Chapter 48
The Evolution of Adjuvant Trials in Pancreatic Cancer

John P. Neoptolemos, Christoph Springfeld, Thilo Hackert, and Markus W. Büchler

Take Home Messages
- Resection with 6 months adjuvant combination chemotherapy provides the best chance for long term survival.
- There is no role for adjuvant chemoradiation.

Pearls and Pitfalls
- Local recurrence occurs a little later than metastatic disease but is not associated with a better overall survival.
- R1-direct margin is associated with local recurrence and is associated with overall survival.
- Local recurrence cannot be used as a surrogate marker for improved overall survival.
- Lung metastasis is associated with longer survival than local recurrence or liver metastasis.

Future Perspectives
- Identifying which patients are more likely to respond to FOLFIRINOX or gemcitabine-capecitabine as first line chemotherapy.
- Association of chemotherapy responsiveness to molecular subtyping.

J. P. Neoptolemos (✉) · T. Hackert · M. W. Büchler
Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany
e-mail: john.neoptolemos@med.uni-heidelberg.de

C. Springfeld
Department of Medical Oncology, National Center for Tumor Diseases, Heidelberg University Hospital, Heidelberg, Germany

K. Søreide, S. Stättner (eds.), *Textbook of Pancreatic Cancer*,
https://doi.org/10.1007/978-3-030-53786-9_48

48.1 Introduction

Pancreatic cancer is one of the most lethal cancers and is predicted to become the second most common cause of cancer related deaths in the United States by 2030 [1]. There has been only very modest improvement in overall 5 year survival for all stages increasing from under 4% to around 9% in the past decade [2, 3]. The genetic characteristics of pancreatic cancer are now well characterized with distinct high frequency of KRAS, TP53, CDKN2A, and SMAD4 mutations and/or loss of heterozygosity, along with molecular subtyping into classical and basal categories [4–9]. Despite an increasing use of next generation sequencing based on these scientific advances only a minority of assay results lead to a change in clinical management with limited clinical efficacy, with the exception of the uncommon situations in patients with NRG1-fusions in KRAS wild-type tumors and patients with germline BRCA-mutated metastatic pancreatic cancer [10–13]. There is however increasing success using combinations of chemotherapy in the advanced setting [3, 14–17]. Despite remarkable improvement of surgical techniques, surgery by itself only provides relatively little extension of life expectancy with a 5-year survival rate of only 8% or less with resectable disease [17, 18].

48.2 Adjuvant Therapy Trials in Pancreatic Cancer

The groundbreaking studies of the European Study Group of Pancreatic Surgery (ESPAC) transformed our understanding of adjuvant chemotherapy in pancreatic cancer, prompting the development of further types of chemotherapy and also more advanced techniques in surgery and the evolution of neoadjuvant therapy [3, 17–23]. Table 48.1 provides an overview of trials investigating adjuvant therapy after primary resection [18–40].

The *ESPAC-1* trial, a multicenter randomized controlled trial of 545 patients utilized a two-by-two factorial design in 289 patients, randomizing each patient twice to either 5-fluorouracil (5-FU) with folinic acid for 6 months versus observation, or chemoradiotherapy (20 with 5-FU radiosensitization) versus observation, plus additionally another 256 patients into a single randomization, comprising 68 patients randomly assigned to chemoradiotherapy or no chemoradiotherapy and 188 to chemotherapy or no chemotherapy [18]. Early publication was recommended because of the lack of evidence to support the use of adjuvant chemoradiation after a median follow-up of 10 months, with a median survival of 15.5 months in 175 patients with chemoradiotherapy versus 16.1 months in 178 patients without chemoradiotherapy. There was evidence of a significant survival benefit for adjuvant chemotherapy with a median survival of 19.7 months in 238 patients with chemotherapy versus 14.0 months in 235 patients without chemotherapy [18]. With mature follow-up 47 months in the pure 2 × 2 factorial design section the estimated 5-year survival rate was 10% among patients assigned to receive chemoradiotherapy and 20%

Table 48.1 Randomized clinical trials investigating the effect of adjuvant treatment following surgical resection

Trial	Reference	Recruitment period	Treatment arms	Number of patients	Median overall survival (months)	5-year overall survival (%)	Comments
Adjuvant trials							
GITSG 9173	Kalser et Ellenberg [24, 25]	1974–1982	CRT + 5FU	21	21.0	19	All R0
			Observation	22	10.9	5	
					P = 0.03		
Norway multi-center	Bakkevold et al. [26]	1984–1987	5-FU/DOX/MMC	30	23	4	Included 14 patients with adenocarcinoma of the ampulla
			Observation	31	11	8	
					P = 0.04		
Japan multi-center	Takada et al. [27]	1986–1992	MMC/Oral 5-FU	81	17.1	11.5	Included patients with metastases MMC/Oral 5-FU: Curative resection in 45 Observation: Curative resection in 47 Not significant
			Observation	77	12.6	18	
EORTC 40891	Klinkenbijl et al. [28] Smeenk et al. [29]	1987–1995	CRT	60	24.5	20	T1–2, N0–1a, M0 pancreatic head cancer. Not significant
			Observation	54	19.0	10	
					P = 0.099		
ESPAC-1 (all patients and early follow-up of 2 × 2 factorial patients)	Neoptolemos et al. [18]	1994–2000	No CRT	178	16.1	19.5	ECOG 0,1,2
			CRT	175	15.5	10.3	R0/R1
				P = 0.24			Significant for chemotherapy overall but not in the 2 × 2 factorial. Not significant for CRT overall or in 2 × 2 factorial
			No chemotherapy	235	14.0	9.9	
			5FU/FA	238	19.7	23.3	
				P = 0.0005			

