Resectable Pancreatic Cancer: Neoadjuvant and Adjuvant Therapy

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy with rising incidence. In Europe and the United States, the 5-year overall survival (OS) after diagnosis is 7–10% [1, 2]. PDAC is projected to become the second leading cause of cancer death in 2030 [3]. Contrary to other cancer types, survival outcomes for PDAC have improved little in the past decades [4].

Non-metastatic, localized PDAC is generally classified according to the extent of vascular involvement on cross-sectional imaging. Categories include resectable, borderline resectable, and locally advanced disease. In the 10–20% of patients that present with resectable disease, upfront surgery is the standard of care [5, 6]. Despite optimal surgery, recurrence rates are high. Apparently, most patients with resectable PDAC have systemic disease at diagnosis [7].

In an effort to improve outcomes, adjuvant therapy has been developed, and its use is supported by level 1 evidence from multiple randomized controlled trials (RCTs). The main problem with adjuvant therapy is that up to half of patients are unable to receive it as result of complications from surgery with clinical deterioration and early recurrence. Therefore, there is a high interest in in the use of neoadjuvant therapy (i.e., before surgery) and perioperative therapy (i.e., both neoadjuvant and adjuvant) to improve outcomes.

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Staging Resectable Pancreatic Cancer

Staging of localized PDAC is historically based on the extent of arterial and venous tumor contact as visible on cross-sectional imaging. In most staging systems, resectable PDAC is defined as the absence of any arterial contact and no or limited venous contact (Table 1.1) [5, 8–10]. The National Comprehensive Cancer Network (NCCN) definition is most permissible as it allows up to 180° of venous contact.

In recent years, there is increasing interest in expanding the anatomy-based staging of localized PDAC with inclusion of biological and conditional factors [11]. For example, several studies have demonstrated that patients with elevated carbohydrate antigen (CA) 19-9 above 500 or 1000 have decreased survival that is similar to patients with borderline resectable disease [12–14]. Similarly, patients with a low performance status have worse survival [12, 14].

The NCCN and American Society of Clinical Oncology (ASCO) guidelines both advice to include CA 19-9 in the decision making between upfront surgery or neoadjuvant therapy in patients with resectable disease [5, 6]. The NCCN guideline states to consider neoadjuvant therapy particularly in patients with high-risk features, including a "markedly elevated CA 19-9." The ASCO guideline recommends upfront surgery only if patients have a CA 19-9 level "suggestive of potentially curable disease." Both guidelines do not provide a precise cut-off level for CA 19-9 above which neoadjuvant therapy is recommended.

Table 1.1 Definitions of resectable PDAC at diagnosis

	NCCN	AHPBA/SSAT/SSO	MD Anderson	DPCG
Arterial	No arterial contact	No arterial contact	No arterial contact	No arterial contact
Venous	No tumor contact with the SMV or PV or ≤180° contact without vein contour irregularity	No SMV or PV abutment, distortion, tumor thrombus, or venous encasement	Patent SMV/PV	No tumor contact with the SMV or PV or ≤90° contact

NCCN National Comprehensive Cancer Network, *AHPBA/SSAT/SSO* Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract, *DPCG* Dutch Pancreatic Cancer Group, *SMV* superior mesenteric vein, *PV* portal vein

Adjuvant Therapy for Resected Pancreatic Cancer

Although earlier trials were performed [15–18], the first RCTs that definitively demonstrated chemotherapy after resection could improve survival were the ESPAC-1 and CONKO-001 trials [19, 20]. Key clinical trials of adjuvant therapy are discussed below and summarized in Table 1.2.

Trials of Adjuvant Chemotherapy

The **ESPAC-1** trial was a multicenter trial in 11 European countries that investigated 5-fluorouracil (5-FU) with folinic acid (FA) chemotherapy and chemoradiotherapy (20 Gray with 5-FU). Between 1994 and 2000, patients were randomized to four arms: 69 to observation, 73 patients to chemoradiotherapy alone, 75 to chemotherapy alone, and 72 patients to both chemoradiotherapy and chemotherapy [19]. After a median follow-up of 47 months, the median OS was 16.9 months with observation, 13.9 months with chemoradiotherapy alone, 21.6 months with chemotherapy alone, and 19.9 months with chemoradiotherapy and chemotherapy. When the 142 patients who received chemotherapy (with or without chemoradiotherapy) were compared with the 147 patient who did not (with or without chemoradiotherapy), adjuvant 5-FU/FA chemotherapy was associated with a superior median OS of 20.1 versus 15.5 months (hazard ratio [HR] 0.71, 95% CI 0.55–0.92, $p = 0.009$).

