.55-1.99)	0.875
Resectability status (preoperative)	34.9 (29.9-39.9)	Ref					
Anatomically resectable	NC	0.63	(0.16-2.57)	0.517			
Borderline resectable							
Tumor size (preoperative)	NA	1.03	(1.01-1.05)	**0.002**			
Preoperative Ca19.9[§]	NA	1.00	(1.00-1.01)	**<0.001**	**1.00**	**(1.00-1.01)**	**0.016**
Preoperative Ca19.9, normal (<37 UI/mL)[§]	37.7 (NC)	Ref					
Normal	34.9 (22.5-43.3)	1.23	(0.78-1.95)	0.371			
Elevated							
Ca19.9 nonsecretors (<5 UI/mL)[§]	NC	Ref					
Nonsecretors	34.9 (30.0-39.7)	1.11	(0.51-2.39)	0.8			
Normal expression							
Tumor location							
Head	34.4 (29.1-39.7)	Ref					
Body-tail	37.7 (28.8-46.6)	0.92	(0.58-1.46)	0.713			
Peripancreatic organ involvement	36.9 (31.9-42.0)	Ref					
No	27.6 (NC)	1.07	(0.34.3.37)	0.914			
Yes							
Type of pancreatectomy							
Pancreatoduodenectomy	36.9 (31.3-42.6)	Ref					
Distal pancreatectomy	37.7 (28.6-46.8)	1.06	(0.66-1.72)	0.802			
Total pancreatectomy	19.7 (12.0-27.4)	1.97	(1.04-3.77)	**0.038**			
Vascular resection							
No	37.2 (32.0-42.3)	Ref			Ref		
Yes	24.0 (13.8-34.3)	1.7	(0.96-3.01)	0.065	0.73	(0.29-1.81)	0.492
Multivisceral resection							
No	36.9 (31.7-42.2)	Ref			Ref		

Yes	18.6 (1.05-36.2)	1.91	(0.88-1.14)	0.094	3.12	(1.00-9.74)	**0.05**
T-status							
T1	NA	Ref			Ref		
T2	34.4 (25.9-42.9)	3.28	(1.58-2.83)	**0.001**	2.68	(1.41-9.65)	**0.008**
T3	27.6 (9.4-45.9)	4.93	(2.04-11.9)	**0.001**	3.39	(0.7-8.15)	**0.065**
N-status							
N0	NA	Ref			Ref		
N1	37.2 (29.5-44.8)	3.04	(1.18-7.81)	**0.021**	2.48	(0.81-7.59)	**0.113**
N2	27.1 (21.1-33.2)	5.82	(2.33-14.6)	**<0.001**	8.60	(2.79-26.5)	**<0.001**
R-status							
R0	37.2 (32.9-41.4)	Ref			Ref		
R1	30.4 (18.8-42.0)	1.37	(0.92-2.09)	0.145	0.8	(0.44-1.44)	0.458
R2	18.6 (3.6-33.6)	3.23	(1.01-10.3)	**0.049**	1.13	(0.29-4.39)	0.854
Perineural invasion							
No	NA	Ref					
Yes	34.9 (29.4-40.4)	5.86	(0.81-42.2)	0.079			
Lymph-vascular invasion							
No	NA	Ref					
Yes	34.9 (30.1-39.7)	3.40	(0.47-24.5)	0.196			
Peripancreatic fat invasion							
No	NA	Ref					
Yes	34.4 (29.1-39.6)	2.31	(0.85-6.29)	0.092			
Grading							
G1	NA	Ref					
G2	34.4 (29.4-39.3)	NC		0.994			
G3	23.4 (16.1-31.8)	NC		0.994			
Postoperative course							
No/mild complications (CD I-II)	37.7 (31.4-43.9)	Ref			Ref		
Severe complication (CD ≥3)	27.6 (20.7-34.6)	1.86	(1.15-2.98)	**0.01**	1.26	(0.68-2.35)	0.467
Adjuvant treatment							
No	24.0 (19.6-28.5)	Ref			Ref		
Yes	41.4 (35.8-47.0)	0.36	(0.23-0.57)	**<0.001**	0.24	(0.12-0.35)	**<0.001**

* Statistical significance for p<0.05. CD, Clavien-Dindo.

† Defined as >2 alcohol units/day for men and >1 alcohol unit/day for women according to the WHO classification.

‡ Symptoms at diagnosis include jaundice, acute pancreatitis, upper abdominal pain, severe weight loss (>10% in six months), and gastric outlet obstruction.

§ Only the continuous Ca 19.9 value was used for multivariable modeling in secretors.

NA = not applicable.

NC = not computable.

Supplementary Table 7
Univariable and multivariable analysis of factors associated with survival in patients who underwent post-treatment operations.

		Univariable analysis			Multivariable analysis		
	OS (months, median with 95%CI)	**HR**	**95% CI**	**P-value***	**HR**	**95% CI**	**P-value***
Gender							
Male	25.6 (21.2-30.0)	Ref			Ref		
Female	29.5 (3.8-35.2)	0.84	(0.62-1.13)	0.257	1.01	(0.71-1.44)	0.949
Age	NA	1.01	(0.99-1.02)	0.401	0.99	(0.98-1.02)	0.706
BMI	NA	0.94	(0.09-0.99)	**0.01**	0.93	(0.88-0.97)	**0.004**
ASA score							
ASA 1-2	28.5 (23.0-33.9)	Ref			Ref		
ASA 3-4	24.4 (19.4-29.5)	1.17	(0.83-1.64)	**0.367**	1.38	(0.95-2.02)	0.102
Age-adjusted CCI	NA	0.99	(0.89-1.10)	0.862			
Cigarette smoking							
No	25.8 (21.5-30.2)	Ref					
Active smoker	27.6 (15.6-39.6)	0.99	(0.67-1.47)	0.968			
Former smoker	28.1 (21.3-34.9)	0.89	(0.63-1.24)	0.491			
Alcohol abuse[†]							
No	27.1 (23.3-30.8)	Ref					
Yes	27.6 (10.1-45.2)	1.25	(0.59-2.68)	0.560			
Diabetes							
No	28.1 (23.4-32.7)	Ref					
Yes	23.7 (15.7-31.7)	1.04	(0.73-1.48)	0.835			
Jaundice							
No	27.1 (22.0-32.3)	Ref					
Yes	27.1 (21.4-32.9)	0.99	(0.74-1.33)	0.952			
Symptoms[‡] **at diagnosis**							
No	23.0 (13.9-32.1)	Ref					
Yes	27.3 (23.6-31.0)	0.89	(0.61-1.31)	0.568			
Resectability status (baseline)							
Anatomically resectable	35.9 (27.6-NR)	Ref					
Borderline resectable	20.4 (16.7-27.1)	1.95	(1.36-2.80)	**<0.001**			
Locally advanced	23.6 (18.3-38.6)	1.81	(1.19-2.73)	**0.005**			
Oligometastatic	29.9 (11.4-NR)	2.23	(0.89-5.62)	**0.088**			
Primary chemotherapy regimen	21.0 (13.4-28.7)	Ref			Ref		
Gemcitabine and Nab-Paclitaxel	26.4 (22.3-30.4)	0.74	(0.54-1.02)	0.063	0.74	(0.50-1.09)	0.137
(m)FOLFIRINOX	40.4 (24.2-56.6)	0.43	(0.26-0.73)	**0.007**	0.55	(0.30-1.03)	0.061
Other							
Primary chemotherapy duration	NA	1.01	(0.94-1.08)	0.917			
Preoperative radiation							
No	24.5 (23.5-33.4)	Ref					
Yes	23.6 (18.7-28.6)	1.20	(0.90-1.63)	0.227			
Resectability status (preoperative) [§]	35.9 (28.2-43.7)	Ref			Ref		
Anatomically resectable	9.1 (15.1-23.0)	2.02	(1.47-2.79)	**<0.001**	1.74	(1.20-2.53)	**0.001**
Borderline resectable	22.3 (18.6-26.0)	1.84	(1.47-2.98)	**0.018**	1.12	(0.63-1.99)	**0.085**
Locally advanced							
Tumor size (preoperative)	NA	1.02	(1.01-1.04)	**0.001**	1.01	(0.99-1.02)	0.5
RECIST response							
Partial/Complete response	29.9 (19.3-40.6)	Ref			Ref		
Stable disease	27.6 (24.9-30.4)	1.03	(0.78-1.43)	0.727	0.96	(0.65-1.42)	0.853
Progressive disease	11.4 (23.4-30-9)	2.53	(1.44-4.47)	**0.001**	1.53	(0.73-3.17)	0.260
Preoperative Ca19.9[¶]	NA	1.00	(1.00-1.01)	**<0.001**	1.01	(1.00-1.01)	**<0.001**
Preoperative Ca19.9, normal							

(<37 UI/mL) ¶	29.5 (24.9-34.2)	Ref		0.141			
Normal	23.7 (18.4-29.0)	1.27	(0.93-1.72)				
Elevated							
Ca19.9 nonsecretors (<5 UI/mL) ¶	21.1 (8.3-34.0)	Ref					
Nonsecretors	27.6 (22.4-32.9)	0.54	(0.32-0.90)	**0.017**			
Normal expression							
Ca19.9 responders (≥50% decrease)	25.6 (21.0-30.0)	Ref					
No	27.6 (20.4-34.9)	0.76	(0.55-1.06)	0.106			
Yes							
Tumor location							
Head	27.3 (23.2-31.3)	Ref					
Body-tail	26.2 (21.4-31.0)	0.95	(0.68-1.33)	0.776			
Peripancreatic organ involvement	27.1 (23.5-30.8)	Ref					
No	26.4 (NC)	0.77	(0.67-1.66)	0.513			
Yes							
Surgery							
Pancreatectomy	29.5 (24.5-34.5)	Ref			Ref		
Non-resectional	11.4 (7.9-15.5)	2.92	(1.97-4.31)	**<0.001**	2.33	(1.33-4.07)	**0.003**
Postoperative course							
No/mild complications (CD I-II)	28.5 (23.8-33.1)	Ref			Ref		
Severe complication (CD ≥3)	17.2 (8.4-26.1)	1.50	(1.03-2.18)	**0.034**	1.41	(0.92-2.15)	0.111

* Statistical significance for p<0.05. CD, Clavien-Dindo.

† Defined as >2 alcohol units/day for men and >1 alcohol unit/day for women according to the WHO classification.

‡ Symptoms at diagnosis include jaundice, acute pancreatitis, upper abdominal pain, severe weight loss (>10% in six months), and gastric outlet obstruction.

§ One patient with oligometastatic disease was excluded from the analysis.

¶ Only the continuous Ca 19.9 value was used for multivariable modeling in secretors.

NA = not applicable.

NC = not computable.

NR = not reached.

Supplementary Table 8

Univariable and multivariable analysis of factors associated with survival in patients who underwent post-treatment pancreatectomy.