(continued)

Table 48.1 (continued)

Trial	Reference	Recruitment period	Treatment arms	Number of patients	Median overall survival (months)	5-year overall survival (%)	Comments
ESPAC-1 (2 × 2 only)	Neoptolemos et al. [19]	1994–2000	No CRT	144	17.9	19.6	ECOG 0,1,2 R0/R1 2 × 2 factorial design: each patient randomized twice to chemotherapy with 5FU/FA or no chemotherapy and CRT vs. no CRT. Significant for chemotherapy in the 2 × 2 factorial with additional target events. Not significant for CRT
			CRT	145	15.9	10.8	
					P = 0.05		
			No chemotherapy	142	15.5	8.4	
			5FU/FA	147	20.1	21.1	
					P = 0.009		
			Observation	69	16.9	10.7	
			CRT	73	13.9	7.3	
			5FU/FA	75	21.6	29.0	
			CRT + 5FU/FA	72	19.9	13.2	
CONKO-001	Oettle et al. [30, 31]	1998–2004	GEM	179	22.1	22.5	Postoperative CA19-9 > 92.5 kU/L = 0.0%
			Observation	175	20.2	11.5	
					P = 0.01		
JSAP-02	Ueno et al. [32]	2002–2005	GEM + IORT in 27	58	22.3	23.9	Karnofsky >50 Not significant
			IORT in 47 then observation	60	18.4	10.6	
					P = 0.19		

RTOG 9704	Regine et al. [33, 34]	1998–2002	5-FU/FA, followed by 5-FU-based CRT, followed by 5-FU/FA	230	–	–	538 patients recruited but then 87 patients were excluded at analysis for being ineligible. Overall results of 451 'eligible' patients were not reported. 388 had pancreatic head tumors with a median survival of 20.5 months and a 3-year survival of 31% in the GEM group vs. 16.9 months and 22% in the 5-FU group (HR, 0.82 [95% CI, 0.65–1.03]; P = 0.09) Not significant
			GEM, followed by 5-FU-based CRT, followed by GEM	231	–	–	
					P = 0.34		
ESPAC-3	Neoptolemos et al. [21]	2000–2007	5-FU/FA	221	23.0	15.9	ECOG 0, 1, 2 R0/R1 Not significant
			GEM		23.6	17.5	
					P = 0.39		
CapRI	Schmidt et al. [35]	2004–2007	5-FU, + cisplatin + IFN-α2b with radiotherapy, then continuous 5-FU infusion	64	32.1	25	ECOG 0, 1, 2 R0/R1 Not significant
			5-FU/FA	68	25.5	25	
					P = 0.49		
JASPAC-01	Uesaka et al. [36]	2007–2010	GEM	190	25.5	24.4	ECOG 0,1 Postoperative CA19-9 > 37 kU/L = 21% R1 positive = 31% Lymph node positive = 62.9% WHO 0 = 68.7%.
			S-1	187	46.5	44.1	
					P < 0.0001		

(continued)

Table 48.1 (continued)

Trial	Reference	Recruitment period	Treatment arms	Number of patients	Median overall survival (months)	5-year overall survival (%)	Comments
CONKO-005	Sinn et al. [37]	2008–2013	GEM	217	26.2	20.0	Karnofsky PS ≥ 60% Only R0 resected patients.
			GEM erlotinib	219	24.5	25.0	
					P = 0.061		
CONKO-006	Sinn et al. [38]	2008–2013	GEM	65	17.1	–	Karnofsky PS ≥ 60% Only R1 patients
			GEM + sorafenib	57	18.2	–	
					P = 0.94		
ESPAC-4	Neoptolemos et al. [23]	2008–2014	GEM	366	25.5	16.3	R0 and R1 patients
			GEM + capecitabine	365	28.0	28.8	
					P = 0.032		
PRODIGE-24	Conroy et al. [39]	2012–2016	GEM	246	35.0	–	R0 and R1 patients ECOG PS 0/1 Post-OP CA 19-9 < 180 KU/L <80 years
			mFOLFIRINOX	247	54.4	–	
					P = 0.003		
APACT	Tempero et al., 2019 [40]	2014–2018	GEM	866 randomized 1:1	36.2		R0 and R1 patients ECOG PS 0/1 Post-OP CA 19-9 < 100 KU/L Primary endpoint = DFS Independent reviewer DFS: • 18.0 months—GEM • 19.4 months—GEM + NabP P = 0.1824 Primary endpoint not met FDA did not approve indication for adjuvant Gem-NabP in PDAC
			GEM + Nab-P		40.5		
					Interim analysis Nominal P = 0.045		

Prep-02/ JSAP-05 Japan, multi-center	Unno et al. 2019 [41]	2013–2016	GEM+S1 + surgery + S1 Upfront resection + S1	82 (not resected = 42)	36.7	–	ECOG = 0,1. Age < 80 years. Neo-adjuvant gemcitabine and S1 for two cycles. Both arms adjuvant S1 for 6 months. Referred to as a trial in resectable pancreatic cancer but not all were resected. In the JASPAC-01 trial the median survival in the S1 adjuvant group was 44.1 months
				180 (not resected = 51)	26.6		
				1	P = 0.015		

CRT chemoradiotherapy, *5-FU* 5-fluorouracil, *DOX* doxorubicin, *MMC* mitomycin C, *FA* folinic acid, *GEM* gemcitabine, *IORT* intra-operative radiotherapy, *mFOLFIRINOX* modified folinic acid, 5-fluorouracil (5-FU), irinotecan and oxaliplatin, *Nab*-P nab-paclitaxel

among patients who did not receive chemoradiotherapy, 21% among patients who received chemotherapy and 8% among patients who did not receive chemotherapy [19]. The survival benefit of chemotherapy persisted after adjustment for major prognostic factors [19].

