Chemoradiation Following Induction Chemotherapy in Locally Advanced, Unresectable Pancreatic Cancer – A Randomised Phase 3 Trial: Chemoradiation Following Induction Chemotherapy Compared with Chemotherapy Alone –

CONKO-007

Final Report

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(federführend: Ethikkommission der
Medizinischen Fakultät der Universität Erlangen-Nürnberg)

Investigational drugs	Gemcitabine, Oxaliplatin, Folinic acid, Irinotecan und 5-Fluorouracil, Radiotherapy
Sponsor	Universitätsklinikum Erlangen, Strahlenklinik, insoweit handelnd für den Freistaat Bayern, vertreten durch den Dekan der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg
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1	**Name of Sponsor/Company**
	Universitätsklinikum Erlangen, Strahlenklinik, insoweit handelnd für den Freistaat Bayern, vertreten durch den Dekan der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg
2	**Name of Finished Product**
	Gemcitabine (GEMCI-cell), Oxaliplatin Hospira, Folinic acid (Leucovorin Pfizer), Irinotecan Kabi, 5-Fluorouracil medac All brands of the active substances were allowed in the study.
3	**Name of Active Substance**
	Gemcitabine, Oxaliplatin, Folinic acid, Irinotecan und 5-Fluorouracil, Radiotherapy
4	**Individual Study Table: Referring to Part of the Dossier (Volume, Page)** **Anmerkung: Diese Angabe ist nur bei Einreichung in Zusammenhang mit einem Zulassungsdossier erforderlich**
	Not applicable
5	**Title of Study** **Anmerkung: Es muss klar hervorgehen, dass die letzte Protokollversion einschließlich aller Amendments gemeint ist, die Amendments sind anzugeben und zu identifizieren**
	Chemoradiation Following Induction Chemotherapy in Locally Advanced, Unresectable Pancreatic Cancer – A Randomised Phase 3 Trial: Chemoradiation Following Induction Chemotherapy Compared with Chemotherapy Alone – Protocol v9.0 Previous Protocol Versions/Amendments: • Protocol v. 4.0 – 19.11.2012 First Submission • Protocol v. 5.0 – 16.07.2013 Amendment 1 • Protocol v. 6.0 – 14.05.2014 Amendment 2 • Protocol v. 7.0 – 19.02.2015 Amendment 3 • Protocol v. 8.1 – 02.05.2018 Amendment 4 • Protocol v. 9.0 – 25.07.2023 Amendment 11 End of Recruitment 08.02.2021 End of Trial (last patient last visit): 08.11.2023
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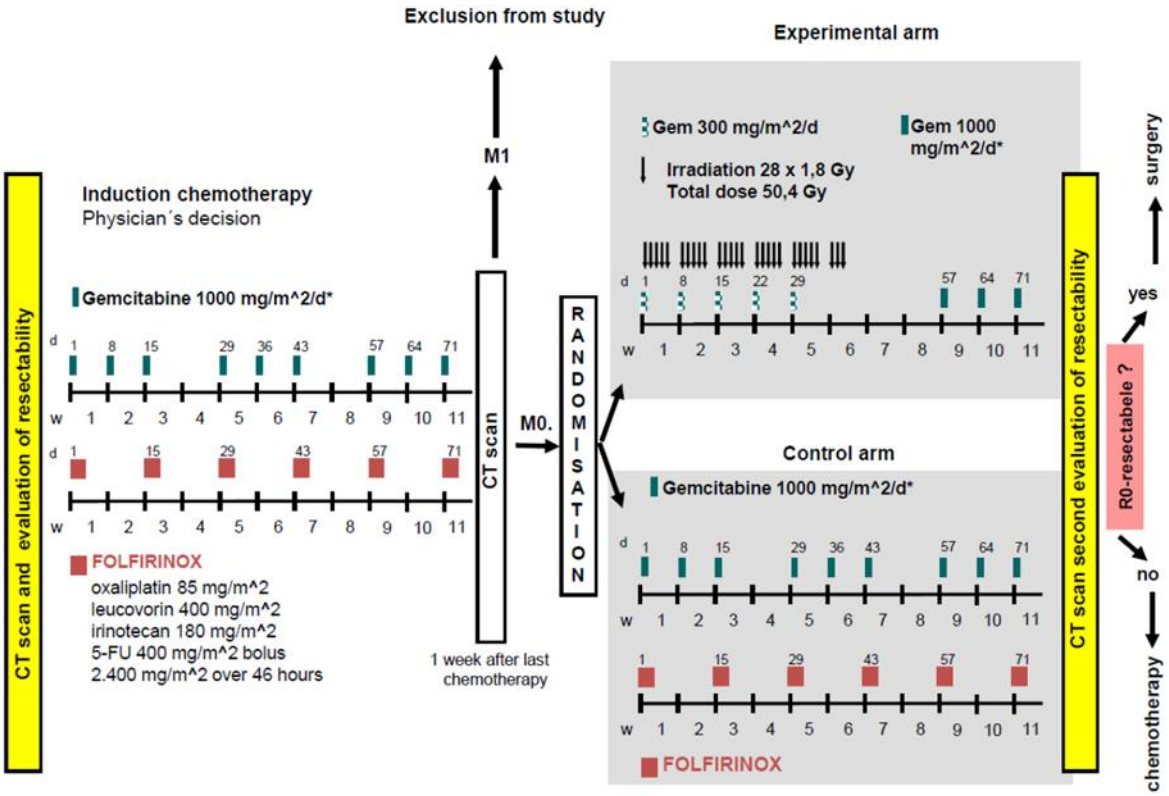
8	**Publication (reference)**	
	Fietkau R, Grützmann R, Wittel UA, et al. **R0 resection following chemo (radio)therapy improves survival of primary inoperable pancreatic cancer patients. Interim results of the German randomized CONKO-007± trial.** *Strahlenther Onkol. 2021;197(1):8-18.* Wittel UA, Lubgan D, Ghadimi M, et al. **Consensus in determining the resectability of locally progressed pancreatic ductal adenocarcinoma - results of the Conko-007 multicenter trial.** *BMC Cancer. 2019;19(1):979.* Rainer Fietkau et al., **Randomized phase III trial of induction chemotherapy followed by chemoradiotherapy or chemotherapy alone for nonresectable locally advanced pancreatic cancer: First results of the CONKO-007 trial.** *JCO 40, 4008-4008(2022).*	
9	**Studied period (years): date of first enrolment, date of last completed** **Anmerkung: Hier sollen auch Studienunterbrechungen und vorzeitige Studienbeendigungen/Studienabbrüche unter Angabe der Gründe aufgeführt werden**	
	First patient in: 15.04.2013 Last patient out of therapy: 07.06.2021 End of Follow up: 08.11.2023 No interruptions of the trial were made.	
10	**Phase of development**	
	Phase III trial	