		Univariable analysis			Multivariable analysis		
	OS (months, median with 95%CI)	**HR**	**95% CI**	**-value***	**HR**	**95% CI**	**-value***
Gender							
Male	27.1 (19.3-34.9)	Ref			Ref		
Female	31.4 (23.9-38.8)	0.86	(0.62-1.19)	0.362	0.88	(0.57-1.34)	0.54
Age	NA	1.01	(0.99-1.03)	0.426	1.04	(0.99-1.09)	0.067
BMI	NA	0.94	(0.90-0.99)	**0.023**	0.96	(0.90-1.01)	0.128
ASA score							
ASA 1-2	32.9 (27.1-38.7)	Ref			Ref		
ASA 3-4	25.6 (20.1-31.0)	1.25	(0.87-1.79)	0.219	0.97	(0.60-1.56)	0.884
Age-adjusted CCI	NA	1.06	(0.93-1.21)	0.373	0.78	(0.56-1.57)	0.12
Cigarette smoking							
No	28.5 (22.8-34.1)	Ref					
Active smoker	28.6 (16.5-40.7)	1.01	(0.66-1.54)	0.964			
Former smoker	34.3 (23.8-44.8)	0.86	(0.54-1.48)	0.426			
Alcohol abuse[†]							
No	29.0 (23.3-34.7)	Ref					
Yes	33.3 (16.7-49.8)	0.95	(0.35-2.56)	0.915			
Diabetes							
No	31.4 (25.4-37.3)	Ref					
Yes	26.4 (17.8-34.9)	1.03	(0.7-1.51)	0.890			
Jaundice							
No	29.5 (21.7-37.3)	Ref					
Yes	31.4 (24.9-37.3)	0.95	(0.68-1.31)	0.745			
Symptoms[‡] **at diagnosis**							
No	32.9 (18.9-46.8)	Ref					
Yes	29.5 (24.1-34.9)	0.93	(0.60-1.43)	0.740			
Resectability status (baseline)	37.1 (28.5-NR)	Ref					
Anatomically resectable	21.0 (16.9-29.9)	1.88	(1.30-2.73)	**0.001**			
Borderline resectable	22.6 (17.1-43.5)	1.82	(1.17-2.81)	**0.044**			
Locally advanced	13.9 (11.4-NR)	2.28	(0.82-6.33)	0.075			
Oligometastatic							
Primary chemotherapy regimen	24.1 (16.9-31.3)	Ref			Ref		
Gemcitabine + Nab-Paclitaxel	28.6 (21.0-32.2)	0.70	(0.5-0.99)	**0.043**	0.68	(0.42-1.09)	0.134
(m)FOLFIRINOX	40.4 (25.6-55.1)	0.47	(0.27-0.82)	**0.008**	0.54	(0.27-1.1)	0.131
Other							
Primary chemotherapy duration	NA	0.99	(0.92-1.07)	0.819			
Preoperative radiation							
No	33.3 (25.1-41.2)	Ref			Ref		
Yes	23.7 (19.1-28.2)	1.37	(0.98-1.90)	0.061	1.01	(0.63-1.63)	0.973
Resectability status (preoperative)[§]	35.9 (27.3-44.6)	Ref			Ref		
Anatomically resectable	21.1 (16.8-25.5)	1.73	(1.22-2.43)	**0.002**	1.27	(0.8-2.0)	0.247
Borderline resectable	22.6 (8.6-36.7)	1.51	(0.82-2.8)	0.187	0.83	(0.36-1.89)	0.913
Locally advanced							
Tumor size (preoperative)	NA	1.03	(1.01-1.05)	**<0.001**			
RECIST response							
Partial/Complete response	35.9 (23.3-48.5)	Ref			Ref		
Stable disease	27.6 (23.6-31.7)	1.11	(0.78-1.58)	0.570	0.79	(0.52-1.22)	0.055
Progressive disease	14.8 (3.7-25.9)	2.71	(1.41-5.21)	**0.003**	2.06	(0.94-4.54)	0.065

Preoperative Ca19.9†	NA	1.00	(1.00-1.01)	**<0.001**	**1.00**	**(1.00-1.01)**	**0.01**
Preoperative Ca19.9, normal (<37 UI/mL)¶	33.1 (24.9-41.3)	Ref					
Normal	26.2 (21.1-31.4)	0.81	(0.57-1.14)	0.227			
Elevated							
Ca19.9 nonsecretors (<5 UI/mL)¶	22.5 (9.8-25.2)	Ref					
Nonsecretors	31.4 (25.3-37.4)	0.58	(0.33-1.02)	0.056			
Normal expression							
Ca19.9 responders (≥50% decrease)¶	27.1 (22.8-32.4)	Ref					
No	33.1 (22.6-43.9)	0.76	(0.53-1.09)	0.97			
Yes							
Tumor location							
Head	29.0 (24.6-33.4)	Ref					
Body-tail	26.2 (13.9-34.5)	0.99	(0.69-1.43)	0.97			
Peripancreatic organ involvement	28.6 (23.3-33.9)	Ref					
No	26.4 (NC)	0.79	(0.35-1.8)	0.581			
Yes							
Type of pancreatectomy							
Pancreatoduodenectomy	29.5 (24.7-34.3)	Ref					
Distal pancreatectomy	38.6 (NC)	0.79	(0.52-1.21)	0.287			
Total pancreatectomy	18.3 (10.9-25.7)	1.48	(0.96-2.3)	0.078			
Vascular resection							
No	33.1 (25.4-40.7)	Ref			Ref		
Yes	23.7 (18.6-28.7)	1.26	(0.9-1.76)	0.17	0.85	(0.53-1.37)	0.513
Multivisceral resection							
No	29.5 (24.1-34.9)	Ref			Ref		
Yes	26.4 (3.4-49.3)	1.39	(0.73-2.36)	0.318	1.79	(0.82-3.92)	0.147
T-status							
T0/T1	43.5 (36.3-50.7)	Ref			Ref		
T2	26.6 (19.3-33.8)	1.81	(1.21-2.72)	0.247	1.15	(0.67-1.97)	0.399
T3	17.2 (12.7-21.8)	2.48	(1.38-4.47)	0.151	1.00	(0.46-1.19)	0.602
T4	17.1 (9.3-24.9)	4.09	(1.95-8.56)	0.061	2.64	(0.98-7.34)	0.846
TX	23.7 (15.1-32.2)	2.21	(1.09-4.47)	0.193	1.39	(0.57-3.39)	0.859
N-status							
N0	NC	Ref			Ref		
N1	24.1 (19.3-28.9)	2.07	(1.36-3.16)	0.001	1.75	(1.03-2.98)	**0.039**
N2	23.7 (13.2-34.1)	2.42	(1.55-3.77)	**<0.001**	1.77	(0.96-3.26)	0.066
R-status							
R0	37.1 (29.8-44.5)	Ref			Ref		
R1	23.0 (14.7-31.3)	1.67	(1.19-2.33)	**0.003**	1.59	(1.05-2.44)	**0.012**
R2	7.4 (NC)	4.89	(1.19-20.1)	**0.028**	6.45	(1.09-37.9)	**0.040**
Perineural invasion							
No	NC	Ref			Ref		
Yes	27.1 (21.9-32.2)	1.78	(1.04-3.04)	0.035	1.22	(0.6-2.49)	0.581
Lymph-vascular invasion	43.5 (NC)	Ref			Ref		
No	27.1 (23.2-30.9)	2.11	(1.14-3.9)	0.015	0.92	(0.41-2.06)	0.833
Yes							
Peripancreatic fat invasion	NC	Ref			Ref		
No	23.4 (22.9-29.8)	2.02	(2.28-3.19)	0.002	1.53	(0.84-2.79)	0.162
Yes							
Grading							
G2	23.6 (16.8-30.5)	Ref					
G3	19.1 (4.6-33.6)	1.01	(0.3-3.41)	0.985			
Not assessed	31.4 (24.7-37.9)	0.78	(0.48-1.26)	0.301			
Postoperative course							
No/mild complications	31.4 (25.3-37.4)	Ref1.70		**0.008**	Ref		0.153

(Clavien-Dindo I-II) Severe complication (Clavien-Dindo ≥3)	17.1 (7.3-26.8)		(1.14-2.54)		1.44	.87-2.37)	
Adjuvant treatment							
No	29.5 (20.5-38.5)	Ref			Ref		
Yes	35.6 (25.8-45.4)	0.74	(0.51-1.05)	0.093	0.61	(0.39-0.95)	**0.030**

* Statistical significance for p<0.05. CD, Clavien-Dindo.

† Defined as >2 alcohol units/day for men and >1 alcohol unit/day for women according to the WHO classification.

‡ Symptoms at diagnosis include jaundice, acute pancreatitis, upper abdominal pain, severe weight loss (>10% in six months), and gastric outlet obstruction.

§ One patient with oligometastatic disease was excluded from the analysis.

¶ Only the continuous Ca 19.9 value was used for multivariable modeling in secretors.

NA = not applicable.

NR = not reached.

NC = not computable.

Study II

Postoperative and survival implications of standard and extended surgery compared to non-resectional procedures for localized pancreatic ductal adenocarcinoma.

Abstract

Objective: To outline real-life postoperative and survival outcomes of standard and extended surgery for PDAC, compared to non-resectional procedures, both in the upfront and post-treatment settings.

Summary Background Data: Pancreatectomies with concomitant venous, arterial, and multivisceral resections are increasingly performed in patients with localized pancreatic cancer (PDAC), especially following primary treatment. However, long-term results of extended procedures have been peripherally investigated.

Methods: Patients undergoing surgical exploration with resection intent for non-metastatic PDAC at a very-high volume institution (2018-2021) were segregated according to surgical management: exploration, *standard,* and *extended* pancreatectomy including vascular and/or multivisceral resection. Clinical and pathological information were correlated to postoperative outcomes, overall survival (OS), and time-to-progression (TTP).

Results: Among 804 patients, 34 (4.2%) had pancreatectomy omitted, while 542 (67.4%) had standard and 228 (28.4%) extended procedures (isolated vascular resection: 85.1%; multi-visceral resection: 10.5%; combined: 4.1%). Extended pancreatectomy increased following primary treatment compared to upfront surgery (39.7 vs 15.7%, $p<0.001$), as did non-resectional procedures (5.3 vs. 2.7%, $p=0.071$). Also, borderline resectable/locally-advanced tumor and extra-pancreatic spread correlated with non-resection and extended pancreatectomy ($p<0.001$).

Extended pancreatectomy resulted in a minor deterioration of postoperative outcomes, yet comparable 90-day mortality rate ($p=0.292$). Overall, pancreatectomy provided substantial OS advantage compared to non-resection (median OS 31 vs. 14.0 months, $p<0.001$), but equivalent TTP (15 months, $p=0.93$).

In the upfront surgery cohort (n=330), 98% of patients had anatomically resectable disease. Extended pancreatectomy was associated with impaired OS compared to standard resection (24 vs.

35 months, p<0.001). Notably, TTP after extended pancreatectomy (12 months) was significantly worse compared to that following standard pancreatectomy (19 months, p=0.004), and comparable to that of resection omission (p=1.0). Distant metastases were the first site of disease progression/recurrence regardless of the surgery.

In the post-treatment cohort (n=471), regimen and duration of chemotherapy did not correlate with surgical procedure, but resection omission increased with escalating anatomical stage (p<0.001). Extended surgery patients showed worse pathological characteristics and diminished OS compared to standard pancreatectomy.

TTP decreased after extended pancreatectomy (11 months) vs. standard pancreatectomy (16 months, p=0.070) and non-resectional surgery (18 months, p=0.044). Again, distant metastases invariably occurred as first recurrence site irrespective of surgery (p=0.49).

On multivariable analyses, escalating AJCC stage and adjuvant treatment omission, but not surgical procedure, predicted post-resection OS and TTP, both upfront and following primary treatment.

Conclusions: Despite acceptable postoperative outcomes, survival gain following extended surgery for localized PDAC remains modest due to early systemic disease dissemination, comparable to that of non-resected patients. Therefore, surgeons should include additional patient-centered metrics, such as time toxicity and longitudinal quality-of-life monitoring, to evaluate treatment appropriateness.

Introduction

Incidence of pancreatic ductal adenocarcinoma (PDAC) is on the rise globally, and it is projected to become the second leading cause of cancer mortality by the end of this decade.[1] Nowadays, surgical resection coupled with systemic therapy provides the only chance for cure. The availability of effective chemo-radiation combination approaches has expanded the pool of patients with localized disease who are candidates for surgery. In parallel, venous and arterial resections coupled with extra-pancreatic organ excision are increasingly performed worldwide to achieve tumor clearance in cases of tumor spread beyond the pancreatic parenchyma.[2, 3] Notably, it has led to an update in the terminology employed by international guidelines to describe the presence of tumor-vessel contact at imaging (i.e. >180° solid tumor contact with superior mesenteric artery [SMA] or celiac trunk [CT] or complete occlusion of the superior mesenteric vein/portal vein [SMV/PV] axis), with the notion of *unresectable* disease being recently dismissed.[4]

Short-term outcomes of such complex procedures have progressively improved at high-volume institutions, overtaking the historical reluctance to commit to extended pancreatic surgery. However, the impact of extended pancreatectomy on long-term survival remains unclear. While some authors reported unprecedented survival outcomes in highly-selected cohorts of patients undergoing extended resection,[5] the inability to predict patients at risk of 'futile' operations (namely, early postoperative recurrence or death)[6] impairs surgical triaging. Intraoperatively, pancreatic surgeons often face the scenario where a vascular and/or multivisceral resection must be considered to achieve tumor clearance, as opposed to a standard resection or a non-resectional procedure. Unfortunately, data to inform decision-making is scant.