The Charité Onkologie *(CONKO)-001* trial randomized 186 patients to adjuvant gemcitabine for 6 months and 182 to observation. Disease free survival, the primary end-point with a median follow-up of 53 months was 13.4 months in the gemcitabine group, significantly longer than the 6.7 months in the observation group. There was no significant difference in median overall survival between the gemcitabine group with 22.1 months versus 20.2 months in the observation group, nor in 5-year survival at 22.5% and 11.5% respectively [30]. At subsequent median follow-up time of 136 months, the 5-year overall survival of 20.7% in the gemcitabine and 10.4% was statistically significant [31].

The *ESPAC-3v2* trial (2000–2007) showed gemcitabine not to be superior to 5-FU with a median overall survival rate of 23.6 months versus 23.0 months but with less cumulative toxicity [21]. Furthermore, additional analysis of the *ESPAC-3* data was able to show that the completion of 6 cycles of chemotherapy, but not early initiation was associated with improvement in overall survival [22]. Presumably, because without full recovery from surgery, the completion of the recommended number of chemotherapy cycles is less likely because of accumulating fatigue and therefore insufficient to treat occult systemic disease. Combining the control arms from ESPAC1 and ESPAC3v2 also established that adjuvant 5-FU with folinic acid was superior to observation [22].

The combination of gemcitabine and capecitabine has been shown to be an effective regimen in the advanced setting [12]. The *ESPAC-4* trial included 730 patients, 366 of which were randomly assigned to gemcitabine, and 364 to gemcitabine and capecitabine. Patients eligible had to be >18 years of age and needed to have an R0 or R1 resection, but there were no other major exclusion criteria such as low carbohydrate antigen (CA)19-9 levels [23]. The median overall survival was 28.0 (95% CI = 23.5–31.5) months in the gemcitabine and capecitabine group versus 25.5 (95% CI 22.7–27.9) months in the gemcitabine group. The number of grade 3–4 adverse events was similar in both groups [23]. The substantive improvement survival of single agent chemotherapy and then doublet chemotherapy compared to chemoradiotherapy or no adjuvant therapy is shown in Fig. 48.1 and Table 48.2.

The *JSAP-05 trial* randomized 182 patients to neoadjuvant chemotherapy with S-1 plus gemcitabine and 180 patients to upfront surgery in resectable and borderline pancreatic cancer followed by 6 months adjuvant chemotherapy with S-1 [41]. In the neoadjuvant group 140 (76.9%) were resected compared to 129 (71.6%) in the upfront surgery group. What remains unexplained is that the adjuvant S-1 arm had a median survival of only 26.6 months, since the *JASPAC-01* trial showed a median overall survival of 46.5 months in patients randomized to adjuvant S-1 [36].

In 2011, a new therapy regimen based containing oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) was introduced in patients with metastatic pancreatic cancer [13]. An improved survival in the FOLFIRINOX group in

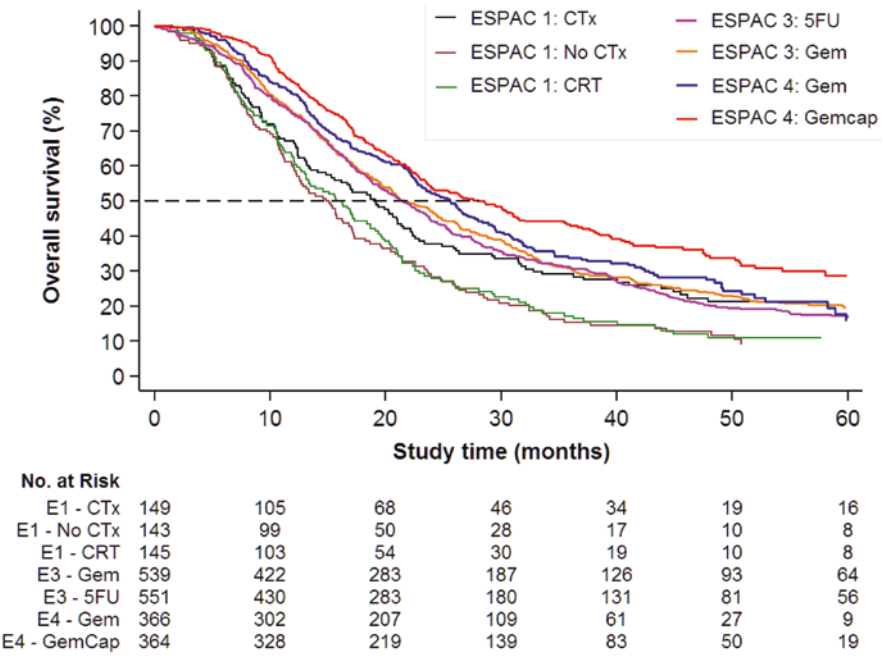


Fig. 48.1 Kaplan Meier survival estimates in the ESPAC trials (From Neoptolemos JP, et al. Lancet. 2017;389(10073):1011–24. Supplementary appendix)

relatively fit patients with metastatic disease was observed compared to gemcitabine, however the more aggressive scheme of FOLFIRINOX was associated with significantly higher rates of grade 3–4 toxicity events and reduced quality of life [42]. To reduce side-effects, modified versions of FOLFIRINOX (mFOLFIRINOX), e.g. without the 5-fluorouracil bolus, with lower irinotecan dose or obligatory hematopoietic growth factor Pegfilgrastim have been described [43]. In a retrospective review of 60 patients with metastatic pancreatic cancer, a modified FOLFIRINOX had similar efficacy in metastatic disease while reducing toxicity and improving safety profiles [43].