The **CONKO-001** trial randomized 368 patients to 6 cycles of adjuvant gemcitabine or to observation in 88 centers in Germany and Austria [20]. After a median follow-up of 53 months, the trial did show an improvement in median disease free survival (13.4 vs. 6.9 months, $p < 0.001$), but did not demonstrate a statistically significant OS benefit (22.1 vs. 20.2 months, $p < 0.06$) [21]. After a longer follow-up of 136 months, however, adjuvant gemcitabine was associated with superior OS (HR 0.76, 95% CI 0.61–0.95, $p = 0.01$). The 5-year OS was 20.7% in the gemcitabine group and 10.4% in the observation group.

The Japanese **JSAP-02** trial had a similar design as the CONKO-001 as it compared adjuvant gemcitabine with observation, but the adjuvant treatment duration was three rather than six cycles. Between 2002 and 2005, 118 patients were randomized in 10 centers. The primary outcome of disease-free survival was significantly improved (11.4 vs. 5.0 months, HR 0.60, 95% CI 0.40–0.89, $p = 0.01$), but a difference in OS could not be demonstrated (22.3 vs. 18.4 months, HR 0.77, 95% CI 0.51–1.14, $p = 0.19$). The 5-year OS rate was 23.9% with gemcitabine and 10.6% with observation.

Table 1.2 Key randomized controlled trials of adjuvant therapy for resected pancreatic cancer

Trial	Inclusion period	No. of patients	Intervention	Comparator	Median OS (months)		5-year OS (%)		HR (95% CI), *p* value
					I	*C*	*I*	*C*	
Chemotherapy									
ESPAC-1	1994–2000	289	5-FU/FA	No chemotherapy	20.1	15.5	21.1	8.4	0.71 (0.55–0.92), $p = 0.009$
CONKO-001	1998–2004	354	GEM	Observation	22.8	20.2	20.7	10.4	0.76 (0.61–0.95), $p = 0.01$
JSAP-02	2002–2005	118	GEM	Observation	22.3	18.4	23.9	10.6	0.77 (0.51–1.14), $p = 0.19$
ESPAC-3	2000–2007	1088	5-FU/FA	GEM	23.0	23.6	15.9	17.5	0.94 (0.81–1.08), $p = 0.39$
JASPAC-01	2007–2010	377	S-1	GEM	46.5	25.5	44.4	24.4	0.57 (0.44–0.72), $p < 0.001$
CONKO-005	2008–2013	436	GEM/erlotinib	GEM	24.5	26.5	25	20	$p = 0.61$[a]
CONKO-006	2008–2013	122	GEM/sorafenib	GEM	17.6	17.5	–	–	$p = 0.48$[a]
ESPAC-4	2008–2014	730	GEM/CAP	GEM	27.7	26.0	28	20	0.84 (0.70–0.99), $p = 0.049$
PRODIGE-24/ CCTG PA.6	2012–2016	793	mFOLFIRINOX	GEM	53.5	35.5	43.2	31.4	0.64 (0.48–0.86), $p < 0.001$
APACT	2014–2016	866	GEM/nab-P	GEM	41.8	37.7	38	31	0.80 (0.68–0.95), $p = 0.009$
Chemoradiotherapy									
GITSG	1974–1982	43	CRT followed by maintenance 5-FU	Observation	21.0	10.9	19	5	$p = 0.03$[a]
EORTC 40891	1987–1995	120	CRT	Observation	17.1	12.6	20	10	0.76 (0.52–1.12), $p = 0.099$
ESPAC-1	1994–2000	289	CRT	No chemoradiotherapy	15.9	17.9	10.8	19.6	1.28 (0.99–1.66), $p = 0.05$
RTOG 9704	1998–2002		GEM followed by 5-FU CRT (50.4 Gy) followed by GEM	5-FU followed by 5-FU CRT (50.4 Gy) followed by 5-FU	20.5	17.1	22	18	0.82 (0.65–1.03), $p = 0.09$

5-FU/FA 5-fluorouracil with leucovorin, *CAP* capecitabine, *CI* confidence interval, *CRT* chemoradiotherapy, *GEM* gemcitabine, *HR* hazard ratio, *mFOLFIRINOX* modified 5-fluorouracil with leucovorin, irinotecan and oxaliplatin, *nab-P* nab-paclitaxel

[a] HR not reported

As both gemcitabine and 5-FU/FA were proven effective as adjuvant therapy, the **ESPAC-3** trial compared both treatments in 1088 patients from 159 centers in 17 countries [22]. After a median follow-up of 34.2 months, the median OS was not different with 23.6 months in the gemcitabine group and 23.0 in the 5-FU/FA group (HR 0.94, 0.81–1.08, $p = 0.39$). Due to the higher rate of adverse events in the 5-FU/FA group, gemcitabine became the preferred adjuvant regimen.