The present study aims to outline postoperative and survival outcomes of extended vs. standard pancreatectomy compared to non-resectional procedures, in a consecutive series of patients with localized PDAC candidates to curative surgery, in both the upfront and post-treatment setting.

Methods

Study design

The local Ethical Committee approved this registry-based observational analysis (n.1101CESC). The study reporting complies with the Strengthening the Reporting of Observational Study in Epidemiology (STROBE) guidelines [7]. Patients who underwent exploration with pancreatectomy intent for localized pancreatic cancer between 2018 and 2021 were extracted from the institutional electronic registry and considered for the analysis.

Patient triaging and Perioperative Management

Institutional practices for perioperative management were discussed elsewhere.[8-11] NCCN criteria were used to define tumor resectability.[4] Patients with radiologically resectable disease and no suspicion of occult metastases were assigned to upfront surgery or neoadjuvant treatment within clinical trials.[12]

In patients who received primary chemo(radio)therapy, restaging was performed using CT and MRI as appropriate; tumor response was defined per the Response Evaluation Criteria in Solid Tumor (RECIST) definition v1.1.[13] Ca19.9 response was defined as a decrease >50% relative to the baseline.[10] All cases were discussed in a multidisciplinary meeting, and patients with non-progressive disease were considered for surgery. The decision to commit to exploration was further agreed upon during a preoperative surgical meeting.[14]

Intraoperatively, after excluding distant metastases and performing a wide Kocher maneuver, an artery-first approach[15] was employed in the presence of suspect SMA/CT tumor involvement. Determinants of resectability were the presence of a free plane around the CT, SMA (both proximally at the origin from the aorta and distally into the mesenteric root), and a reconstructible SMV/PV. When periarterial solid tissue was found, biopsies were sent for frozen section analysis.

The decision to commit to pancreatectomy was made based on the opportunity to achieve macroscopic tumor clearance after consulting a senior pancreatic surgeon. When periarterial infiltration was ascertained with no plane for divestment, en bloc arterial resection was considered. Circumferential divestment of peri-vascular neuro-lymphatic tissue was performed in every other case.[16] When macroscopic involvement of contiguous organs (i.e., colon or mesocolon, adrenal gland, kidney, stomach) was confirmed, resection of the involved tissue was accomplished en bloc with the pancreatic specimen to minimize tumor manipulation.

All patients underwent postoperative oncological evaluation. Follow-up was carried out through abdominal CT/MRI imaging, lab tests including serum Ca19.9 measurement, and a physical assessment on a three-month basis for the first year, and at 6-month intervals thereafter. The last update was closed on May 31st, 2024.

Study population

The study population were divided into three groups according to surgical management: non-resectional procedures (exploration with or without cholecystectomy/gastric bypass), *standard* pancreatectomy, and *extended* pancreatectomy including a concomitant vascular resection (PV/SMV, hepatic artery [HA], SMA, CT) or peri-pancreatic organ excision (kidney and/or adrenal gland, colon and/or mesocolon, more than antrum of the stomach, or small bowel) as per the ISGPS definition[17]. The venous resection and reconstruction technique was also classified using the ISGPS terminology.[18] Reasons for resection omission were captured.

Outcome Measures

This study aimed to define postoperative and survival outcomes associated with operative management (non-resectional surgery, standard and extended pancreatectomy) for candidates to curative-intent surgery for localized pancreatic cancer.

The severity of 90-day postoperative complications was graded using the Clavien-Dindo classification.[19] For patients undergoing pancreatectomy, pathological tumor characteristics included margin status, tumor grading, T-status, N-status, and final stage per the AJCC classification, 8th edition.

The site (local versus distant metastases) of first disease progression/recurrence was recorded.

Analyses of surgical and survival outcomes were reported separately for patients who underwent surgery and following primary treatment.

Statistical Analysis

Categorical variables were expressed as frequencies with percentages and compared using the Chi-Square or Fisher's exact test. Continuous variables were expressed as medians with interquartile ranges (IQR) and compared using the Mann-Whitney or Kruskall-Wallis test.

Overall survival (OS) was calculated from the date of surgery to death or last follow-up. Time-to-progression (TTP) was calculated from surgery to the date of local progression or occurrence of metastases,[20] defined as the first radiological evidence of local recurrence/progression per the RECIST criteria, or distant metastases with/without persistent increase of serum Ca19.9. Survival functions were calculated using the Kaplan-Meier method; pairwise comparisons were performed through the log-rank test with the Bonferroni method to adjust for type I error inflation. Factors associated with survival were identified using Cox regression after confirming model assumptions. Both clinically relevant variables and those associated with survival at the univariable analysis ($p \geq 0.1$) were considered for model construction. All analyses were performed using R 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

General characteristics

Eight hundred ninety-three patients underwent surgical exploration during the study period. After excluding patients with metastatic disease (n=82) and R2 resection (n=7), the final study population comprised 804 patients (Supplementary Figure 1), of whom 333 (41.4%) were operated upfront and 471 (58.6%) after primary treatment.

Surgical procedures

Overall, thirty-four patients (4.2%) did not undergo pancreatectomy, with resection omission occurring more frequently following primary treatment than upfront (5.3 vs. 2.7%, p = 0.071). Reasons for resection omission were tumor involvement of the SMA (n=11, 32.3%), HA (n=9, 26.5%), mesenteric root/transverse mesocolon (n=7, 20.5%), SMV-PV confluence (n=6, 17.6%), and CT (n=1, 2.9%). Pathologic confirmation of peri-vascular tumor infiltration was obtained through frozen section analysis in 88.2% of the cases (n=30).

Of 770 patients undergoing pancreatectomy, 542 (70.4%) received standard pancreatectomy and 228 (29.6%) extended pancreatectomy. The chance of receiving extended surgery was higher following primary treatment compared to upfront surgery (39.7 vs 15.7%, p<0.001).

Details regarding operative procedures are reported in Table 1. Vascular resections accounted for 194/228 procedures (85.1%), while multi-visceral resections for 24 (10.5%). Ten patients (4.1%) received combined multi-visceral and vascular resections.

One hundred seventy-five patients (90.2%) received an isolated venous resection, while 20 (9.8%) underwent isolated arterial resections and 9 patients (4.4%) received combined resection. Resection of the SMV (n=76, 41.3%) and SMV-PV confluence (n=72, 32.9%) were the most common procedures, with a direct venorraphy (ISGPS type I, n=144, 78.3%) being the primary technique for

reconstruction, followed by end-to-end anastomosis (ISGPS type III, n=36, 19.6%). Finally, 29 patients (9.8%) underwent pancreatectomy with concomitant arterial resection (CT [n=14, 48.3%], HA [n=11, 37.9%], and SMA [n=4, 13.8%]). Notably, 34/36 (94.5%) ISGPS type III venous resections and 27/29 (93.1%) arterial resections were performed following primary treatment.

Multi-visceral resections (n=34, 4.4%) were performed consistently between upfront and post-treatment operations, and included removal of the kidney or adrenal gland (n=7, 20.6%), mesocolon (n=7, 20.6%), colon (n=6, 17.6%), stomach (n=6, 17.6%), or multiple organ resections (n=8, 23.5%), with no difference between upfront and post-treatment operations.

Overall, patients undergoing extended pancreatectomy had longer operations (median: 464 minutes, IQR 386-546 vs. 392 minutes, IQR 308-467; p<0.001) and higher estimated blood loss (median: 600mL, IQR 400-1000 vs. 500 mL, IQR 300-800; p<0.001) compared to those undergoing standard pancreatectomy.

Peri-operative information and survival outcomes in the overall population

Preoperative characteristics and surgical outcomes are reported in Supplementary Tables 1-2. Patients receiving extended pancreatectomy showed higher rates of overall (74.1% vs. 61.2% vs. 26.5%, p<0.001) and severe complications (22.8% vs. 18.8% vs. 8.8%, p=0.122) compared to those undergoing standard pancreatectomy and non-resectional procedures, yet no significant difference in 90-day mortality rate (p=0.292).

The median postoperative follow-up was 28.3 months (IQR 15.0-43.4). Overall, pancreatectomy provided a significant OS advantage compared to non-resection (median 31.2 months, 95%CI 29.4-34.4 vs. 14.0 months, 95%CI 10.3-21.0, p<0.001), but no differences were observed for TTP (median 15.5 months, 95%CI 13.8-17.5, vs. 14.9 months, 95%CI 10.8-not reached, p=0.93). Notably, distant metastases were the first site of disease progression/recurrence regardless of the

surgery (non-resectional surgery: 93.3%; standard pancreatectomy: 76.2%; extended pancreatectomy: 72.4%; p=0.08). Uni- and multi-variable analyses of OS and TTP adjusted for peri-operative and pathological variables are reported in Supplementary Tables 3-5.

Cohort of patients receiving upfront surgery

Among 330 patients who were operated upfront, 328 (98.5%) had anatomically resectable disease; yet those who had resection omitted displayed greater tumor size and peri-pancreatic organ involvement (p<0.001). Extended resection correlated with higher serum Ca19.9, escalating T-status and R1 resection rate (54.9 vs. 32.3%, p=0.002), but no significant differences were observed regarding other pathological parameters or stage (p>0.1).

While extended surgery resulted in escalating overall complication rates, this did not translate into a higher rate of severe complications and mortality. Complete data are reported in Supplementary Tables 6-8. Notably, access to adjuvant treatment was slightly higher after standard vs. extended resection (72.9 vs. 63%, p=0.170).

Survival outcomes

After excluding patients who died within 90 days postoperatively, the median OS was 32.6 months (95%CI 30.1-37.7) following pancreatectomy and 11.7 months (95%CI 10.2-n.r.) after non-resectional procedures (p=0.001). Pairwise comparisons revealed that extended pancreatectomy (median OS: 24.0 months, 95%CI 17.1-31.6) was associated with impaired OS compared to standard resection (35.2 months, 95%CI 31.2-41.9; p<0.001; Table 2). Multivariable analysis (Supplementary Table 9) confirmed that escalating disease stage and incomplete resection correlated with worse OS, while adjuvant treatment deliver significantly improved survival (HR 0.40, 95%CI 0.29-0.57; p<0.001).

Patients receiving pancreatectomy displayed longer, yet non-significant, TTP compared to those who had resection omitted (median TTP 16.9 months, 95%CI 14.3-22.2, vs. 9.2 months, 95%CI

5.1-not reached, p=0.13). TTP after extended pancreatectomy (11.6 months, 95%CI 7.8-20.9) was significantly worse compared to that following standard pancreatectomy (18.7 months, 95%CI 15.4-25.9, p=0.004), and comparable to that of resection omission (p=1.0; overall p<0.001, Table 2). Distant metastases were the first site of disease progression/recurrence regardless of the surgery (non-resectional surgery: 100%; standard pancreatectomy: 81.5%; extended pancreatectomy: 70.3%; p=0.585). Multivariable analysis of TTP (Supplementary Table 10) revealed that extended surgery marginally correlated with shorter TTP (HR 1.36, 95%CI 0.92-2.02, p>0.1), while escalating AJCC stage and adjuvant treatment omission strongly predicted recurrence.

Cohort of patients receiving post-treatment surgery

Among 471 patients, 285 had received chemotherapy alone (60.6%), 179 (38.1%) received chemo-radiation therapy, and six (1.3%) radiation therapy only. Details regarding chemotherapy regimens are provided in Supplementary Table 11. Overall, while patients undergoing extended surgery were more likely to receive chemo-radiotherapy (50.3 vs. 28.7%, p<0.001), the regimen and duration of chemotherapy did not correlate with the surgical procedure. Resection omission was associated with escalating anatomical stage (p<0.001); however, RECIST response and Ca19.9 response were only marginally associated with surgical attitude.

Overall complication rate and duration of stay significantly escalated for those receiving extended resection vs. standard pancreatectomy or non-resectional procedures (p<0.001), with a trend towards worsening outcomes also observed for severe complications and reoperation (p>0.5, Supplementary Table 12). Patients undergoing extended pancreatectomy exhibited worse pathological characteristics compared to standard procedures (Supplementary Table 13), with a significant escalation in T-status, N-status and R1 rate (44.6 vs. 25.3%; p<0.001). Notably, the administration of adjuvant treatment declined after extended resections (32.5 vs. 47.1%, p=0.002).