11	**Objective**
	Main question 2012-2018: Primary objective of the study is overall survival. **Following interim analysis 2018:** To determine the benefit, measured as R0 resection rate, of neoadjuvant chemoradiotherapy compared to chemotherapy alone for locally advanced pancreatic cancer (LAPC).
12	**Methodology**
	CONKO-007, an investigator-initiated open-label, multicenter, phase III randomized clinical trial was performed at 54 sites in Germany. The protocol was centrally approved by the local ethics committee of Friedrich-Alexander-Universität Erlangen-Nurnberg. Eligibility criteria for the trial were: age ≥18 years, histologically confirmed LAPC, no evidence of distant metastasis as determined by computed tomography of the thorax and abdomen, and an ECOG performance status ≤2. After inclusion, each patient's diagnostic images (computed tomography or, magnetic resonance imaging) were anonymized using a GCP-certified, commercially available clinical trials management system (SecuTrial, interActive Systems, Berlin, Germany) and submitted blinded electronically to a five-surgeon interdisciplinary tumor board. Each case was rated as either "unresectable," "complete R0 resection possible," or "R0 resection undetermined" with a standard questionnaire. Tumor resectability was reassessed by the panel at week 11 (after randomization) after completion of neoadjuvant therapy. The panel ratings were not binding. However, the study protocol recommended surgery in cases determined to be resectable.
13	**Number of patients (planned and analysed)**
	Planned: • Enrolment: 830 • Randomization: 590 Amendment 2018: • Enrolment: 525 • Randomization: 350 Analysed: • Enrolment: 525 • Randomization: 336
14	**Diagnosis and main criteria for inclusion**
	Diagnosis: Histologically confirmed, locally advanced unresectable pancreatic cancer UICC III, no distant metastasis present **Main criteria for inclusion:**