The **JASPAC-01** trial compared adjuvant S-1 with adjuvant gemcitabine in 385 patients in 33 centers in Japan. The median OS was 46.5 months with S-1 and 25.5 months with gemcitabine (HR 0.57, 95% CI 0.44–0.72, $p < 0.0001$) [23]. The 5-year OS rate was 44.1% in the S-1 group and 24.4% in the gemcitabine group. These results made S-1 the preferred adjuvant regimen for Japanese patients. A difference in pharmacokinetics of S-1 in Asian and Western populations and a lack of registration limit the use of S-1 in Western countries.

The **CONKO-005** and **CONKO-006** trials studied whether the addition of erlotinib or sorafinib to adjuvant gemcitabine could improve survival in patients who underwent R0 and R1 resection, respectively [24, 25]. Both trials failed to show an OS benefit of adding erlotinib or sorafinib to gemcitabine as adjuvant therapy.

The **ESPAC-4** trial randomized 730 patients in 92 centers to the combination of gemcitabine with capecitabine or gemcitabine monotherapy as adjuvant therapy [26]. After a median follow-up of 60 months, the median OS showed a modest improvement with 27.7 months in the gemcitabine/capecitabine group as compared with 26.0 months in the gemcitabine monotherapy group (HR 0.84, 95% CI 0.70–0.99, $p = 0.049$) [27]. The 5-year OS rate was 28% in the gemcitabine/capecitabine group and 20% in the gemcitabine group.

In 2011, the PRODIGE 4 ACCORD 11 trial showed an improvement in OS with FOLFIRINOX compared with gemcitabine in patients with metastatic PDAC [28]. On the basis of these results, the French-Canadian **PRODIGE-24/CCTG PA.6** trial was initiated to compare 12 cycles of adjuvant modified FOLFIRINOX with 6 cycles of adjuvant gemcitabine in 493 patients in 77 centers [29]. After a median follow-up of 33.6 months, median OS was an unprecedented 54.4 months with mFOLFIRINOX and 35.0 months with gemcitabine (HR 0.64, 95% CI 0.48–0.86, $p = 0.003$) [29]. In the long-term analysis with a median follow-up of 69.7 months, these results were confirmed with a 5-year OS of 43.2% with mFOLFIRINOX and 31.4% with gemcitabine [30].

In 2013, the MPACT trial demonstrated improved survival with the addition of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) to gemcitabine in metastatic PDAC [31]. Following these results, the **APACT** trial investigated the addition of nab-paclitaxel to adjuvant gemcitabine [32]. Between 2014 and 2016, 866 patients were randomized to 6 cycles of adjuvant gemcitabine with nab-paclitaxel or to 6 cycles of gemcitabine alone in North America, Europe, Asia, and Australia. The trial did not meet its primary endpoint of improving independently assessed disease free survival (HR 0.88, 95% CI 0.73–1.06, $p = 0.18$) [33]. After a median follow-up of 63.2 months, however, the median OS was 41.8 months with gemcitabine/nab-paclitaxel compared with 37.7 months with gemcitabine alone (HR 0.80, 95% CI 0.68–0.95, $p = 0.009$) [32]. The 5-year OS was 38% with gemcitabine/nab-paclitaxel and 31% with gemcitabine monotherapy.

Trials of Adjuvant Chemoradiotherapy

The **GITSG** trial compared adjuvant 5-FU chemoradiotherapy (total 40 Gray) followed by maintenance 5-FU during a maximum of 2 years with observation in 43 patients with margin-negative resected PDAC [34]. Median OS was 21 months with adjuvant chemoradiation and 10.9 months with observation (p = 0.03). At 5-year follow-up, 19% of patients were alive in the chemoradiotherapy group and 5% in the observation group [34].

The **EORTC 40891** trial compared adjuvant 5-FU chemoradiotherapy with observation in 218 patients with pancreatic and periampullary cancer [17]. In the long-term analysis, no improvement in OS was observed in the 120 patients with PDAC (median OS 17.1 vs. 12.6 months, HR 0.76, 95% CI 0.52–1.12) [35].