The French-Canadian *PRODIGE* [Partenariat de Recherche en Oncologie Digestive] *24-ACCORD* [Actions Concertées dans les Cancers Colorectaux et Digestifs] *24* and *CCTG PA.6* [Canadian Cancer Trials Group Pancreatic Adnocarcinoma] trial showed that in a selected group of macroscopically resected patients the estimated 5-year survival rate could be pushed towards 50% with a modified FOLFIRINOX regimen—the best 5-year survival ever reported. The investigators randomized 493 patients to receive either mFOLFIRINOX or gemcitabine for 24 weeks. Patients with CA19-9 > 180 U/ml within 21 days before randomization and WHO performance status of >1 were not eligible for randomization. Median survival reached 54.4 months in the mFOLFIRINOX group compared to 35 months in the gemcitabine group. Interestingly, while the median

Table 48.2 Five year overall survival rates in the ESPAC trials

Trial		Treatment	Number of patients (total = 2092)	5-Year overall survival (95% confidence interval)	Stratified log-rank χ^2	*P*-value
ESPAC-1	Neoptolemos et al. [18] Neoptolemos et al. [19]	5-fluorouracil/ folinic acid	149	21 (14.6–28.5) %	7.03	0.030[a]
		No chemotherapy	143	8.0 (3.8–14.1) %		
		Chemoradiotherapy (5-fluorouracil Radiotherapy)	145	10.8 (6.1–17.0) %		
ESPAC-3	Neoptolemos et al. [21]	Gemcitabine	539	17.5 (14.0–21.2) %	0.74	0.390[a]
		5-fluorouracil/ folinic acid	551	15.9 (12.7–19.4) %		
ESPAC-4	Neoptolemos et al. [23]	Gemcitabine	366	16.3 (10.2–23.7) %	4.61	0.032[b]
		Gemcitabine and capecitabine	364	28.8 (22.9–35.2) %		

From Neoptolemos JP, et al. Lancet. 2017;389(10073):1011–24. Supplementary appendix
[a]Stratification factor: resection margin status
[b]Stratification factors: resection margin status and country

disease free survival in the gemcitabine group was similar to the previous trials, median overall survival was longer, potentially pointing to the selected patient population or frequent use of mFOLFIRINOX in patients showing relapse [39]. It should be noted that mFOLFIRINOX is suitable only for relatively fit patients applicable to around 30–40%, the remainder needing to be given gemcitabine and capecitabine.

In patients with metastatic pancreatic cancer increased survival has also been shown with nanoalbumin-bound (nab)-paclitaxel plus gemcitabine [14]. The *APACT study* assessed effects of nab-paclitaxel and gemcitabine versus gemcitabine monotherapy in surgically resected pancreatic cancer patients. Exclusion criteria were CA19-9 levels ≥100 U/ml and ECOG performance status ≥1, with a primary end-point of disease-free survival. There were 866 patients randomized with median disease-free survival of 19.4 months in the nab-paclitaxel and gemcitabine group, not significantly different from 18.8 months in the gemcitabine group, hazard ratio of 0.88, 95% CI = 0.729–1.063 (P = 0.1824) [40]. As the primary end-point was not met the use of nab-paclitaxel as adjuvant treatment in pancreatic cancer is not approved by the Federal Drugs Administration.

48.3 Adjuvant Chemoradiotherapy Trials in Pancreatic Cancer

Adjuvant chemoradiation is still used in some countries, especially the USA, and the National Comprehensive Cancer Network guideline lists adjuvant chemoradiation as an option, although no evidence level for this recommendation is provided [44]. European and UK guidelines do not support the use of adjuvant chemoradiation for pancreatic cancer [45, 46]. Previous studies such as the *EORTC 40891* (1987–1995), *ESPAC-1* (1994–2000), and *RTOG 9704* (1998–2002) trials failed to show improved survival using adjuvant radiotherapy and or chemoradiation either with or without additional chemotherapy [18, 19, 28, 29, 33, 34]. The Gastro-Intestinal Study Group *(GITSG) trial 9173* randomized 43 patients to split-course radiotherapy with radiosensitising 5-FU and maintenance systemic weekly 5-FU after surgery or surgery alone. There was a survival benefit for adjuvant treatment, with a median survival of 20 versus 11 months and a 2-year survival of 42% vs. 15%, respectively [24]. A further 30 patients were added to the adjuvant therapy arm, and the outcome became modified to a median survival of 18 months and a 2-year survival of 46% [25]. The GITSG trial only included negative resection margins, thereby preselecting a prognostically favorable group. A Phase III multicenter trial by the European Organization for Research and Treatment of Cancer trial (EORTC) randomized 218 patients with T1-2,N0-1a, M0 pancreatic ductal adenocarcinoma and T1-3, N0-1a, M0 periampullary adenocarcinoma, either to adjuvant chemoradiotherapy as in the GITSG trial but without maintenance chemotherapy, or to observation [28, 29]. There were 114 patients with pancreatic ductal carcinoma, of whom 60 were randomized to treatment and 54 to observation with median survivals of 17.1 and 12.6 months, respectively [28]. This difference was not statistically significant (P = 0.09) [28]. After a median follow-up of 11.7 years, 173 deaths (79%) were then reported but with the overall survival still did not differ sufficiently between the chemoradiation treatment versus the control groups confirming the previous short-term analysis, indicating no benefit of adjuvant chemoradiation over observation in patients with resected pancreatic cancer or periampullary cancer [29]. The ESPAC 1 trial also reported no significant difference in survival between patients randomized to chemoradiotherapy (as in the GITSG trial), with a median of 15.5 months versus 16.1 months for patients randomized to no chemoradiotherapy (P = 0.24) [18]. The *RTOG 0848 trial*, a large randomized phase III study with 952 patients that investigates the value of additional chemoradiation for patients with no progression after standard adjuvant chemotherapy with gemcitabine is currently ongoing.