Survival Outcomes

Extended pancreatectomy was associated with significantly worse OS with respect to standard pancreatectomy (median 25.4 months, 95%CI 22.2-30.0 vs. 33.9, 95%CI 29.9-40.4 months, p=0.018; Table 2); however, OS significantly improved with respect to those who received exploration only (median 14.6 months, 95%CI 8.77-23.4; p=0.018; overall p<0.001). Multivariable analysis of OS (Table 3) revealed that increasing AJCC stage and peripancreatic fat invasion, but not surgery type, significantly correlated with poorer prognosis, whereas administration of adjuvant treatment predicted longer OS (HR 0.48, 95%CI 0.34-0.69, p<0.001).

Extended pancreatectomy displayed a trend towards worse median TTP (10.9 months, 95%CI 8.9-13.9) compared to standard pancreatectomy (16.3 months, 95%CI 13.9-20.3, p=0.070) and non-resectional surgery (17.9 months, 95%CI 13.6-not reached, p=0.416; overall p=0.044; Table 2). Patterns of disease recurrence/progression indicated distant metastases as the first site of recurrence (exploration: 88.9%; standard pancreatectomy: 76.9%; extended pancreatectomy: 73.1%; p=0.49).

On multivariable analysis (Table 4), escalating AJCC stage and peripancreatic fat infiltration, but not surgical procedure, were significantly associated with worse TTP. In contrast, adjuvant treatment administration improved TTP (HR 0.69, 95% CI 0.52-0.89, p= 0.004).

Discussion

This study reports on postoperative and survival outcomes following surgery in approximately 800 PDAC patients treated at a high-volume institution, with no restrictions on preoperative resectability status or primary treatment administration. The whole spectrum of surgical procedures performed, including non-resectional surgery, was scrutinized.

Pancreatectomy with concomitant vascular and/or multivisceral resections was performed in almost one-third of the patients, particularly following primary chemo(radiation) treatment (40 vs. 15%). These figures reflect institutional practices where a major surgical endeavor is undertaken to achieve tumor excision primarily for patients with stable/responsive disease following neoadjuvant/induction treatment. While an overall increase in the complication rate was observed following extended resections, it did not translate into a surge in severe event or 90-day mortality rates compared to standard surgery (4.4 vs 2.6%). These results align with contemporary studies reporting comparable outcomes of pancreatectomies with and without concomitant vascular resections performed at high-volume institutions. [2, 3, 21, 22] Notably, complication burden can significantly affect the chance of accessing postoperative chemotherapy and achieving long-term survival.[23] A previous study highlights that PDAC patients who suffered major complications following upfront resection had a twofold risk of experiencing delay in treatment initiation and being denied adjuvant treatment.[24] Therefore, referral to a specialized center with documented proficiency in surgical techniques and complication management should be offered to every PDAC patient who is a candidate for surgery.

Notably, arterial resections were completed in 29 patients. In fact, circumferential peri-adventitial divestment [16, 25, 26] rather than en-bloc artery resection was the preferred approach whenever possible in the case of tumor encasement of CT, HA or SMA, with the intent of avoiding

anastomotic stricture/thrombosis consequent to resection with an end-to-end reconstruction. Despite being technically demanding, this technique does not fall within the ISGPS definition of extended procedures. Although still preliminary, recent data suggest that arterial divestment approaches might be equivalent to formal arterial resections concerning pathological and survival results,[27-29] and should enter every pancreatic surgeon's skillset.

Four percent of patients eligible for resection had pancreatectomy omitted due to the presence of non-reconstructible SMV/PV axis and/or CT/SMA infiltration at the time of exploration. A previous study from our center identified preoperative anatomical resectability status as the primary predictor of resection failure, both upfront and following primary treatment.[11] In the present, enriched cohort, only 28% of the patients who did not achieve resection had borderline resectable/locally advanced disease, confirming that standard imaging is barely accurate in assessing tumor-vessel involvement.[30] Interestingly, almost 90% of such a cohort had a frozen section analysis performed intraoperatively, confirming microscopic infiltration of the adventitia of peripancreatic vessels. The accuracy of peri-adventitial tissue sampling to assess local cancer spread has been scarcely investigated thus far,[16, 31] and its application is likely dependent on institutional practices and pathology team expertise.[27] Patrons of such an approach claim that ruling out the presence of viable cancer cells invading the vessel adventitia can assist in the operative planning, in order to spare unnecessary resections when (macroscopic) tumor clearance is unlikely to be obtained. Conversely, chemo/radiation-induced modification of (peri)pancreatic tissue may affect the interpretation of frozen section analyses, limiting the capability to discern between tumor-free, fibrotic scars and hypo-cellular cancer residuals. Standardization of the sampling technique and pathological examination is therefore warranted to provide consistency to the approach.

Compelling information pertaining to post-operative survival is also provided. First, pancreatectomy yielded a significant survival benefit compared to non-resectional procedures, thereby strengthening the notion that tumor resection is necessary to achieve prolonged survival. Overall, the life expectancy of patients deemed unsuitable for resection slightly surpassed one year, in line with what other authors have reported.[5, 32-34] However, analysis of time-to-progression showed no advantage of pancreatectomy compared to exploration, with distant metastatization invariably being the first modality of disease progression/recurrence. Notably, TTP of patients receiving *extended* pancreatectomy was comparable to that of patients who had surgery aborted in the upfront surgery cohort (median 12 vs. 9 months, p=1.0), and poorer in the post-treatment cohort (median 11 vs. 18 months, p=0.04). Such data were further confirmed in the subset of patients who received arterial and/or circumferential venous resection only. Finally, multivariable analyses assessing survival predictors for resected patients indicated that only an escalating pathological stage and omission of adjuvant therapy – but not the type of surgery or margin status – consistently correlated with both overall survival and time-to-progression.

Collectively, such information adds to the existing literature on the impact of surgery for localized PDAC and provides real-life, reference data for the pancreatic surgeon. As of today, most series reporting on the oncological outcomes of extended pancreatectomy focus on patients with borderline resectable/locally advanced cancer (LAPC) who received preoperative treatment[27, 29, 32, 35, 36] or excluded patients who were eventually denied resection because of unresectability at the time of exploration.[37-42] These limitations might overestimate surgical outcomes by restricting the study denominator to highly-selected patient cohorts who achieved resection. Moreover, focusing only on patients with LAPC might be inappropriate from a clinical standpoint. In fact, while baseline anatomical resectability remains a pivotal parameter for treatment allocation in clinical practice (upfront exploration vs. induction systemic treatment), our group and others have demonstrated that it is unable to predict survival once resection is achieved.[2, 11, 42]

Furthermore, while postoperative survival is routinely reported, progression-free survival after extended surgery has been rarely analyzed. A recent study by Ishida et al.[27] reports a median recurrence-free survival of 12 months after pancreatectomy with combined venous/arterial resection for locally advanced pancreatic cancer. Similarly, a nationwide study from the Netherlands [42] reports a disease-free interval of 13 months for patients resected for LAPC. Overall, such data align with the results of the present series (15 months) and suggest that the likelihood and speed of metastatization are barely influenced by primary tumor removal or surgery extension, but by pathological parameters and the chance of receiving systemic treatment.

Ultimately, this data prompts pancreatic cancer specialists to reassess commonly employed treatment outcome metrics. When crude post-surgical survival gain is marginal and disease recurrence occurs early, time-to-event outcomes can no longer be considered the only metric of surgical efficacy and appropriateness. In fact, most patients experience physical and psychological deterioration due to surgical sequelae and oncological treatment toxicities, particularly in the end stage of disease.[43-45] Therefore, health-related quality-of-life metrics assessing personal and social functioning, their modification over time, as well as time toxicity[46] should be investigated thoroughly to inform shared decision-making. In this respect, a prospective, observational trial will soon be initiated at the authors' institution to longitudinally investigate quality-of-life domains following surgery for PDAC.

In conclusion, while acknowledging the inherent limitations of a retrospective, single-center study, this data raises critical considerations for the practicing surgeon regarding the *biologic* implications of extended surgery. Pancreatectomy with concomitant vascular/multivisceral resections can be safely performed, yet provides marginal overall and progression-free survival gain compared to standard resection and non-resectional procedures. As of today, biological markers to

identify ideal candidates for (extended) surgical resection are lacking. Therefore, the decision to commit to extended pancreatectomy in the case of local, extra-pancreatic tumor spread at the risk of escalating complication burden must be tailored on a patient-level.

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Tables

Table 1
Operative details for patients receiving pancreatectomy.

	Overall population (n=770)	**Standard pancreatectomy** (n=542)	**Extended pancreatectomy** (n=228)	**P-value***
Type of pancreatectomy				
Pancreatoduodenectomy	500 (64.9%)	376 (69.4%)	124 (54.4%)	**<0.001**
Distal pancreatectomy	184 (23.9%)	123 (22.7%)	61 (26.8%)	
Total pancreatectomy	86 (11.2%)	43 (7.1%)	43 (18.9%)	
Type of non-resectional procedure				
Exploration only		19 (56.0%)		
Biliary/gastric bypass or cholecystectomy		15 (44.0%)		
Type of extended resection				
Vascular resection			194 (85.1%)	
Multivisceral resection			24 (10.5%)	
Combined			10 (4.4%)	
Organ resected				
Adrenal gland/kidney			7 (20.6%)	
Right/left colon			6 (17.6%)	
Mesocolon			7 (20.6%)	
Stomach (wedge or total)			6 (17.6%)	
Multiple organs			8 (23.6%)	
Vascular resection type				
Venous			175 (85.8%)	
Arterial			20 (9.8%)	
Combined			9 (4.4%)	
Vein resected				
PV			31 (16.8%)	
SMV			76 (41.3%)	
PV-SMV confluence			72 (32.9%)	
Other			5 (2.7%)	
Reconstruction technique†				
ISGPS I			144 (78.3%)	
ISGPS II			3 (1.6%)	
ISGPS III			36 (19.6%)	
ISGPS IV			0	
No reconstruction			1 (0.5%)	
Artery resected				
CT			14 (48.3%)	
HA			11 (37.9%)	
SMA			4 (13.8%)	
Duration of surgery (minutes), median (IQR)	415 (327-491)	392 (308-467)	464 (386-546)	**<0.001**
Estimated blood loss (mL), median (IQR)	500 (300-800)	500 (300-800)	600 (400-1000)	**<0.001**

* Statistical significance for $p<0.05$.

† Venous resection only.

CT: celiac trunk; HA: hepatic artery; ISGPS: International Study Group of Pancreatic Surgery; PV: portal vein; SMA: superior mesenteric artery; SMV: superior mesenteric vein.

Table 2
Overall survival and Time-to-progression of patients receiving upfront and post-treatment surgery, stratified by surgical procedure.