The **ESPAC-1** trial investigated both chemotherapy and chemoradiotherapy, as described in the previous section on chemotherapy. The chemoradiotherapy group included 145 patients and the no chemoradiotherapy group 144 patients. Chemoradiotherapy was associated with worse survival with a median OS of 15.9 months in the chemoradiotherapy group as compared with 17.9 months in the no chemoradiotherapy group (HR 1.28, 95% CI 0.99–1.66, p = 0.05) [19]. On the basis of these results, adjuvant chemoradiotherapy became controversial and its use declined.

The **RTOG 9704** trial investigated whether the addition of adjuvant gemcitabine to adjuvant 5-FU chemoradiation could improve survival. Between 1998 and 2002, 451 patients were randomized in 164 centers in the United States and Canada [36]. In the long-term analysis, the median OS was 20.5 months in the gemcitabine group as compared with 17.1 months without gemcitabine (HR 0.82, 95% CI 0.65–1.03, p = 0.09) [37].

Neoadjuvant Therapy for Resectable Pancreatic Cancer

Until recently, the best available evidence for neoadjuvant therapy consisted of meta-analyses of mostly non-randomized studies [38, 39]. These meta-analyses consistently demonstrated similar or improved OS with neoadjuvant therapy even though resection rates were lower. The first phase three trials that completed accrual and reported results are the PREOPANC and Prep 02/JSAP-05 trials [40, 41]. More recently, results of the SWOG S1505, NEONAX, and PANACH01-PRODIGE48 trials have been reported [42–44]. Key RCTs of neoadjuvant therapy for resectable PDAC are discussed below and presented in Table 1.3.

Table 1.3 Key studies of neoadjuvant therapy for resectable pancreatic cancer

Trial/study	Inclusion period	No. of patients	Intervention (no. of cycles)	Comparator (no. of cycles)	Median OS (months)		HR (95% CI), *p* value	Resection rate (%)	
					I	*C*		*I*	*C*
RCTs									
Prep 02/ JSAP-05[a]	2013–2016	362	Neoadj. GEM/S-1 + adj. S-1 (6 mo.)	Adj. S-1 (6 mo.)	36.7	26.6	0.72 (0.55–0.94), $p = 0.015$	86	87
PREOPANC[a]	2013–2017	246	Neoadj. GEM-based CRT + adj. GEM (4)	Adj. GEM (6)	15.7	14.3	0.73 (0.56–0.96), $p = 0.025$	61	72
SWOG S1505	2015–2018	102	Periop. mFOLFIRINOX (6+6)	Periop. GEM/ nab-P (3+3)	22.4	23.6	NR	73	70
NEONAX	2015–2019	118	Periop. GEM/nab-P (2+4)	Adj. GEM/nab-P (6)	25.2	16.7	NR	70	78
PANACHE01-PRODIGE48	2017–2020	146	Neoadj. mFOLFIRINOX (4) Neoadj. FOLFOX (4)	Adj. mFOLFIRINOX (12)	1-yr OS: mFOLFIRINOX, 84.1 FOLFOX, 71.8	1-yr OS: 80.8%	NR	mFOLFIRINOX, 71 FOLFOX, 68	81
Retrospective cohort study									
TAPS cohort	2012–2019	346	mFOLFIRINOX	–	31.2	–	–	71	–

Adj adjuvant, *CI* confidence interval, *CRT* chemoradiotherapy, *FOLFOX* 5-fluorouracil, leucovorin, and oxaliplatin, *GEM* gemcitabine, *HR* hazard ratio, *mFOLFIRINOX* modified 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin, *nab-P* nab-paclitaxel, *NR* not reported, *OS* overall survival

[a] Includes patients with both resectable and borderline resectable pancreatic cancer

Trials of Neoadjuvant Chemotherapy

In the Japanese phase 3 **Prep 02/JSAP-05** trial, 362 patients with resectable or borderline resectable PDAC were randomized to neoadjuvant chemotherapy or to upfront surgery [41]. Patients in the neoadjuvant chemotherapy arm received two cycles of neoadjuvant gemcitabine with S-1. In both arms, 6 months of adjuvant S-1 was administered after resection. In an abstract publication from 2019, the median OS was 36.7 months for the neoadjuvant arm compared with 26.6 months with upfront surgery (HR 0.72, 95% CI 0.55–0.94, $p = 0.015$). The resection rates were similar (86% vs. 87%).