	Biopsy-confirmed pancreatic adenocarcinoma No evidence of distant metastasis as determined by computed tomography of the thorax and abdomen Unresectable pancreatic cancer ECOG performance status ≤2 Age ≥ 18 Written informed consent for the participation in the clinical trial
15	**Test product, dose and mode of administration, batch number**
	The IMPs are only defined only by active substance – all brands are allowed in the study. A panel of five experienced surgeons reviewed each case for resectability and only unresectable patients were included. **Induction therapy:** Depending on their general health, patients received either gemcitabine or FOLFIRINOX as induction chemotherapy at the discretion of their attending physician. • Gemcitabine 1000mg/m2 was administered as a 30-min infusion on days 1, 8, 15 (cycle 1), days 29, 36, 43 (cycle 2), and days 57, 64, 71 (cycle 3). • FOLFIRINOX was performed according to Conroy et al. on days 1, 15, 29, 43, 57, and 71. *(*Conroy et al, **FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer.** *N Engl J Med 364:1817-25, 2011)* **After randomisation:** • Following randomization into the chemotherapy arm (CT) the same regimen was continued until PD or unacceptable toxicity. • In the chemoradiotherapy arm (CRT), intensity-modulated radiation therapy (IMRT) or three-dimensional radiotherapy (3DRT) techniques were used to deliver a total radiation dose of 50.4 Gy in 28 fractions (1.8Gy/day at a minimum energy of 6 MV) to the post-chemotherapy residual macroscopic tumor and suspected lymph nodes only with a safety margin of 1cm. Respiratory motion management was recommended during planning and administration of treatment. During radiotherapy, patients received gemcitabine 300mg/m2 by a 30-min intravenous infusion on days 1, 8, 15, 22 and 29, followed by 3 doses of gemcitabine 1000mg/m2 at weekly intervals. Following initial neoadjuvant chemo- or radio-chemo study treatment, the surgeon panel re-assessed resectability and recommended surgery in patients whose cancer was found to be resectable following study treatment. All surgical procedures had been performed according to the institutional standards in consideration of contemporary guidelines. Per protocol, surgery was not regarded as an integral part of the tested study regimen.

Flow chart



The baseline assessment (screening) included signature to ICF, history taking, physical examination, quality of life questionnaire, electrocardiogram, pregnancy test, extensive haematological tests, baseline toxicity grading, ECOG performance test and staging examinations (histology, abdomen and chest CT).

The weekly assessments during induction therapy included physical and neurological examination, haematological tests, and toxicity assessment according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.0.

One week after last cycle of induction therapy, assessments included physical and neurological examination, ECOG performance test, tumor marker blood tests and chest CT.

Within one week after randomization and then weekly the following assessments were needed: physical examination, extensive haematological tests and toxicity evaluation.

In week 11 after randomisation the resectability assessment requires physical and neurological examination, ECOG performance test, quality of life questionnaire, extensive haematological tests, abdomen and chest CT and toxicity evaluation.

After surgery (if performed) staging examination (histology) are necessary as well as toxicity evaluation.

Follow-up examinations were scheduled 3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months after the end of treatment visit and included physical examination, ECOG performance test, quality of life questionnaire, tumor marker blood tests, abdominal ultrasound and chest CT and a toxicity assessment according to NCI CTCAE v.4.0 with respect to late complications.

Procedures

	Screening			Induction chemotherapy	Restaging	RANDOMIZATI	Experimental arm / Control arm		Resectability Reassessment	Surgery [5]	Follow-up
Assessments / Visit	-14 days	-7 days	Enrolment	Weekly	Before randomization, one week after last cycle of induction chemotherapy		Day -7 to day 0	Weekly	Week 11	30 days after surgery	Every 3 months [9]
Informed consent	X										
Reference pathology lab	X									X	
Medical history	X										
Concomitant diseases and medications	X										
Physical & neurological exam	X			X	X			X	X		
Weight and height		X		X			X	X	X		X
Vital signs (blood pressure, heart rate)		X					X				
ECOG performance status		X			X				X		X
Quality of life		X			X				X		X
Complete blood count [1]		X		X			X	X	X		
Blood chemistry panel [2]		X		X			X	X	X		
Tumor markers Ca19-9, CEA		X			X				X		X
Creatinine clearance [3])	X						X				
Pregnancy test [4]	X										
Electrocardiogram (EKG)	X										
Chest CT	X				X				X		X[6]
Upper abdominal ultrasound											X
Abdominal / pelvic CT	X				X				X		X[7]
Uploading of CT images for panel surgeons			X						X		
Biliary stenting, if needed	X										
Adverse events/toxicities				X			X	X	X	X	X
Histological remission										X	
Blood collection for TL [7]		X[8]			X[8]				X[8]		

1 Complete blood count (CBC): Hemoglobin, erythrocyte count (RBC), platelet count, leukocyte count (WBC)
2 Blood chemistry panel: Electrolytes, creatinine, urea, bilirubin, total protein, albumin, AST, ALT, alkaline phosphatase, gamma-GT, and C-reactive protein
3 Or comparable test, such as Cystatin C
4 For women of childbearing potential only
5 For patients who have undergone surgery only
6 If there is clinical suspicion of metastasis or tumor progression, the examination should be performed earlier if warranted.
7 CT should be performed if the upper abdominal ultrasound assessment of disease progress is inconclusive; TL, translational research
8 Additional consent form has been received
9 In 6-month intervals from the second year on