Radiotherapists from the USA especially have been critical of the ESPAC trials whilst promoting non-significant findings such as those from the RTOG 9704 adjuvant chemoradiation trial [33, 34, 47]. In the *RTOG 9704* trial there was no significant difference in survival between patients randomized to chemoradiation plus fluorouracil and those randomized to chemoradiation plus gemcitabine with a median overall survival of around 16 months, identical to that of patients who

received chemoradiation in the ESPAC-1 trial [18, 19]. This was after exclusion of 87 of the 531 patients that had already been randomized in RTOG 9704 to ensure that all of those eventually analyzed had adhered to the protocol. In comparison, patients randomized in the ESPAC-1, ESPAC-3 and ESPAC-4 trials to single agent chemotherapy (either 5-fuorouracil or gemcitabine) had survival rates of 21–26 months with 5 year survival rates of 16–18% based on intention to treat analysis (even if reduced doses or no adjuvant therapy was received) and a median survival rates of 28 months with 5 year survival rates of and 29% respectively in those randomized to gemcitabine and capecitabine [18, 19, 21, 23]. No randomized adjuvant chemoradiation trial has even got close to matching these survival data. In experimental studies the pancreata of genetically engineered KC mice exposed to radiation had significantly more advanced pancreatic intraepithelial lesions and more invasive cancer foci than pancreata of control mice, and as a corollary radiation exposure reduced median survival by more than 6 months [48]. Radiotherapists have been criticised in an editorial in the Journal of the National Cancer Institute for "few good data, much debate" [49]. A network meta-analysis from 2013 for adjuvant treatments for resected pancreatic cancer by Liao et al. concluded that chemotherapy with fluorouracil or gemcitabine was the optimum adjuvant treatment for pancreatic cancer and reduced mortality after surgery by about a third whilst chemoradiation plus chemotherapy was less effective in prolonging survival and was more toxic than chemotherapy alone [50].

48.4 Local/Distant Recurrence

A secondary analysis of ESPAC-3 has demonstrated that resection margin (R) involvement, specifically R1-direct tumor margins, poor tumor differentiation, positive lymph node status, WHO performance status ≥1, maximum tumor size, and an R1-direct posterior resection margin were all independently significantly associated with reduced overall and recurrence-free survival [51]. Moreover, overall R1-direct positive resection margin status, positive lymph node status, WHO performance status ≥1, and R1-direct positive superior mesenteric/medial margin resection status were all significantly associated with local recurrence [51].

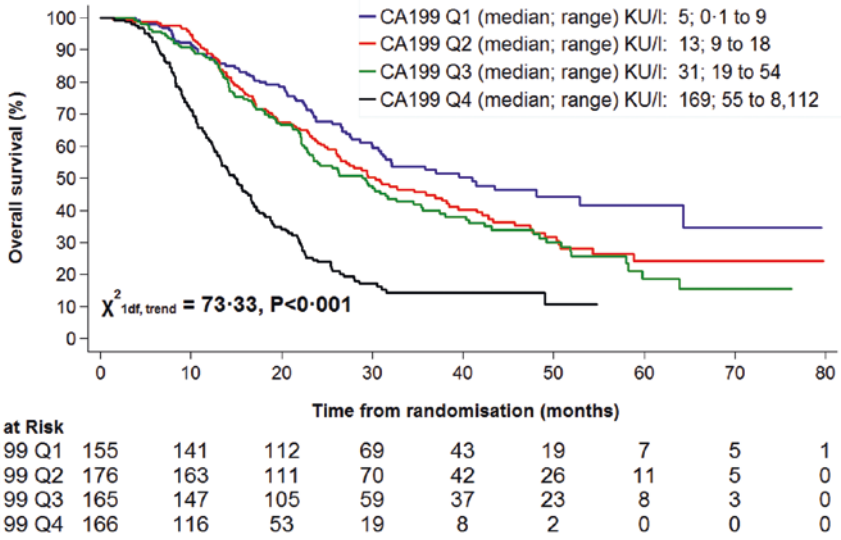
A further secondary analysis of ESPAC-4 demonstrated that there were no significant differences between the time to recurrence and subsequent and overall survival between local and distant recurrence [52]. The median overall survival of patients with distant-only recurrence (23.0 months) or local with distant recurrence (23.8 months) was not significantly different from those with only local recurrence (24.8 months). Patients with metastases to the lungs had a much longer survival compared to those with local recurrence or metastases to other sites such as the liver. Gemcitabine plus capecitabine had a 21% reduction of death following recurrence compared with monotherapy. Thus, pancreatic cancer appears to behave as a *systemic disease* requiring effective systemic therapy after resection [53].