Upfront surgery					
	Overall population (n=325)	**Non-resectional surgery** (n=9)	**Standard pancreatectomy** (n=265)	**Extended pancreatectomy** (n=51)	**P-value***
Overall survival, months (95%CI) †	**32 (27.9-37.0)**	**11.7 (10.2-NR)**	**35.2 (31.2-41.9)**	**24.0 (17.1-31.6)**	**<0.001**
12-month OS rate, % (95%CI)	85.2% (81.4-89.2)	44.4% (21.4-92.3)	88.3% (84.5-92.2)	76.5% (66.6-89.1)	
24-month OS rate, % (95%CI)	62.3% (57.3-67.8)	33.3% (13.2-83.9)	65.5% (60.0-71.5)	50.8% (38.9-66.6)	
36-month OS rate, % (95%CI)	44.6% (39.4-50.5)	11.1% (1.7-7.5)	49.1% (43.4-55.6)	26.2% (16.0-42.7)	
60-month OS rate, % (95%CI)	27.7% (22.7-33.7)	-	32.4% (26.8-39.3)	5.8% (1.1-29.9)	
Time-to-progression, months (95%CI) ‡	**16.9 (14.2-22.1)**	**9.2 (5.07-NR)**	**18.7 (15.4-25.9)**	**11.6 (7.8-20.9)**	**0.005**
12-month TTP rate, % (95%CI)	61.6% (56.4-67.4)	33.3% (10.8-100)	65.0% (59.3-71.2)	46.7% (34.1-63.8)	
24-month TTP rate, % (95%CI)	41.1% (35.8-47.1)	16.7% (2.8-99.7)	44.3% (38.5-51.0)	26.3% (16.1-43.1)	
36-month TTP rate, % (95%CI)	31.7% (26.7-37.6)	-	34.9% (29.3-41.5)	16.2% (8.1-32.3)	
60-month TTP rate, % (95%CI)	27.1% (22.2-33.0)	-	30.1% (24.7-36.8)	12.1% (5.0-29.6)	
Post-treatment surgery					
	Overall population (n=451)	**Non-resectional surgery** (n=23)	**Standard pancreatectomy** (n=261)	**Extended pancreatectomy** (n=167)	**P-value***
Overall survival, months (95%CI) §	**29.3 (26.1-32.9)**	**14.6 (8.77-23.4)**	**33.9 (29.9-40.4)**	**25.4 (22.2-30.0)**	**<0.001**
12-month OS rate, % (95%CI)	80.0% (76.3-83.7)	60.9% (43.9-84.5)	83.8% (79.4-88.4)	76.6% (70.4-83.3)	
24-month OS rate, % (95%CI)	57.1% (52.7-61.9)	21.7% (10.0-47.2)	64.4% (58.8-70.5)	50.6% (43.5-58.8)	
36-month OS rate, % (95%CI)	41.9% (37.5-46.9)	16.3% (6.2-42.6)	47.7% (41.8-54.4)	36.5% (29.8-44.8)	
60-month OS rate, % (95%CI)	26.2% (21.5-32.1)	-	31.4% (24.8-39.8)	21.8% (15.3-31.2)	
Time-to-progression, months (95%CI) ¶	**14.2 (12.4-17.4)**	**17.9 (13.6-NR)**	**16.3 (13.9-20.3)**	**10.9 (8.9-13.9)**	**0.044**
12-month TTP rate, % (95%CI)	55.0% (54.4-60.1)	71.9% (51.6-100.0)	59.4% (53.6-65.9)	46.0% (38.6-54.7)	
24-month TTP rate, % (95%CI)	35.9% (31.5-41.0)	33.7% (14.4-78.6)	38.7% (33.0-45.3)	31.1% (24.4-39.7)	
36-month TTP rate, % (95%CI)	29.0% (24.8-33.9)	33.7% (14.4-78.6)	31.8% (26.3-38.3)	24.0% (17.8-32.3)	
60-month TTP rate, % (95%CI)	23.3% (12.8-28.8)	-	25.9% (20.0-33.4)	18.5% (12.4-27.6)	

* Statistical significance for $p<0.05$.

† The median follow-up was 30.4 months (IQR 16.4-46.9). At the time of last contact, 106/325 patients (32.6%) were still alive, with a median follow-up of 59.0 months (reverse Kaplan-Meier estimator, 95%CI 55.4-62.0).

‡ The median follow-up was 16.0 months (IQR 7.8-35.8). At the time of last contact, 95/301 patients (31.6%) were progression-free with a median follow-up of 53.2 months (reverse Kaplan-Meier estimator, 95%CI 48.5-59.0).

§ The median follow-up was 27.1 months (IQR 14.3-41.3). At the time of last contact, 155/428 patients (36.2%) were still alive, with a median follow-up of 45.8 months (reverse Kaplan-Meier estimator, 95%CI 44.0-50.2).

¶ The median follow-up was 12.8 months (IQR 5.9-32.0). At the time of last contact, 122/410 patients (29.8%) were progression-free, with a median follow-up of 43.7 months (reverse Kaplan-Meier estimator, 95%CI 41.9-46.2).

OS = overall survival.
TTP = time-to-progression.
NR = not reached.

Table 3
Factors associated with overall survival for patients receiving post-treatment pancreatectomy (uni- and multi-variable analysis).

		Univariable analysis			Multivariable analysis		
	OS (months, median with 95%CI)	**HR**	**95% CI**	**P-value***	**OR**	**95% CI**	**P-value***
Sex				0.637			
Male	30.7 (26.2-35.9)	Ref					
Female	26.9 (25.8-37.8)	0.94	(0.74-1.20				
ASA score				0.318			
ASA 1-2	30.7 (26.6-36.5)	Ref			Ref		0.972
ASA 3-4	29.3 (24.1-37.8)	1.14	(0.88-1.47)		0.99	(0.75-1.33)	
Tumor location				0.720			
Head	29.6 (27.1-33.4)	Ref					
Body-tail	31.0 (25.4-48.6)	0.95	(0.73-1.25)				
Primary treatment type							
Chemotherapy only	31.4 (27.1-37.4)	Ref					
Chemo-radiation	27.3 (22.7-33.8)	1.03	(0.81-1.32)	0.808			
Radiation only	58.5 (58.5-NR)	0.38	(0.09-1.52)	0.169			
Resectability status (preoperative)							
Resectable	36.3 (31.0-43.7)	Ref			Ref		
Borderline resectable	22.2 (18.9-29.4)	1.56	(1.21-2.00)	**0.001**	1.33	(0.98-1.79)	0.066
Locally advanced	30.6 (21.6-NR)	1.21	(0.76-1.93)	0.427	1.05	(0.63-1.74)	0.852
RECIST response							
Complete/partial	33.1 (25.8-45.5)	Ref			Ref		
Stable	29.9 (27.0-35.0)	1.10	(0.85-1.43)	0.449	0.92	(0.69-1.23)	0.086
Progressive	13.4 (10.0-43.7)	1.85	(1.14-2.99)	**0.013**	1.41	(0.82-2.43)	0.211
Preoperative Ca19.9, normal (<37 UI/mL)				0.065			0.375
Elevated	26.4 (23.5-32.6)	Ref			Ref		
Normal	33.1 (28.6-43.7)	0.79	(0.62-1.01)		0.89	(0.68-1.16)	
Ca19.9 responders (≥50% decrease)				0.208			
No	27.3 (24.1-33.8)	Ref					
Yes	31.0 (26.6-39.0)	0.85	(0.66-1.10)				
Peripancreatic organ involvement				0.95			
No	30.2 (27.1-34.3)	Ref					
Yes	26.4 (11.7-nr)	1.11	(0.75-1.65)				
Surgery				**0.006**			0.491
Standard	33.9 (29.9-40.4)	Ref			Ref		
Extended	25.4 (22.2-30.0)	1.40	(1.10-1.17)		1.11	(0.83-1.47)	
Postoperative course				0.081			0.31
No/mild complications (Clavien-Dindo I-II)	31.1 (28.5-36.3)	Ref			Ref		
Severe complication (Clavien-Dindo ≥III)	23.8 (16.9-38.4)	1.31	(0.97-1.79)		1.20	(0.85-1.69)	
AJCC stage							
0-I	50.1 (38.6-NR)	Ref		**<0.001**	Ref		
II	28.5 (24.4-33.3)	1.68	(1.22-2.30)		1.36	(0.95-1.96)	**0.096**
III	22.6 (16.9-27.3)	2.75	(2.00-3.80)		2.20	(1.49-3.23)	**<0.001**
R status							
R0	35.9 (29.8-43.5)	Ref		**<0.001**	Ref		0.815
R1	24.5 (19.4-29.6)	1.58	(1.24-2.01)		1.06	(0.64-1.77)	
Lymph-vascular infiltration							
No	na (43.5-NR)	Ref		**<0.001**	Ref		0.777
Yes	28.6 (25.6-31.7)	2.06	(1.39-3.07)		1.08	(0.65-1.79)	
Peri-neural infiltration							
No	57.7 (43.2-NR)	Ref		**<0.001**	Ref		0.289
Yes	28.5 (25.4-31.7)	1.92	(1.30-2.82)		1.29	(0.80-2.09)	
Peri-pancreatic fat infiltration				**<0.00**			

No	50.1 (35.0-NR)	Ref		**1**	Ref		**0.020**
Yes	26.6 (23.7-30.2)	1.90	(1.43-2.53)		1.52	(1.07-2.17)	
Adjuvant treatment							
No	29.6 (25.4-36.5)	Ref		**<0.00**	Ref		**<0.00**
Yes	23.3 (28.6-43.5)	0.88	(0.69-1.13)	**1**	0.48	(0.34-0.69)	**1**

* Statistical significance for p<0.05.
NR = not reached.
[Patients included in the multivariable analysis: 366.]

Table 4
Factors associated with time-to-progression for patients receiving post-treatment pancreatectomy (uni- and multi-variable analysis).

		Univariable analysis			Multivariable analysis		
	OS (months, median with 95%CI)	**HR**	**95% CI**	**P-value***	**OR**	**95% CI**	**P-value***
Sex				0.179			
Male	13.2 (10.9-17.2)	Ref					
Female	14.9 (11.4-19.9)	0.85	(0.68-1.08)				
ASA score				0.276			0.319
ASA 1-2	13.9 (11.9-17.5)	Ref			Ref		
ASA 3-4	14.6 (10.2-20.3)	1.15	(0.89-1.48)		1.14	(0.88-1.49)	
Tumor location				0.459			
Head	14.1 (11.1-17.6)	Ref					
Body-tail	13.9 (11.4-22.7)	0.90	(0.69-1.18)				
Primary treatment type							
Chemotherapy only	14.9 (12.7-18.4)	Ref					
Chemo-radiation	11.0 (8.77-17.5)	1.16	(0.91-1.47)	0.232			
Radiation only	37.0 (16.27-NR)	0.62	(0.20-1.93)	0.408			
Resectability status (preoperative)							
Resectable	18.2 (15.0-22.8)	Ref			Ref		
Borderline resectable	8.97 (7.9-11.1)	1.60	(1.25-2.05)	**0.001**	1.37	(1.03-1.82)	0.054
Locally advanced	7.45 (6.2-34.6)	1.40	(0.89-2.20)	0.151	1.34	(0.83-2.16)	0.236
RECIST response							
Complete/partial	15.2 (13.3-24.7)	Ref					
Stable	12.6 (10.9-17.6)	1.19	(0.92-1.52)	0.179			
Progressive	9.1 (5.8-NR)	1.45	(0.87-1.42)	0.159			
Preoperative Ca19.9, normal (<37 UI/mL)				0.576			0.780
Elevated	13.7 (10.2-18.5)	Ref			Ref		
Normal	14.2 (11.3-17.6)	0.93	(0.73-1.19)		0.97	(0.75-1.24)	
Ca19.9 responders (≥50% decrease)				0.166			
No	13.8 (10.6-17.0)	Ref					
Yes	15.0 (11.9-21.3)	0.84	(0.66-1.07)				
Peripancreatic organ involvement				0.45			
No	14.2 (11.9-17.5)	Ref					
Yes	12.4 (7.3-NR)	1.16	(0.79-1.69)				
Surgery				**0.024**			0.29
Standard	16.3 (13.9-20.3)	Ref			Ref		
Extended	10.9 (8.9-13.9)	1.31	(1.04-1.66)		0.97	(0.74-1.17)	
Postoperative course				0.464			
No/mild complications (Clavien-Dindo I-II)	14.6 (12.6-17.6)	Ref			Ref		0.29
Severe complication (Clavien-Dindo ≥III)	11.1 (8.4-18.4)	1.12	(0.82-1.53)		0.83	(0.59-1.17)	
AJCC stage							
0-I	34.7 (18.2-NR)	Ref		**<0.001**	Ref		
II	13.2 (11.0-18.3)	1.99	(1.46-2.70)		1.77	(1.26-2.49)	**0.001**
III	9.1 (7.8-11.9)	2.96	(2.15-4.08)		2.5	(1.72-3.63)	**<0.001**
R status							
R0	17.6 (14.7-22.6)	Ref		**<0.001**	Ref		0.134
R1	9.7 (7.7-12.4)	1.71	(1.35-2.17)		1.24	(0.94-1.66)	
Lymph-vascular infiltration							
No	58.2 (18.3-NR)	Ref		**<0.001**	Ref		0.612
Yes	12.6 (10.9-15.1)	2.23	(1.52-3.28)		1.14	(0.69-1.86)	
Peri-neural infiltration							
No	43.0 (18.3-NR)	Ref		**<0.001**	Ref		0.264
Yes	12.6 (11.0-15.0)	2.03	(1.40-2.95)		1.30	(0.82-2.04)	
Peri-pancreatic fat infiltration				**<0.001**			
No	25.1 (18.7-58.2)	Ref			Ref		**0.014**
Yes	11.1 (9.7-13.9)	1.90	(1.45-2.48)		1.49	(1.09-2.05)	

Adjuvant treatment							
No	10.9 (9.10-15.1)	Ref		0.061	Ref		**0.004**
Yes	16.7 (14.3-20.7)	0.80	(0.63-1.01)		0.68	(0.52-0.89)	

* Statistical significance for $p<0.05$.