16 Duration of treatment

Induction therapy: 11 weeks

Therapy after randomization: 11 weeks

17 Reference therapy, dose and mode of administration, batch number

Not applicable

18 Criteria for evaluation Efficacy, Safety

Efficacy

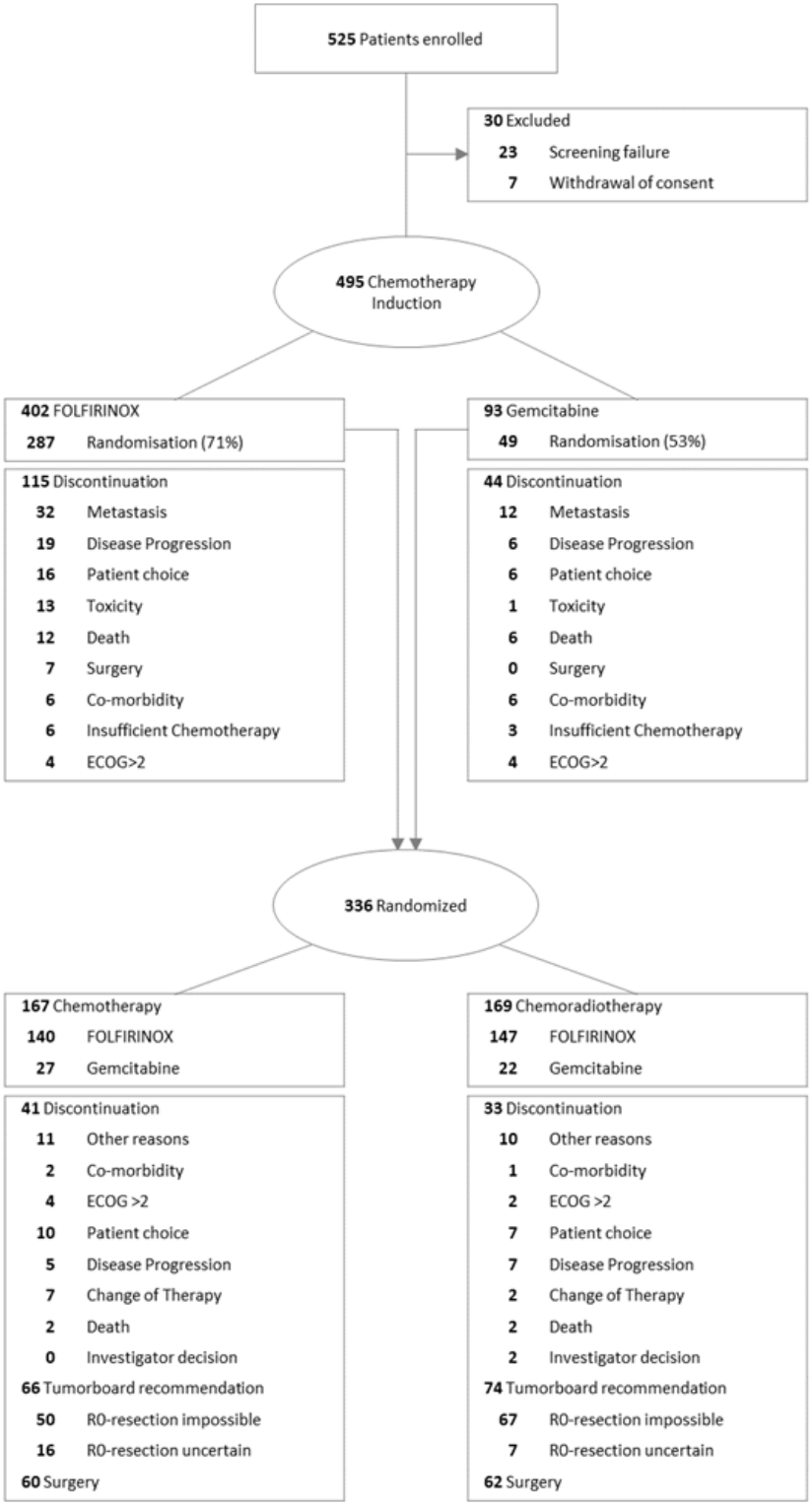
After an interim analysis in 2018 the primary efficacy endpoint was changed to R0 resection rate.