These studies show that a positive resection margin is associated with a reduction in overall survival, for example in the ESPAC-4 trial a reduction in 5-year survival from 40% to 20% [23]. Whilst a positive resection margin is also associated with an increased likelihood of local recurrence, this of itself is not the contributor to reduced survival, but rather reflects the increased likelihood of systemic disease [51, 52]. Thus, strategies aimed at local control, may reduce subsequent local progression, but will not improve overall survival.

48.5 Prognostic Factors

It is very important to be aware of key prognostic factors when comparing survival outcomes from different trials and differing therapeutic regimens as this will have a powerful effect on survival outcomes. Multivariate analysis of 17 prospectively determined clinical, biochemical, pathological and treatment factors in the ESPAC-4 trial, identified the following as independent prognostic risk factors: gemcitabine plus capecitabine treatment, R1 resection margin, postoperative CA19-9 levels, moderately well differentiated tumors, poorly differentiated tumors, undifferentiated tumors, positive lymph nodes, and maximum tumor size [23]. In a single center cohort study from the Nanjing University Pancreas Center comprising 432 patients who had resected pancreatic cancer (2009–2014), the independent predictive factors for overall survival also included adjuvant chemotherapy along with the preoperative neutrophil-lymphocyte ratio and CA19-9 levels, tumor differentiation, tumor stage, lymph node ratio, microscopic nerve and vascular invasion and the presence of metastases [53].

Unlike a number of other trials, the ESPAC trials did not have restrictive criteria which otherwise are liable to produce favorable outcomes. Figure 48.2 illustrates survival by postoperative CA19-9 levels in the ESPAC-4 trial [23]. The CONKO-001 trial excluded patients with postoperative CA19-9 levels >92.5 KU/L [30]. Exclusion of patients in the ESPAC-4 trial by postoperative CA19-9 levels >92.5 KU/L would directly result in improved survival rates in both arms of the trial [23]. The APACT trial also restricted patients to the trial with postoperative CA19-9 levels <100 KU/L leading to apparently favorable survival rates [40]. Clear resection margin R0 rates were 83% in CONKO-001, 87% in JASPAC-01, and 76.3% in APACT [30, 36, 40]. The PRODIGE-24/CCTAG-PA6 trial had 57.2% R0 resections with the effect for mFOLFIRINOX being strongest for R1 resections [39]. On the other hand, ESPAC-4 had only 40% R0 resections and with a 5-year survival estimate in R0 patients of 40% in patients given gemcitabine plus capecitabine [23]. Lymph node clear N0 was present in 28.2% of patients in CONKO-001, 37.1% in JASPAC-01, 25.5% in the PRODIGE-24/CCTAG-PA6 trial, and 28.7% in APACT. In the ESPAC-4 trial only 19.6% of patients had an N0 resection but in these the 5-year survival rate nearly reached 50% [23]. Restrictive selection criteria will also result in a higher proportion of patients with a normal postoperative CA19-9 level, even if this was



No. at Risk									
CA199 Q1	155	141	112	69	43	19	7	5	1
CA199 Q2	176	163	111	70	42	26	11	5	0
CA199 Q3	165	147	105	59	37	23	8	3	0
CA199 Q4	166	116	53	19	8	2	0	0	0

Fig. 48.2 Kaplan Meier survival estimates for postoperative carbohydrate antigen (CA)19-9 levels by quartile (25%) levels, 1–4 (Q1, Q2, Q3, and Q4) in the ESPAC4 trial (From Neoptolemos JP, et al. Lancet. 2017;389(10073):1011–24. Supplementary appendix)

not a specific selection criterion, for example, this was found in 77% of patients in the JASPAC-01 trial [36]. In APACT 80.4% had a postoperative CA19-9 level <37 KU/L [40].

48.6 Conclusion

Significant progress in the treatment of pancreatic cancer has been made in the last 20 years [3, 17, 54]. A major impact has been the dramatic improvements in surgical technique, management of post-operative complications facilitated by the centralization of pancreatic cancer surgery [17, 54–56]. The development of international guidelines for the definition of surgical techniques and postoperative complications for pancreatic cancer has been essential for objective assessment of outcomes helping to drive technical progress. This has been most noticeably from the *International Study Group on Pancreatic Surgery* that includes definitions on the extent of pancreatectomy and lymphadenectomy, the pancreatic anastomosis and post-operative complications including pancreatic fistula, hemorrhage, and delayed gastric emptying [57–67]. The impact of next generation sequencing to improve survival by targeted therapy has so far proved to be rather limited [3, 10–13, 17]. The major impact on improvement on survival by systemic therapies has come from chemotherapy [3, 17, 68]. This approach may offer further opportunities to improve survival even more by the use patient-derived tumor organoids from pancreatic cancer as preclinical models to predict response to chemotherapy [69].