[Patients included in the multivariable analysis: 372.]

Supplementary Tables

Supplementary Table 1
Preoperative features of the overall study population stratified by surgical procedure.

	Overall population (n=804)	**Non-resectional surgery** (n=34)	**Standard pancreatectomy** (n=542)	**Extended pancreatectomy** (n=228)	**P-value***
Sex					
Male	405 (50.4%)	19 (55.9%)	278 (51.3%)	108 (47.4%)	0.492
Female	399 (49.6%)	15 (44.1%)	264 (48.7%)	120 (52.6%)	
Age, median (IQR)	66 (59-72)	67 (61-72)	66 (59-72)	66 (58-72)	0.897
ASA score					
1-2	562 (59.9%)	26 (76.5%)	380 (70.1%)	156 (68.4%)	0.623
3-4	242 (30.1%)	8 (23.5%)	162 (29.9%)	72 (31.6%)	
Age-adjusted CCI	5 (4-6)	2 (2-6)	5 (5-6)	6 (4-6)	**0.005**
Primary chemo(radiation)					
No	333 (41.4%)	9 (26.5%)	273 (50.4%)	51 (22.4%)	**<0.001**
Yes	471 (58.6%)	25 (73.5%)	269 (49.6%)	177 (77.6%)	
Tumor location					
Head	587 (73.0%)	26 (76.5%)	406 (74.9%)	155 (68.0%)	0.127
Body-tail	217 (27.0%)	8 (23.5%)	136 (25.1%)	73 (32.0%)	
Resectability Status (preoperative)					**<0.001**
Resectable	580 (72.1%)	10 (29.4%)	451 (83.2%)	119 (52.2%)	
Borderline resectable	179 (22.3%)	12 (35.3%)	77 (14.2%)	90 (39.5%)	
Locally advanced	45 (5.6%)	12 (35.3%)	14 (2.6%)	19 (8.3%)	
Tumor size, median (IQR)	25 (20-30)	26 (22-36)	23 (18-30)	25 (20-33)	**<0.001**
Ca19.9, median (IQR)	42 (15-117)	50 (24-167)	40 (15-114)	42 (14-139)	0.540
Ca19.9, normal (≤37 UI/mL)					
No	400 (53.1%)	20 (62.5%)	265 (52.4%)	115 (53.5%)	0.534
Yes	353 (46.9%)	12 (37.5%)	241 (47.6%)	100 (46.5%)	
Peripancreatic organ involvement					
No	771 (96.0%)	30 (88.2%)	530 (98.1%)	206 (91.2%)	**<0.001**
Yes	32 (4.0%)	4 (11.8%)	10 (1.9%)	20 (8.8%)	

* Statistical significance for $p<0.05$.

Supplementary Table 2
Postoperative outcomes for the overall study population stratified by surgical procedure.

	Overall population (n=804)	**Non-resectional surgery** (n=34)	**Standard pancreatectomy** (n=542)	**Extended pancreatectomy** (n=228)	**P-value***
Complications (any)					
No	292 (36.3%)	25 (73.5%)	208 (38.4%)	59 (25.9%)	**<0.001**
Yes	512 (63.7%)	9 (26.5%)	334 (61.2%)	169 (74.1%)	
Severe complications (Clavien-Dindo ≥3)					
No	647 (80.5%)	31 (91.2%)	440 (81.2%)	176 (77.2%)	0.122
Yes	157 (19.5%)	3 (8.8%)	102 (18.8%)	52 (22.8%)	
Reoperation					
No	778 (96.8%)	34 (100.0%)	503 (92.8%)	209 (91.7%)	0.215
Yes	26 (3.2%)	0	39 (7.2%)	19 (8.3%)	
Length of stay (days), median (IQR)	9 (7-16)	6 (4-7)	8 (7-16)	10 (7-20)	**<0.001**
Readmission					
No	730 (92.4%)	32 (97.0%)	497 (92.6%)	201 (91.4%)	0.513
Yes	60 (7.6%)	1 (3.0%)	40 (7.4%)	19 (8.6%)	
90-day mortality					
No	778 (96.8%)	32 (94.1%)	528 (97.4%)	218 (95.6%)	0.292
Yes	26 (3.2%)	2 (5.9%)	14 (2.6%)	10 (4.4%)	
Adjuvant treatment					
No	314 (44.0%)		195 (38.2%)	119 (58.9%)	**<0.001**
Yes	399 (56.0%)		316 (61.8%)	83 (41.1%)	

* Statistical significance for p<0.05.

Supplementary Table 3
Overall survival and Time-to-progression for the overall population stratified by surgical procedure.

	Overall population (n=776)	**Non-resectional surgery** (n=32)	**Standard pancreatectomy** (n=526)	**Extended pancreatectomy** (n=218)	**P-value***
Overall survival, months (95%CI)	30.6 (27.6-32.9)	**14.2 (10.3-21.0)**	**35.0 (31.7-38.6)**	**24.8 (22.4-29.6)**	**<0.001**
12-month OS rate, % (95%CI)	82.2% (79.5-84.9)	56.3% (41.4-76.4)	86.1% (83.2-89.1)	76.6% (71.1-82.4)	
24-month OS rate, % (95%CI)	59.3% (55.9-62.9)	25.0% (13.7-45.6)	65.0% (61.0-69.0)	50.6% (43.6-57.8)	
36-month OS rate, % (95%CI)	43.0% (39.6-46.8)	15.0% (6.5-34.9)	48.4% (44.2-53.0)	34.2% (28.4-41.4)	
60-month OS rate, % (95%CI)	26.8% (23.3-30.9)	-	31.9% (27.6-37.0)	18.1% (12.7-25.9)	
Time-to-progression, months (95%CI)	15.3 (13.9-17.5)	**14.9 (10.8-NR)**	**17.3 (15.3-20.7)**	**10.9 (9.1-13.3)**	**0.004**
12-month TTP rate, % (95%CI)	57.8% (54.3-61.5)	60.8% (42.6-86.8)	62.2% (58.1-66.7)	46.1% (39.6-53.7)	
24-month TTP rate, % (95%CI)	38.1% (34.6-41.9)	28.4% (13-0-62.0)	41.5% (37.4-46.1)	29.9% (24.2-37.3)	
36-month TTP rate, % (95%CI)	30.1% (26.8-33.8)	28.4% (13-0-62.0)	33.3% (29.3-37.9)	22.2% (16.9-29.2)	
60-month TTP rate, % (95%CI)	25.0% (21.7-28.9)	-	28.3% (24.3-32.9)	16.9% (11.6-24.5)	

* Statistical significance for p<0.05.
OS = overall survival.
TTP = time-to-progression.
NR = not reached.

Supplementary Table 4

Factors associated with overall survival for patients receiving pancreatectomy (uni- and multi-variable analysis) in the overall population.

		Univariable analysis			Multivariable analysis		
	OS (months, median with 95%CI)	**HR**	**95% CI**	**P-value***	**OR**	**95% CI**	**P-value***
Sex				0.395			
Male	31.5 (28.6-35.2)	Ref					
Female	31.2 (27.3-36.9)	0.93	(0.77-1.11				
ASA score				0.082			0.659
ASA 1-2	31.6 (29.5-35.9)	Ref			Ref		
ASA 3-4	30.2 (25.6-35.0)	1.19	(0.98-1.44)		1.05	(0.85-1.30)	
Primary chemo(radiation)				0.41			0.367
No	32.6 (30.1-37.7)	Ref			Ref		
Yes	30.0 (27.1-33.9)	1.27	(1.01-1.29)		1.12	(0.88-1.42)	
Tumor location				0.134			0.546
Head	30.4 (27.9-33.1)	Ref			Ref		
Body-tail	36.9 (26.6-47.2)	0.86	(0.70-1.05)		0.93	(0.75-1.17)	
Resectability status (preoperative)							
Resectable	34.4 (31.1-38.4)	Ref			Ref		
Borderline resectable	22.6 (19.4-29.4)	1.50	(1.21-	**0.001**	1.29	(0.98-1.67)	0.074
Locally advanced	30.6 (21.6-NR)	1.16	1.85) (0.74-1.82)	0.567	0.94	(0.57-1.55)	0.812
Preoperative Ca19.9, normal (<37 UI/mL)				**0.018**			0.106
Elevated	28.6 (25.4-32.7)	Ref			Ref		
Normal	35.0 (30.6-43.5)	0.80	(0.66-0.97)		0.85	(0.69-1.04)	
Peripancreatic organ involvement				0.95			
No	31.2 (29.5-34.5)	Ref					
Yes	37.7 (26.4-NR)	0.95	(0.60-1.48)				
Surgery				**<0.001**			0.203
Standard	35.0 (31.7-38.6)	Ref			Ref		
Extended	24.8 (22.4-29.6)	1.51	(1.25-1.83)		1.16	(0.92-1.497	
Postoperative course				**0.002**			0.321
No/mild complications (Clavien-Dindo I-II)	32.7 (30.6-36.9)	Ref			Ref		
Severe complication (Clavien-Dindo ≥III)	23.8 (17.6-29.6)	1.42	(1.13-1.78)		1.14	(0.88-1.47)	
AJCC stage							
0-I	57.7 (48.5-n.r.)	Ref		**<0.001**	Ref		
II	31.8 (27.6-39.4)	1.76	(1.34-		1.46	(1.07-1.99)	**0.018**
III	23.7 (21.1-27.3)	2.89	2.31) (2.22-3.77)		2.55	(1.85-3.51)	**<0.001**
R status							
R0	37.2 (32.9-43.0)	Ref		**<0.001**	Ref		**0.050**
R1	25.3 (22.7-28.5)	1.69	(1.39-1.99)		1.24	(1.01-1.53)	
Lymph-vascular infiltration							
No	na (43.5-NR)	Ref		**<0.001**	Ref		0.987
Yes	30.4 (27.6-32.9)	1.89	(1.26-2.83)		1.00	(0.62-1.60)	
Peri-neural infiltration							
No	50.7 (43.2-NR)	Ref		**<0.001**	Ref		0.17
Yes	30.3 (27.3-32.7)	1.89	(1.28-2.77)		1.35	(0.88-2.08)	
Peri-pancreatic fat infiltration				**<0.001**			
No	50.2 (38.6-na)	Ref			Ref		**0.011**

Yes	29.5 (26.6-31.7)	1.88	(1.43-2.47)		1.49	(1.09-2.02)	
Adjuvant treatment							
No	26.1 (22.6-30.7)	Ref		**<0.001**	Ref		**<0.001**
Yes	37.4 (33.1-43.0)	0.72	(0.60-0.86)		0.62	(0.50-0.78)	

* Statistical significance for p<0.05.
NR = not reached.
[Patients included in the multivariable analysis: 659.]

Supplementary Table 5

Factors associated with time-to-progression for patients undergoing resection (uni- and multi-variable analysis) in the overall population.