The first published RCT that compared two neoadjuvant multi-agent regimens in resectable PDAC was the phase 2 **SWOG S1505** trial. The trial compared neoadjuvant mFOLFIRINOX with neoadjuvant gemcitabine/nab-paclitaxel in 147 patients. After central review, 44 patients were excluded, and 1 patient withdrew informed consent leaving 102 patients for analysis. No difference in OS was observed with a median OS of 23.2 with mFOLFIRINOX and 23.6 months with gemcitabine/nab-paclitaxel. The resection rate was 73% in the mFOLFIRINOX group and 70% in the gemcitabine/nab-paclitaxel group. Compliance with adjuvant therapy was low as 56% started adjuvant therapy in the mFOLFIRINOX group and 55% in the gemcitabine/nab-paclitaxel group.

The first RCT to compare perioperative with adjuvant administration of multi-agent chemotherapy is the phase 2 **NEONAX** trial. The trial compared 6 cycles of perioperative gemcitabine/nab-paclitaxel (2 neoadjuvant, 4 adjuvant) with 6 cycles of adjuvant gemcitabine/nab-paclitaxel in 127 patients with resectable PDAC from 22 German centers [45]. According to an abstract published in 2022, median OS was 25.2 months with perioperative treatment compared with 16.7 with adjuvant treatment [43]. The resection rate in the perioperative arm was 70% compared with 78% in the adjuvant arm. In the perioperative arm, 54 (91.5%) started neoadjuvant therapy, while in the adjuvant arm, only 25 patients (42.4%) started adjuvant therapy.

The three-arm phase 2 **PANACHE01-PRODIGE48** trial randomized (2:2:1) 153 patients to 4 cycles of neoadjuvant mFOLFIRINOX, 4 cycles of neoadjuvant FOLFOX, or 12 cycles of adjuvant mFOLFIRINOX for resectable PDAC [46]. Additional adjuvant chemotherapy (8 cycles) was scheduled in the neoadjuvant therapy arms. Following the interim analysis, the FOLFOX arm was closed early for lack of efficiency. In an abstract publication in 2022, the 1-year OS rates were 84.1%, 71.8%, and 80.8%, and the resection rates were 74%, 68%, and 81%, respectively [44].

Trials of Neoadjuvant Chemoradiotherapy

The Dutch phase 3 **PREOPANC** trial compared neoadjuvant gemcitabine-based chemoradiotherapy with upfront surgery in 246 patients with resectable and borderline resectable PDAC. Neoadjuvant chemoradiotherapy consisted of three cycles of neoadjuvant gemcitabine combined with 36 Gy radiotherapy in 15

fraction during the second cycle. Following surgery, patients received four cycles of adjuvant gemcitabine. In the upfront surgery group, patients received six cycles of adjuvant gemcitabine. After a median follow-up of 27 months, median OS was 16.0 months with neoadjuvant chemoradiotherapy and 14.3 months with adjuvant gemcitabine (HR 0.78; 95% CI 0.58–1.05, $p = 0.096$) [47]. However, after a median follow-up of 59 months, 5-year OS was 20.5% with neoadjuvant chemoradiotherapy compared with 6.5% with adjuvant gemcitabine (HR 0.73; 95% CI 0.56–0.96, $p = 0.025$) [40]. Only 51% started adjuvant therapy in the adjuvant gemcitabine group.

A recent meta-analysis including 6 RCTs including 938 patients with resectable or borderline resectable PDAC found improved OS with neoadjuvant therapy (HR 0.66, 95% CI 0.52–0.85, $p = 0.001$) [48]. In the subgroup of patients with resectable PDAC, however, no significant treatment effect was found (HR 0.77, 95% CI 0.53–1.12, $p = 0.18$). A limitation of the meta-analysis was that none of the trials included adjuvant mFOLFIRINOX as the trials were started before the publication of the PRODIGE 24/CCTG PA. 6 trial.

Few non-randomized studies reported on neoadjuvant FOLFIRINOX for resectable PDAC [14, 49]. The largest study is a retrospective study by the Trans-Atlantic Pancreatic Surgery consortium from five centers in the United States and the Netherlands [14]. The study included 346 patients with resectable PDAC who received neoadjuvant (m)FOLFIRINOX. The median OS was 31 months and the resection rate was 71%.

Comparing Neoadjuvant and Adjuvant Therapy

Advantages of Neoadjuvant Therapy

The most important advantage of neoadjuvant therapy is that patients are guaranteed to receive systemic chemotherapy. Nationwide studies show that a considerable proportion of patients who underwent successful resection for PDAC do not receive adjuvant therapy. In a National Cancer Data Base study from the United States including 7967 patients who underwent resection between 2010 and 2012, 47% did not receive adjuvant chemotherapy. In a more recent nationwide analysis from the Netherlands, 433 of 1306 (33%) patients who underwent resection between 2014–2017 did not receive adjuvant therapy. Compliance remains the main concern with adjuvant therapy.