References

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913–21.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. Neoptolemos JP, Kleeff J, Michl P, Costello E, Greenhalf W, Palmer DH. Therapeutic developments in pancreatic cancer: current and future perspectives. Nat Rev Gastroenterol Hepatol. 2018;15(6):333–48.
4. Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science. 2008;321(5897):1801–6.
5. Collisson EA, Sadanandam A, Olson P, et al. Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. Nat Med. 2011;17:500–3.
6. Moffitt RA, Marayati R, Flate EL, et al. Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. Nat Genet. 2015;47:1168–78.
7. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature 2016;531(7592):47–52.
8. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518(7540):495–501.
9. Connor AA, Denroche RE, Jang GH, Timms L, Kalimuthu SN, Selander I, et al. Association of distinct mutational signatures with correlates of increased immune activity in pancreatic ductal adenocarcinoma. JAMA Oncol. 2017;3:774–83.
10. Aung KL, Fischer SE, Denroche RE, Jang GH, Dodd A, Creighton S, et al. Genomics-driven precision medicine for advanced pancreatic cancer: early results from the COMPASS trial. Clin Cancer Res. 2018;24(6):1344–54.
11. Davis W, Makar G, Mehta P, Zhu GG, Somer R, Morrison J, Kubicek GJ. Next-generation sequencing in 305 consecutive patients: clinical outcomes and management changes. J Oncol Pract. 2019;15(12):e1028–34.
12. Heining C, Horak P, Uhrig S, Codo PL, Klink B, Hutter B, et al. NRG1 fusions in KRAS wild-type pancreatic cancer. Cancer Discov. 2018;pii:CD-18-0036. https://doi.org/10.1158/2159-8290.CD-18-0036.
13. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019;381(4):317–27.
14. Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol. 2009;27(33):5513–8.
15. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
16. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
17. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, et al. Pancreatic cancer. Nat Rev Dis Primers. 2016;2:16022.
18. Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet. 2001;358(9293):1576–85.
19. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350(12):1200–10.
20. Neoptolemos JP, Stocken DD, Tudur Smith C, Bassi C, Ghaneh P, Owen E, et al. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. Br J Cancer. 2009;100(2):246–50.

21. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304(10):1073–81.
22. Valle JW, Palmer D, Jackson R, Cox T, Neoptolemos JP, Ghaneh P, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. J Clin Oncol. 2014;32(6):504–12.
23. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389(10073):1011–24.
24. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg (Chicago, Ill 1960). 1985;120(8):899–903.
25. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Cancer. 1987;59(12):2006–10.
26. Bakkevold KE, Arnesjo B, Dahl O, Kambestad B. Adjuvant combination chemotherapy (AMF) following radical resection of carcinoma of the pancreas and papilla of Vater--results of a controlled, prospective, randomised multicentre study. E J Cancer (Oxford, England: 1990). 1993;29(5):698–703.
27. Takada T, Amano H, Yasuda H, Nimura Y, Matsushiro T, Kato H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer. 2002;95(8):1685–95.
28. Klinkenbijl JH, Jeekel J, Sahmoud T, van Pel R, Couvreur ML, Veenhof CH, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999;230(6):776–82; discussion 82–4.
29. Smeenk HG, van Eijck CH, Hop WC, Erdmann J, Tran KC, Debois M, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. Ann Surg. 2007;246(5):734–40.
30. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007;297(3):267–77.
31. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310(14):1473–81.
32. Ueno H, Kosuge T, Matsuyama Y, Yamamoto J, Nakao A, Egawa S, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. Br J Cancer. 2009;101(6):908–15.
33. Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA. 2008;299(9):1019–26.
34. Regine WF, Winter KA, Abrams R, Safran H, Hoffman JP, Konski A, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. Ann Surg Oncol. 2011;18(5):1319–26.
35. Schmidt J, Abel U, Debus J, Harig S, Hoffmann K, Herrmann T, et al. Open-label, multicenter, randomized phase III trial of adjuvant chemoradiation plus interferon Alfa-2b versus fluorouracil and folinic acid for patients with resected pancreatic adenocarcinoma. J Clin Oncol. 2012;30(33):4077–83.
36. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3,

open-label, randomised, non-inferiority trial (JASPAC 01). Lancet (London, England). 2016;388(10041):248–57.
37. Sinn M, Bahra M, Liersch T, Gellert K, Messmann H, Bechstein W, et al. CONKO-005: adjuvant chemotherapy with gemcitabine plus erlotinib versus gemcitabine alone in patients after R0 resection of pancreatic cancer: a multicenter randomized phase III trial. J Clin Oncol. 2017;35(29):3330–7.
38. Sinn M, Liersch T, Gellert K, Riess H, Stübs P, Waldschmidt DT, et al. CONKO-006: a randomized double-blinded phase IIB-study of adjuvant therapy with gemcitabine + sorafenib/placebo for patients with R1-resection of pancreatic cancer. Ann Oncol. 2014;25(Suppl 4):mdu438.18-mdu.18. LBA18.
39. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379(25):2395–406.
40. Tempero MA, Reni M, Riess H, Pelzer U, O'Reilly EM, Winter JM, et al. APACT: phase III, multicenter, international, open-label, randomized trial of adjuvant nab paclitaxel plus gemcitabine (nab-P/G) vs gemcitabine (G) for surgically resected pancreatic adenocarcinoma. J Clin Oncol. 2019;37(15 Suppl):4000–40.
41. Unno M, Motoi F, Matsuyama Y, Satoi S, Matsumoto I, Aosasa S, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). J Clin Oncol. 2019;37(4 Suppl):189.
42. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouché O, Guimbaud R, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. J Clin Oncol. 2013;31(1):23–9.
43. Mahaseth H, Brutcher E, Kauh J, Hawk N, Kim S, Chen Z, et al. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. Pancreas. 2013;42(8):1311–5.
44. Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, et al. Pancreatic adenocarcinoma, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw.
45. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goere D, et al. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v56–68.
46. O'Reilly D, Fou L, Hasler E, Hawkins J, O'Connell S, Pelone F, et al. Diagnosis and management of pancreatic cancer in adults: a summary of guidelines from the UK National Institute for Health and Care Excellence. Pancreatology. 2018;18(8):962–70.
47. Boyle J, Czito B, Willett C, Palta M. Adjuvant radiation therapy for pancreatic cancer: a review of the old and the new. J Gastrointest Oncol. 2015;6(4):436–44.
48. Seifert L, Werba G, Tiwari S, Giao Ly NN, Nguy S, et al. Radiation therapy induces macrophages to suppress T-cell responses against pancreatic tumors in mice. Gastroenterology. 2016;150(7):1659–72.
49. Twombly R. Adjuvant chemoradiation for pancreatic cancer: few good data, much debate. J Natl Cancer Inst. 2008;100(23):1670–1.
50. Liao WC, Chien KL, Lin YL, Wu MS, Lin JT, Wang HP, et al. Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. Lancet Oncol. 2013;14(11):1095–103.
51. Ghaneh P, Kleeff J, Halloran CM, Raraty M, Jackson R, Melling J, et al. The impact of positive resection margins on survival and recurrence following resection and adjuvant chemotherapy for pancreatic ductal adenocarcinoma. Ann Surg. 2019;269(3):520–9.
52. Jones RP, Psarelli EE, Jackson R, Ghaneh P, Halloran CM, Palmer DH, et al. Patterns of recurrence after resection of pancreatic ductal adenocarcinoma: a secondary analysis of the ESPAC-4 randomized adjuvant chemotherapy trial. JAMA Surg. 2019; https://doi.org/10.1001/jamasurg.2019.3337.