		Univariable analysis			Multivariable analysis		
	OS (months, median with 95%CI)	**HR**	**95% CI**	**P-value***	**OR**	**95% CI**	**P-value***
Sex				**0.047**			0.53
Male	14.9 (13.1-17.3)	Ref			Ref		
Female	16.3 (13.8-20.9)	0.84	(0.7-1.00)		0.83	(0.69-1.01)	
ASA score				0.159			
ASA 1-2	15.1 (13.3-18.2)	Ref			Ref		0.361
ASA 3-4	16.1 (12.0-19.6)	1.15	(0.95-1.39)		1.10	(0.90-1.35)	
Primary chemo(radiation)				0.095			0.12
No	16.9 (14.3-22.2)	Ref			Ref		
Yes	13.9 (11.9-17.0)	1.16	(0.97-1.39)		1.20	(0.95-1.51)	
Tumor location				0.107			
Head	15.0 (13.2-17.6)	Ref					
Body-tail	16.3 (13.4-26.0)	0.85	(0.69-1.04)				
Resectability status (preoperative)							
Resectable	17.6 (16.0-21.1)	Ref			Ref		
Borderline resectable	9.1 (8.2-11.1)	1.61	(1.30-1.99)	**<0.001**	1.31	(1.01-1.69)	**0.042**
Locally advanced	7.5 (6.2-34.6)	1.4	(0.90-2.17)	0.136	1.22	(0.76-1.96)	0.406
Preoperative Ca19.9, normal (<37 UI/mL)							0.462
Elevated	14.2 (12.3-18.3)	Ref		0.264	Ref		
Normal	16.0 (13.9-20.8)	0.90	(0.75-1.08)		0.93	(0.77-1.13)	
Peripancreatic organ involvement				0.477			
No	15.3 (13.9-17.6)	Ref					
Yes	14.8 (10.1-35.7)	1.12	(0.82-1.52)				
Surgery				**<0.001**			0.575
Standard	17.3 (15.3-20.7)	Ref			Ref		
Extended	10.9 (9.1-13.3)	1.47	(1.21-1.78)		1.07	(0.85-1.34)	
Postoperative course				**0.056**			0.446
No/mild complications (Clavien-Dindo I-II)	16.3 (14.2-18.7)	Ref			Ref		
Severe complication (Clavien-Dindo ≥III)	11.3 (9.4-17.4)	1.26	(0.99-1.59)		0.9	(0.70-1.17)	
AJCC stage							
0-I	43.0 (30.5-n.r.)	Ref		**<0.001**	Ref		
II	16.7 (13.2-21.0)	1.92	(1.47-2.49)		1.80	(1.34-2.41)	**<0.001**
III	10.9 (10.0-13.0)	2.97	(2.30-3.85)		2.92	(2.15-3.96)	**<0.001**
R status							
R0	19.3 (16.2-24.4)	Ref		**<0.001**	Ref		0.08
R1	11.3 (10.5-13.4)	1.65	(1.38-1.98)		1.20	(0.98-1.48)	
Lymph-vascular infiltration							
No	58.2 (23.1-NR)	Ref		**<0.001**	Ref		0.754
Yes	14.3 (13.2-16.7)	2.00	(1.41-2.83)		1.07	(0.68-1.69)	
Peri-neural infiltration							
No	43.2 (24.3-NR)	Ref		**<0.001**	Ref		0.231
Yes	14.2 (13.2-16.3)	1.94	(1.38-2.72)		1.29	(0.85-1.94)	
Peri-pancreatic fat							

infiltration				**<0.001**			
No	27.4 (19.9-42.1)	Ref			Ref		**0.014**
Yes	13.8 (11.9-15.3)	1.69	(1.34-2.14)		1.41	(1.07-1.87)	
Adjuvant treatment							
No	10.6 (8.8-13.8)	Ref		**<0.001**	Ref		**<0.001**
Yes	18.2 (16.1-22.3)	0.70	(0.58-0.83)		0.59	(0.48-0.74)	

* Statistical significance for p<0.05.
NR = not reached.
[Patients included in the multivariable analysis: 649.]

Supplementary Table 6
Preoperative features of patients receiving upfront surgery.

	Overall population (n=333)	**Non-resectional surgery** (n=9)	**Standard pancreatectomy** (n=273)	**Extended pancreatectomy** (n=51)	**P-value***
Sex					
Male	167 (50.2%)	2 (22.2%)	141 (51.6%)	4 (47.1%)	0.197
Female	166 (49.8%)	7 (77.8%)	132 (48.4%)	27 (52.9%)	
Age, median (IQR)	69 (62-73)	69 (63-74)	69 (63-73)	62 (61-77)	0.333
ASA score					
1-2	240 (72.1%)	7 (77.8%)	196 (71.8%)	37 (72.5%)	0.922
3-4	93 (27.9%)	2 (22.2%)	77 (28.2%)	14 (27.5%)	
Age-adjusted CCI	6 (5-7)	2 (2-6)	6 (5-7)	6 (5-7)	0.288
Tumor location					
Head	235 (70.6%)	6 (66.7%)	196 (71.8%)	33 (64.7%)	0.575
Body-tail	98 (29.4%)	3 (33.3%)	77 (28.2%)	18 (35.3%)	
Resectability Status (preoperative)					**-**
Resectable	328 (98.5%)	6 (66.7%)	271 (99.3%)	51 (100%)	
Borderline resectable	3 (0.9%)	1 (11.1%)	2 (0.7%)	0	
Locally advanced	2 (0.6%)	2 (22.2%)	0	0	
Tumor size, median (IQR)	25 (20-30)	35 (27-40)	25 (20-30)	27 (20-33)	**0.051**
Ca19.9, median (IQR)	73 (26-204)	35 (25-380)	58 (22-179)	156 (24-380)	**0.005**
Ca19.9, normal (≤37 UI/mL)					
No	204 (66.2%)	4 (62.5%)	161 (52.4%)	39 (81.3%)	**0.041**
Yes	104 (33.8%)	4 (37.5%)	91 (47.6%)	9 (18.8%)	
Peripancreatic organ involvement					
No	321 (96.4%)	7 (77.8%)	269 (98.5%)	45 (88.2%)	**<0.001**
Yes	12 (3.6%)	2 (22.2%)	4 (1.5%)	6 (11.8%)	

* Statistical significance for p<0.05.

Supplementary Table 7
Pathological details of patients receiving upfront pancreatectomy.

	Overall population (n=333)	**Standard pancreatectomy** (n=273)	**Extended pancreatectomy** (n=51)	**P-value***
Tumor size (mm), median (IQR)	28 (22-35)	28 (22-35))	27 (22-36)	0.538
T-status				
T1	64 (19.9%)	162 (30.9%)	9 (18.0%)	**0.023**
T2	222 (69.2%)	315 (60.1%)	30 (60.0%)	
T3	35 (10.9%)	41 (7.8%)	11 (22.0%)	
T4	0	0	0	
Harvested lymph nodes, median (IQR)	42 (33-53)	42 (33-53)	41 (34-52)	0.966
Positive lymph nodes, median (IQR)	4 (1-7)	3 (1-7)	4 (1-7)	0.587
N-status				
N0	48 (14.8%)	44 (16.1%)	4 (7.8%)	0.271
N1	114 (35.2%)	93 (34.1%)	21 (41.2%)	
N2	162 (50.0%)	136 (49.8%)	26 (51.0%)	
AJCC stage				
0-I	45 (13.9%)	42 (15.4%)	3 (5.9%)	0.168
II	118 (36.4%)	96 (35.2%)	22 (43.1%)	
III	162 (49.7%)	136 (49.5%)	26 (51.0%)	
R status				
R0	208 (64.2%)	185 (67.8%)	23 (45.1%)	**0.002**
R1	116 (35.8%)	88 (32.3%)	28 (54.9%)	
Lymph-vascular infiltration				
No	11 (3.4%)	10 (3.7%)	1 (2.0%)	0.538
Yes	313 (96.6%)	263 (96.3%)	50 (98.0%)	
Peri-neural infiltration				
No	11 (3.4%)	9 (3.3%)	2 (3.9%)	0.821
Yes	313 (96.6%)	264 (96.7%)	49 (96.1%)	
Peri-pancreatic fat infiltration				
No	30 (9.3%)	28 (10.3%)	2 (3.9%)	0.152
Yes	294 (90.7%)	245 (89.7%)	49 (96.1%)	
Grading				
G1	15 (4.6%)	13 (4.8%)	2 (3.9%)	0.111
G2	189 (58.5%)	165 (60.7%)	24 (47.1%)	
G3	93 (28.8%)	72 (26.5%)	21 (41.2%)	
Anaplastic	10 (3.1%)	10 (3.7%)	0	
Not assessed	16 (5.0%)	12 (4.4%)	4 (7.8%)	

* Statistical significance for $p<0.05$.

Supplementary Table 8
Postoperative outcomes of patients receiving upfront surgery.

	Overall population (n=333)	**Non-resectional surgery** (n=9)	**Standard pancreatectomy** (n=273)	**Extended pancreatectomy** (n=51)	**P-value***
Complications (any)					
No	137 (41.1%)	9 (100%)	114 (41.8%)	14 (27.5%)	**<0.001**
Yes	196 (58.6%)	0	159 (58.2%)	37 (72.5%)	
Severe complications (Clavien-Dindo ≥3)					
No	271 (81.4%)	9 (100%)	218 (79.9%)	44 (86.3%)	0.193
Yes	62 (18.6%)	0	55 (20.1%)	7 (13.78%)	
Reoperation					
No	305 (91.6%)	9 (100%)	249 (91.2%)	47 (92.2%)	0.638
Yes	28 (8.4%)	0	24 (8.8%)	4 (7.8%)	
Length of stay (days), median (IQR)	8 (7-17)	5 (4-6)	8 (7-19)	10 (8-14)	**<0.001**
Readmission					
No	327 (98.2%)	9 (100%)	255 (94.1%)	49 (96.1%)	0.650
Yes	6 (1.8%)	0	16 (5.9%)	2 (3.9%)	
90-day mortality					
No	778 (96.8%)	9 (100%)	267 (97.8%)	51 (100%)	0.511
Yes	26 (3.2%)	0	6 (2.2%)	0	
Adjuvant treatment					
No	89 (28.6%)	-	72 (27.1%)	17 (37.0%)	0.170
Yes	222 (71.4%)	-	194 (72.9%)	29 (63.0%)	

* Statistical significance for p<0.05.

Supplementary Table 9
Factors associated with overall survival for patients receiving upfront pancreatectomy (uni- and multi-variable analysis).

		Univariable analysis			Multivariable analysis		
	OS (months, median with 95%CI)	**HR**	**95% CI**	**P-value***	**OR**	**95% CI**	**P-value***
Sex				0.444			
Male	32.9 (27.2-39.3)	Ref					
Female	32.2 (27.6-45.2)	0.90	(0.69-1.18)				
ASA score				0.161			0.687
ASA 1-2	32.7 (30.1-39.4)	Ref			Ref		
ASA 3-4	32.6 (23.6-39.3)	1.24	(0.92-1.67)		1.07	(0.77-1.49)	
Tumor location				0.081			0.283
Head	31.2 (27.2-35.6)	Ref			Ref		
Body-tail	41.9 (30.7-57.2)	0.76	(0.56-1.03)		0.83	(0.59-1.16)	
Resectability status (preoperative)							
Resectable	32.6 (30.1-38.4)						
Borderline resectable	-						
Locally advanced	-						
Preoperative Ca19.9, normal (<37 UI/mL)				0.067			0.594
Elevated	30.7 (25.5-36.9)	Ref			Ref		
Normal	37.7 (31.5-50.8)	0.75	(0.55-1.02)		0.92	(0.66-1.26)	
Peripancreatic organ involvement				0.774			
No	32.6 (30.0-37.7)	Ref					
Yes	31.6 (14.8-NR)	0.92	(0.52-1.63)				
Surgery				**<0.001**			**0.069**
Standard	35.2 (31.2-41.9)	Ref			Ref		
Extended	24.0 (17.1-31.6)	1.89	(1.34-2.66)		1.45	(0.97-2.15)	
Postoperative course				**0.008**			0.567
No/mild complications (Clavien-Dindo I-II)	35.2 (31.2-41.9)	Ref			Ref		
Severe complication (Clavien-Dindo ≥III)	24.3 (16.8-33.9)	1.57	(1.13-2.19)		1.13	(0.75-1.70)	
AJCC stage							
0-I	NR	Ref			Ref		
II	40.3 (34.4-50.8)	2.49	(1.40-4.42)	**0.002**	1.75	(1.92-2.31)	**0.088**
III	26.9 (21.1-30.7)	4.45	(2.55-7.78)	**<0.001**	3.51	(1.85-6.66)	**<0.001**
R status							
R0	39.3 (32.9-47.2)	Ref		**<0.001**	Ref		**0.025**
R1	26.2 (23.1-30.9)	1.79	(1.36-2.35)		1.46	(1.05-2.03)	
Lymph-vascular infiltration				0.322			
No	31.2 (21.5-NR)	Ref					
Yes	32.6 (30.0-37.6)	1.57	(0.64-3.81)				
Peri-neural infiltration				0.072			
No	NR (32.0-NR)	Ref			Ref		0.567
Yes	32.3 (29.9-37.2)	2.26	(0.93-5.50)		1.06	(0.38-2.98)	
Peri-pancreatic fat infiltration				**0.015**			
No	50.2 (39.4-NR)	Ref			Ref		0.561
Yes	31.7 (27.6-35.8)	2.01	(1.15-3.53)		1.25	(0.66-2.37)	
Adjuvant treatment							

No	18.1 (14.9-25.0)	Ref		**<0.001**	Ref		**<0.001**
Yes	39.2 (34.4-45.6)	0.48	(0.36-0.65)		0.40	(0.29-0.57)	

* Statistical significance for p<0.05.