Second, the time period of neoadjuvant therapy allows for the tumor biology to declare itself. Patients with tumors that progress during neoadjuvant therapy are unlikely to have benefitted from a pancreatic resection. Consequently, neoadjuvant therapy allows for a better selection of those patients who may benefit from a potentially morbid operation.

Third, neoadjuvant therapy improves the R0 resection rate. In the PREOPANC trial, the R0 resection rate was 72% in the neoadjuvant CRT arm vs. 43% in the upfront surgery arm ($p < 0.001$).

Fourth, neoadjuvant therapy may reduce postoperative complications. An analysis of the PREOPANC trial found 0% postoperative pancreatic fistula after neoadjuvant chemoradiotherapy and no increase in overall major complications [50]. Several other non-randomized studies had similar results [51, 52].

Disadvantages of Neoadjuvant Therapy

Upfront surgery with adjuvant therapy has some small advantages over neoadjuvant therapy.

First, neoadjuvant chemotherapy requires a tissue diagnosis of PDAC, while most patients with a hypo-intense pancreatic mass on CT undergo a resection without tissue diagnosis. Diagnostic procedures to obtain tumor tissue are endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) or bile duct brushing. These procedures are associated with complications including acute pancreatitis, hemorrhage, and perforation of the gastrointestinal tract [53].

Second, both cross-sectional imaging and a biopsy cannot distinguish periampullary cancer from PDAC with 100% accuracy. In a nationwide analysis from the Netherlands, the misdiagnosis rate was 13% in patients who were preoperatively thought to have PDAC. With upfront surgery, the full histopathology specimen is available for the correct diagnosis and appropriate adjuvant treatment.

Third, the majority of patients with resectable PDAC present with obstructive jaundice. These patients need a stent for biliary decompression to tolerate neoadjuvant therapy. Placement of a biliary stent with endoscopic retrograde cholangiopancreatography is associated with a non-negligible risk of complications and even death. Biliary drainage can be omitted in patients treated with upfront surgery. An RCT showed an increased rate of complications in patients with tumors in the pancreatic head who underwent preoperative biliary drainage as compared with patients who proceeded to surgery without drainage [54].

Comparing Neoadjuvant and Adjuvant Trials

Survival is lower in RCTs investigating neoadjuvant and perioperative treatment as compared with RCTs that compare only adjuvant therapy (Tables 1.2 and 1.3). Some have misinterpreted this as evidence of inferior survival after neoadjuvant therapy [55]. For example, the median survival in the PREOPANC trial (comparing a neoadjuvant with adjuvant treatment) of patients in the adjuvant gemcitabine arm was 14 months, while the median survival in the PRODIGE 24/CCTG PA.6 trial (comparing two adjuvant regimens) of patients in the same adjuvant gemcitabine arm was 36 months (Tables 1.1 and 1.2) [29, 40]. This large difference is explained by an entirely different selection of patients for an RCT comparing one or more neoadjuvant regimens with an RCT with only adjuvant regimens. Adjuvant RCTs include only a subgroup of all patients who would have been eligible for a neoadjuvant trial. In order for a patient presenting with resectable PDAC to become eligible

for inclusion in an adjuvant RCT, the patient has to overcome many hurdles: (1) no occult metastases at staging laparoscopy (about 5–10% drops out), (2) a resection without postoperative mortality (about 2–5% drops out), (3) recover sufficiently from surgery to receive adjuvant chemotherapy (about 30% drops out), (4) no early recurrence on postoperative CT scan (about 5% drops out), and (5) no elevated postoperative CA 19-9 levels (about 5% drops out). In summary, up to 50% of all patients randomized in an RCT with one or more neoadjuvant treatment arms would have never become eligible for an RCT comparing only adjuvant therapy.

Most trials of neoadjuvant therapy have demonstrated a lower resection rate as compared with upfront surgery. This is explained by patients that progress during neoadjuvant therapy. Some argue that this is a disadvantage of a neoadjuvant approach. However, it is unlikely that patients who progress during neoadjuvant therapy would have benefitted from a pancreatic resection. These patients would likely have developed disease recurrence within 3–6 months after upfront resection.

Future Directions

Ongoing Clinical Trials

Several ongoing studies investigate neoadjuvant and adjuvant therapy for resectable PDAC (Table 1.4).