53. Xu D, Zhang K, Li M, Neoptolemos JP, Wu J, Gao W, Wu P, et al. Prognostic nomogram for resected pancreatic adenocarcinoma: a TRIPOD-compliant retrospective long-term survival analysis. World J Surg. 2020; https://doi.org/10.1007/s00268-019-05325-z.
54. Strobel O, Neoptolemos J, Jäger D, Büchler MW. Optimizing the outcomes of pancreatic cancer surgery. Nat Rev Clin Oncol. 2019;16(1):11–26.
55. Klaiber U, Roth S, Hackert T, Neoptolemos JP. Evolution of oncosurgical management of pancreatic cancer. Eur Surg. 2019;51(3):165–73.
56. Schneider M, Strobel O, Hackert T, Büchler MW. Pancreatic resection for cancer-the Heidelberg technique. Langenbeck's Arch Surg. 2019;404(8):1017–22.
57. Bassi C, Butturini G, Fingerhut A, Yeo C, Izibicki J, Neoptolemos JP, et al. for the International Study Group on Pancreatic Fistula Definition. Post-operative pancreatic fistula: an International Study Group (ISGPF) definition. Surgery. 2005;138(1):8–13.
58. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying after pancreatic surgery – a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142(5):761–8.
59. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Postpancreatectomy hemorrhage (PPH) – an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007;142(1):20–5.
60. Shukla PJ, Barreto SG, Fingerhut A, Bassi C, Büchler MW, Dervenis C, et al. Toward improving uniformity and standardization in the reporting of pancreatic anastomoses: a new classification system by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2010;147(1):144–53.
61. Asbun HJ, Conlon K, Fernandez-Cruz L, Friess H, Shrikhande SV, Adham M. et al; International Study Group of Pancreatic Surgery. When to perform a pancreatoduodenectomy in the absence of positive histology? A consensus statement by the International Study Group of Pancreatic Surgery. Surgery. 2014;155(5):887–92.
62. Hartwig W, Vollmer CM, Fingerhut A, Yeo CJ, Neoptolemos JP, Adham M. et al; International Study Group on Pancreatic Surgery. Extended pancreatectomy in pancreatic ductal adenocarcinoma: Definition and consensus of the International Study Group for Pancreatic Surgery (ISGPS). Surgery. 2014;156(1):1–14.
63. Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA. et al; International Study Group of Pancreatic Surgery. Borderline resectable pancreatic cancer: A consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2014;155(6):977–88.
64. Tol JA, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, Andrén-Sandberg A, Asbun HJ, Bockhorn M, Büchler MW, Conlon KC, Fernández-Cruz L, Fingerhut A, Friess H, Hartwig W, Izbicki JR, Lillemoe KD, Milicevic MN, Neoptolemos JP, Shrikhande SV, Vollmer CM, Yeo CJ, Charnley RM, International Study Group on Pancreatic Surgery. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2014;156(3):591–600.
65. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adam M. et al; International Study Group on Pancreatic Surgery (ISGPS). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery. 2017;161(3):584–91.
66. Shrikhande SV, Sivasanker M, Vollmer CM, Friess H, Besselink MG, Fingerhut A, et al. International Study Group of Pancreatic Surgery (ISGPS). Pancreatic anastomosis after pancreatoduodenectomy. A position statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2017;161(5):1221–34.
67. Besselink MG, van Rijssen LB, Bassi C, Dervenis C, Montorsi M, Adham M, et al. International Study Group on Pancreatic Surgery. Definition and classification of chyle leak after pancreatic

operation: a consensus statement by the International Study Group on Pancreatic. Surgery. 2017;161(2):365–72.
68. Springfeld C, Jäger D, Büchler MW, Strobel O, Hackert T, Palmer DH, Neoptolemos JP. Chemotherapy for pancreatic cancer. Presse Med. 2019;48(3 Pt 2):e159–74.
69. Tiriac H, Belleau P, Engle DD, Plenker D, Deschenes A, Somerville TDD, et al. Organoid profiling identifies common responders to chemotherapy in pancreatic cancer. Cancer Discov. 2018;8(9):1112–29.