NR = not reached.

[Patients included in the multivariable analysis: 282.]

Supplementary Table 10
Factors associated with time-to-progression for patients undergoing upfront pancreatectomy (uni- and multi-variable analysis).

		Univariable analysis			Multivariable analysis		
	OS (months, median with 95%CI)	**HR**	**95% CI**	**P-value***	**OR**	**95% CI**	**P-value***
Sex				0.119			
Male	16.6 (14.2-22.2)	Ref					
Female	18.6 (13.7-29.7)	0.80	(0.61-1.06)				
ASA score				0.473			
ASA 1-2	16.9 (13.7-23.8)	Ref					
ASA 3-4	18.7 (14.2-30.4)	1.12	(0.82-1.52)				
Tumor location				0.137			
Head	16.7 (13.8-21.0)	Ref					
Body-tail	23.8 (14.2-42.1)	0.79	(0.58-1.08)				
Resectability status (preoperative)				0.183			
Resectable	17.3 (14.9-22.3)	Ref					
Borderline resectable	10.7 (9.17-NR)	1.58	(0.81-3.08)				
Locally advanced	-	-					
Preoperative Ca19.9, normal (<37 UI/mL)							0.389
Elevated	15.4 (12.3-19.6)	Ref		0.093	Ref		
Normal	24.8 (16.1-31.6)	0.77	(0.57-1.04)		0.87	(0.64-1.19)	
Peripancreatic organ involvement				0.929			
No	16.9 (14.2-22.2)	Ref					
Yes	20.1 (6.5-NR)	1.02	(0.60-1.75)				
Surgery				**0.002**			0.119
Standard	18.7 (15.4)	Ref			Ref		
Extended	11.6 (7.57-20.9)	1.76	(1.24-2.51)		1.36	(0.92-2.02)	
Postoperative course				**0.037**			0.582
No/mild complications (Clavien-Dindo I-II)	19.1 (15.5-24.8)	Ref			Ref		
Severe complication (Clavien-Dindo ≥III)	13.8 (9.4-20.5)	1.46	(1.02-2.09)		0.12	(0.74-1.71)	
AJCC stage							
0-I	NR (41.8-NR)	Ref			Ref		
II	22.2 (16.9-34.7)	2.25	(1.32-3.82)	**0.003**	1.99	(1.12-3.54)	**0.018**
III	11.9 (10.6-15.1)	4.13	(2.47-6.89)	**<0.001**	3.77	(2.12-6.69)	**<0.001**
R status							
R0	24.4 (18.3-31.5)	Ref		**<0.001**	Ref		0.23
R1	13.2 (11.0-16.6)	1.63	(1.23-2.15)		1.22	(0.88-1.68)	
Lymph-vascular infiltration							
No	66.9 (13.1-NR)	Ref		0.229			
Yes	16.7 (14.2-22.1)	11.73	(0.71-4.20)				
Peri-neural infiltration							
No	69.9 (24.3-NR)	Ref		**0.072**	Ref		0.889
Yes	16.6 (14.2-21.1)	2.26	(0.93-5.51)		1.07	(0.43-2.67)	
Peri-pancreatic fat infiltration				**0.046**			
No	31.5 (18.4-NR)	Ref			Ref		0.767
Yes	16.0 (13.9-20.9)	1.68	(1.01-		1.09	(0.63-1.89)	

			2.80)				
Adjuvant treatment							
No	8.8 (6.1-15.4)	Ref		**<0.001**	Ref		**<0.001**
Yes	20.9 (16.3-27.9)	0.56	(0.41-0.76)		0.48	(0.34-0.69)	

* Statistical significance for p<0.05.
NR = not reached.
[Patients included in the multivariable analysis: 277.]

Supplementary Table 11
Preoperative features of patients receiving primary treatment, stratified by surgical procedure.

	Overall population (n=471)	**Non-resectional surgery** (n=25)	**Standard pancreatectomy** (n=269)	**Extended pancreatectomy** (n=177)	**P-value***
Sex					
Male	238 (50.5%)	17 (68.0%)	137 (50.9%)	84 (47.5%)	0.153
Female	233 (49.5%)	8 (32.0%)	132 (49.1%)	93 (52.5%)	
Age, median (IQR)	64 (51-71)	66 (61-70)	63 (57-70)	65 (57-71)	0.298
ASA score					
1-2	322 (68.4%)	19 (76.0%)	184 (68.4%)	119 (67.2%)	0.727
3-4	149 (31.6%)	6 (24.0%)	85 (31.5%)	58 (32.8%)	
Age-adjusted CCI	5 (4-6)	2 (2-6)	5 (4-6)	6 (4-6)	**0.004**
Primary treatment type					
Chemotherapy only	285 (60.6%)	12 (48.0%)	187 (69.8%)	86 (48.6%)	**<0.001**
Chemo-radiation	179 (38.1%)	13 (52.0%)	77 (28.7%)	89 (50.3%)	
Radiation only	6 (1.3%)	0	4 (1.5%)	2 (1.1%)	
Chemotherapy regimen					
Gem-Abra	148 (31.7%)	10 (40.0%)	83 (31.1%)	55 (31.4%)	0.314
(m)FOLFIRINOX	297 (63.6%)	13 (52.0%)	170 (63.7%)	114 (65.1%)	
Gem alone	2 (0.4%)	0	1 (0.4%)	1 (0.6%)	
Gem-based combo	7 (1.5%)	0	7 (2.6%)	0	
Other	13 (2.8%)	2 (8.0%)	6 (2.2%)	5 (2.9%)	
Number of cycles	6 (5-10)	6 (6-8)	6 (4-10)	7 (6-10)	0.467
Tumor location					
Head	352 (74.7%)	26 (80.0%)	210 (78.1%)	122 (68.9%)	0.079
Body-tail	119 (25.3%)	8 (20.0%)	59 (21.9%)	55 (31.1%)	
Resectability Status (Preoperative)					**<0.001**
Resectable	261 (55.4%)	4 (16.0%)	186 (69.1%)	71 (40.1%)	
Borderline resectable	167 (35.5%)	11 (44.0%)	69 (25.7%)	87 (49.2%)	
Locally advanced	43 (9.1%)	10 (40.0%)	14 (5.2%)	19 (10.7%)	
Tumor size (preoperative), median (IQR)	23 (19-30)	25 (22-32)	20 (18-28)	25 (20-32)	**<0.001**
RECIST response					
Complete/partial	178 (39.6%)	7 (31.8%)	108 (41.9%)	63 (37.1%)	0.184
Stable	242 (53.8%)	11 (50.0%)	136 (52.7%)	95 (55.9%)	
Progressive	30 (6.7%)	4 (18.2%)	14 (5.4%)	12 (7.1%)	
Preoperative Ca19.9, median (IQR)	30 (12-75)	54 (22-128)	27 (12-69)	33 (12-92)	0.180
Preoperative Ca19.9, normal (≤37 UI/mL)					
No	196 (44.0%)	16 (66.7%)	104 (40.9%)	76 (45.5%)	**0.048**
Yes	249 (56.0%)	8 (33.3%)	50 (59.1%)	91 (54.5%)	
Ca19.9 responders (≥50% decrease)					
No	179 (42.2%)	12 (63.2%)	99 (40.6%)	68 (42.2%)	0.067
Yes	245 (57.2%)	7 (36.8%)	145 (59.4%)	93 (57.8%)	
Peripancreatic organ involvement					
No	450 (95.7%)	23 (92.0%)	264 (98.5%)	163 (92.1%)	**0.002**
Yes	20 (4.3%)	2 (8.0%)	4 (1.5%)	14 (7.9%)	

* Statistical significance for p<0.05.

Supplementary Table 12
Postoperative outcomes of patients receiving primary treatment, stratified by surgical procedure.

	Overall population (n=471)	**Non-resectional surgery** (n=25)	**Standard pancreatectomy** (n=269)	**Extended pancreatectomy** (n=177)	**P-value***
Complications (any)					
No	155 (32.9%)	16 (64.0%)	94 (34.9%)	45 (25.4%)	**<0.001**
Yes	316 (67.1%)	9 (36.0%)	175 (65.1%)	132 (74.6%)	
Severe complications (Clavien-Dindo ≥III)					
No	376 (79.8%)	22 (88.0%)	222 (82.5%)	132 (74.6%)	0.080
Yes	95 (20.2%)	3 (12.0%)	47 (17.5%)	45 (25.4%)	
Reoperation					
No	441 (93.6%)	25 (100.0%)	254 (94.%)	162 (91.5%)	0.239
Yes	30 (6.4%)	0	15 (5.6%)	15 (8.5%)	
Length of stay (days), median (IQR)	9 (7-18)	6 (5-8)	8 (7-14)	11 (7-21)	**<0.001**
Readmission					
No	417 (90.8%)	23 (97.0%)	242 (91.0%)	152 (89.9%)	0.793
Yes	42 (9.2%)	1 (3.0%)	24 (9.0%)	17 (10.1%)	
90-day mortality					
No	451 (95.8%)	23 (92.0%)	261 (97.0%)	167 (94.4%)	0.180
Yes	20 (4.2%)	2 (8.0%)	8 (3.0%)	10 (5.6%)	
Adjuvant treatment					
No	249 (57.2%)		137 (52.9%)	112 (67.5%)	**0.003**
Yes	186 (42.8%)		122 (47.1%)	54 (32.5%)	

* Statistical significance for p<0.05.

Supplementary Table 13
Pathological data of patients undergoing post-treatment pancreatectomy, stratified by surgical procedure.

	Overall population (n=446)	**Standard pancreatectomy** (n=269)	**Extended pancreatectomy** (n=177)	**P-value***
Tumor size (mm), median (IQR)	25 (18-30)	23 (17-28)	25 (20-36)	**<0.001**
T-status				
T0	8 (1.9%)	5 (2.0%)	3 (1.9%)	**<0.001**
T1	149 (35.9%)	107 (42.3%)	42 (25.9%)	
T2	201 (48.4%)	123 (48.6%)	78 (48.1%)	
T3	45 (10.8%)	17 (6.7%)	28 (17.3%)	
T4	12 (2.9%)	1 (0.4%)	11 (6.8%)	
Harvested lymph nodes, median (IQR)	43 (33-54)	42 (32-51)	45 (35-57)	**0.017**
Positive lymph nodes, median (IQR)	1 (0-4)	1 (0-4)	2 (0-5)	0.084
N-status				
N0	156 (35.0%)	108 (40.1%)	48 (27.1%)	**0.007**
N1	165 (37.0%)	86 (32.0%)	79 (44.6%)	
N2	125 (28.0%)	75 (27.9%)	50 (28.2%)	
AJCC stage				
0-I	134 (30.8%)	97 (36.9%)	37 (21.5%)	**0.003**
II	168 (38.6%)	91 (34.6%)	77 (44.8%)	
III	133 (30.6%)	75 (28.5%)	58 (33.7%)	
R status				
R0	299 (67.0%)	201 (74.7%)	98 (55.4%)	**<0.001**
R1	147 (33.0%)	68 (25.3%)	79 (44.6%)	
Lymph-vascular infiltration				
No	74 (16.6%)	54 (20.1%)	20 (11.3%)	**0.015**
Yes	372 (83.4%)	215 (79.9%)	157 (88.7%)	
Peri-neural infiltration				
No	72 (16.1%)	52 (19.3%)	20 (11.3%)	**0.024**
Yes	374 (83.9%)	217 (80.7%)	157 (88.7%)	
Peri-pancreatic fat infiltration				
No	137 (30.7%)	89 (33.1%)	48 (27.1%)	0.181
Yes	309 (69.3%)	180 (66.9%)	129 (72.9%)	
Grading				
G1	0	0	0	0.684
G2	50 (12.1%)	32 (12.7%)	18 (11.2%)	
G3	13 (3.2%)	6 (2.4%)	7 (4.3%)	
Anaplastic	2 (0.5%)	1 (0.4%)	1 (0.6%)	
Not assessed	347 (84.2%)	212 (84.5%)	135 (83.9%)	

* Statistical significance for $p<0.05$.