The **NorPACT-1** trial investigates perioperative mFOLFIRINOX for resectable PDAC. In the intervention arm, patients receive four cycles of neoadjuvant mFOLFIRINOX followed by surgery. After surgery, eight cycles of mFOLFIRINOX are planned. In the comparator arm, patients receive 12 cycles of adjuvant mFOLFIRINOX. In the original design, the adjuvant therapy was gemcitabine/capecitabine, but this was changed after the publication of the PRODIGE-24/CCTG PA.6 trial results. Between 2016 and 2020, 140 patients were randomized in Norway, Sweden, Finland, and Denmark, and results are expected at the end of 2022.

The Dutch **PREOPANC-2** compared neoadjuvant FOLFIRINOX with neoadjuvant gemcitabine-based chemoradiotherapy. In the intervention arm, patients receive neoadjuvant FOLFIRINOX without adjuvant therapy. The comparator arm is based on the superior arm of the PREOPANC-1 trial, consisting of 3 cycles of neoadjuvant gemcitabine whereby the second cycle is combined with 36 Gray radiotherapy in 15 fractions. After surgery, four cycles of adjuvant gemcitabine are planned. The trial included patients with both resectable and borderline resectable PDAC. Between 2018 and 2021, 368 patients were randomized and results are expected in 2023.

The **ALLIANCE A021806** trial from the United States compares perioperative mFOLFIRINOX with adjuvant mFOLFIRINOX. In the intervention arm, patients receive eight cycles of neoadjuvant mFOLFIRINOX, and after surgery, four cycles of adjuvant mFOLFIRINOX are planned. In the comparator arm, 12 cycles of adjuvant mFOLFIRINOX are planned. The trial opened for accrual in July 2020, and as of 1 August 2023, 193 patients have been randomized.

Table 1.4 Ongoing or pending randomized controlled trials of (neo)adjuvant therapy for resectable pancreatic cancer

Trial name and registration	Inclusion period	Target sample size	Primary outcome	Intervention (no. of cycles)	Comparator (no. of cycles)
Adjuvant trials					
RTOG 0848 NCT01013649	2009–2014	545	DFS	Adjuvant CRT after adjuvant GEM	Adjuvant GEM without CRT
ESPAC-6 NCT05314998	Not yet recruiting	394	DFS	Adj. GEM/CAP (6) or adj. mFOLFIRINOX (12) based on transcriptomic signature	Adj. mFOLFIRINOX (12)
Neoadjuvant trials					
NorPACT-1 NCT02919787	2016–2020	140	OS at 18 months	Periop. mFOLFIRINOX (4+8)	Adj. mFOLFIRINOX (12)
PREOPANC-2[a] EudraCT 2017-002036-17	2018–2021	368	OS	Neoadj. FOLFIRINOX (8)	Neoadj. GEM-based CRT + adj. GEM (4)
ALLIANCE A021806 NCT04340141	2020–	352	OS	Periop. mFOLFIRINOX (8+4)	Adj. mFOLFIRINOX (12)
PREOPANC-3 NCT04927780	2021–	378	OS	Periop. mFOLFIRINOX (8+4)	Adj. mFOLFIRINOX (12)

Adj adjuvant, *CRT* chemoradiotherapy, *DFS* disease free survival, *GEM* gemcitabine, *OS* overall survival, *mFOLFIRINOX* neoadj, neoadjuvant, modified 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin, *periop* perioperative

[a] Includes patients with both resectable and borderline resectable pancreatic cancer

The **PREOPANC-3** trial from the Netherlands investigates perioperative mFOLFIRINOX and has a similar design as the ALLIANCE A021806 trial with 378 patients needed. The trial opened for accrual in August 2021, and as of 1 August 2023, 171 patients have been randomized.

The **RTOG 0848** trial investigates whether the addition of adjuvant chemoradiotherapy after adjuvant gemcitabine improves OS in patients with resected PDAC. In the two-step design, patients were first randomized to adjuvant gemcitabine or to adjuvant gemcitabine with erlotinib. Patients were restaged after five cycles of gemcitabine and, if without progression, randomized again to one cycle of gemcitabine followed by adjuvant capecitabine or 5-FU-based chemoradiotherapy (50.4 Gray) or to one cycle of gemcitabine. The results of step 1 were reported in 2020 and did not show a benefit of adding erlotinib to gemcitabine [56]. The step 2 result on the use of adjuvant chemoradiotherapy is pending.

The **ESPAC-6** trial from Germany investigates whether selecting an adjuvant regimen based on tumor characteristics can improve survival. In the intervention arm, patients will either receive adjuvant mFOLFIRINOX or adjuvant gemcitabine

with capecitabine based on the transcriptomic signature of the tumor. In the comparator arm, patients receive adjuvant mFOLFIRINOX. The trial plans to accrue 394 patients.

Neoadjuvant Therapy Based on Treatment Response

Neoadjuvant therapy allows for evaluating treatment response. This provides the opportunity to adapt or "switch" the neoadjuvant regimen in the absence of treatment response. As radiologic indicators of treatment response are generally unreliable in localized PDAC [57], serum CA 19-9 is often used to assess response.

Several studies have reported on the effect of a treatment "switch" of the neoadjuvant regimen. A single-institution study included 25 patients with borderline resectable and locally advanced PDAC who were switched from FOLFIRINOX to gemcitabine nab-paclitaxel [58]. Of the 25 patients, 21 showed radiographic or CA 19-9 response after switching and 11 patients underwent resection. Another study described the outcomes of 468 patients with borderline resectable and locally advanced PDAC of whom 139 (30%) had chemotherapy switch [59]. The majority (89%) switched from 5-FU-based therapy (FOLFIRINOX or FOLFOX) to gemcitabine with nab-paclitaxel. Of the 139 patients with chemotherapy switch, 100 underwent resection, and their survival was not different from the patients without chemotherapy switch (36.4 vs. 41.4 months; $p = 0.94$).

Several ongoing studies are investigating whether adaptive neoadjuvant therapy can improve survival. A study from the University of Wisconsin (NCT03322995) investigates whether switching based on treatment response can improve outcomes in patients with resectable or borderline resectable PDAC. Treatment response is assessed using CT imaging, serum CA 19-9, and performance status. All patients start with FOLFIRINOX. In case of response, patients continue with FOLFIRINOX. In case of stable disease, patients switch to gemcitabine-based therapy. In case of local progression, patients receive chemoradiation. The primary outcome of the study is completion of all neoadjuvant therapy and resection. Another study, from the Oregon Health and Science University (NeoOPTIMIZE; NCT04539808), follows the same principle. Patients with localized PDAC start with four cycles of FOLFIRINOX, and in case of progression at evaluation (by CT imaging or increase of CA 19-9 >30%), they switch to gemcitabine with nab-paclitaxel. The primary endpoint is the proportion of patients that undergo R0 resection. Finally, a study from the University of Cincinnati (NCT04594772) investigates whether a neoadjuvant chemotherapy switch improves the resection rate in 32 patients with resectable and borderline resectable PDAC.

Adjuvant Therapy After Neoadjuvant therapy

Current guidelines recommend a total duration of systemic therapy (combining neoadjuvant and adjuvant therapy) of 6 months [5, 6]. This recommendation is based on

extrapolation of treatment duration in the metastatic and adjuvant setting. No RCTs are available that investigate the duration of chemotherapy for PDAC or the use of adjuvant therapy after neoadjuvant therapy and resection.

An international, multi-institutional, retrospective analysis investigated adjuvant therapy after neoadjuvant FOLFIRINOX and resection in 520 patients of all stages of localized PDAC [60]. Adjuvant therapy was gemcitabine-based in 59% and 20% received FOLFIRINOX. Improved survival with adjuvant chemotherapy was observed only in patients with node-positive disease (median OS, 26 vs. 13 months, $p = 0.004$). Another study, based on the National Cancer Database, included patients who underwent a resection between 2004–2016 and used propensity score matching to account for selection bias [61]. A total of 2016 patients who received adjuvant therapy after neoadjuvant therapy and resection were successfully matched to 2016 patients who did not. Median OS was 29.4 months in patients who received adjuvant therapy compared with 24.9 months in patients who did not ($p < 0.001$). These results were irrespective of nodal or margin status. A total neoadjuvant therapy approach is increasingly used, because it avoids the challenge of administering adjuvant chemotherapy to all patients.

Conclusions

Progress has been made over the last decades in the treatment of resectable PDAC. Systemic therapy in the form of neoadjuvant or adjuvant therapy is an integral part of multimodality treatment and improves OS. The main concern with adjuvant therapy is compliance, and neoadjuvant therapy has the potential to improve outcomes in this regard. Two phase 3 RCTs have shown improved survival with neoadjuvant therapy, but both trials used single-agent systemic therapy. In patients with resectable PDAC, high-quality evidence for a survival benefit of neoadjuvant therapy over upfront surgery with multi-agent adjuvant therapy is therefore lacking. Current RCTs, including the ALLIANCE A021806 and PREOPANC-3 trials, will answer the question whether perioperative mFOLFIRINOX improves OS compared with upfront surgery with adjuvant mFOLFIRINOX.

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