From April 2013 to February 2021, 525 patients were enrolled. The trial ended in November 2023 according to protocol.

484/495 patients (97.8%) rated to be unresectable by the local surgeon had an external review concerning resectability (median 3/5 votes). In 2/484 cases (0.4%) there was a unanimous vote against the local surgeon, i.e., the tumor was classified as resectable by all panel surgeons. Both patients did not reach randomization.

495 patients received induction CT with FOLFIRINOX (N=402) or gemcitabine (N=93). Following induction CT, 159 (32.1%) patients with disease progression were excluded; significantly more patients with gemcitabine (44/93, 47%) compared to FOLFIRINOX (115/402, 29%; p<0.001). The reasons for study withdrawal are listed in the CONSORT diagram.

CONSORT diagram



ECOG: Eastern Cooperative Oncology Group

After completion of the neoadjuvant treatment, 336 (67.8%) patients could be randomized: 167 (33.7%) to CT and 169 (34.1%) to the CRT. Randomization (1:1) was done with computer-generated block-randomization codes stratified by center, gender, and type of induction chemotherapy. These patients entered the intention-to-treat (ITT) analysis.

Baseline characteristics of patients in each treatment arm are reported in Table 1.

Table 1: Baseline Patient and Tumor Characteristics of the Intention-to-Treat Population (all Randomized Patients) by Treatment Regimen (CT or CRT)

	CT (n=167)	CRT (n=169)	*p*
Age (years), median IQR	64 (57-71)	65 (57-71)	*0.454*
Sex, No. (%)			*0.913*
female	76 (46)	75 (44)	
male	91 (55)	94 (56)	
Induction Therapy, No. (%)			*0.443*
Gemcitabine	27 (16)	22 (13)	
FOLFIRINOX	140 (84)	147 (87)	
WHO Performance Status score, No. (%)			*0.527*
0	94 (56)	105 (62)	
1	67 (40)	58 (34)	
2	4 (2)	4 (2)	
unknown	2 (1)	2 (1)	
Clinical Tumor stage, No. (%)			*0.779*
cT1	2 (1)	1 (1)	
cT2	7 (4)	9 (5)	
cT3	50 (30)	45 (27)	
cT4	106 (64)	113 (67)	
unknown	2 (1)	1 (1)	
Clinical Nodal status, No. (%)			*0.098*
cN0	65 (39)	82 (49)	
cN1	99 (59)	86 (51)	
unknown	3 (2)	1 (1)	
Grading, No. (%)			*0.463*
G1 (well differentiated)	8 (5)	4 (2)	
G2 (moderately differentiated)	55 (33)	62 (37)	
G3 (poorly differentiated)	40 (24)	44 (26)	
unknown	64 (38)	59 (35)	
Tumor Localization in the Pancreas, No. (%)			*0.771*
Head	106 (64)	101 (60)	
Body	53 (32)	60 (36)	
Tail	7 (4)	8 (5)	
Pancreatic duct	1 (1)	0	
Ca-19-9, (%) at diagnosis			*0.651*
Mean value U/ml (Min; Max)	1626 (40; 25768)	1678 (39; 26081)	
<500U/ml	98 (59)	104 (62)	
≥500U/ml	64 (38)	61 (36)	
unknown	5 (3)	4 (2)	

Resection specimens were graded and classified according to the seventh UICC TNM system; CT: chemotherapy; CRT: chemoradiotherapy

Surgery

If surgery is performed, standard histopathology of the tumor biopsy specimen will be performed for the determination of tumor histomorphology (type, grade), tumor extent (ypTNM, R classification) and for tumor regression grading.

Central histopathological analysis

Central histopathological analysis was performed including classification of the tumor resection status (R0, R1, R2) and circumferential margin status (CRM-positive defined as R0 resection, but tumor within $\leq$ 1 mm of resection margin, CRM-negative defined as R0 resection, but no tumor within 1mm of resection margin) for each patient as described previously *(*Weyhe D. et al*,* **Predictive factors for long-term survival after surgery for pancreatic ductal adenocarcinoma: Making a case for standardized reporting of the resection margin using certified cancer center data.** *PLoS One 16:e0248633, 2021)* Resection specimens were graded and classified according to the seventh UICC TNM system *(*Sobin L.H. GMK et al*,* **TNM Classification of Malignant Tumours, 7th Edition.** *Chichester, UK, Wiley-Blackwell, 2009).*

Safety

Toxicities were evaluated following randomization. Side effects were comparable between the two arms except that grade 3 and 4 leukopenia and thrombocytopenia rates were higher with CRT (Table 3).

Treatment compliance was comparable in the two arms: CT: 41/167 patients (24.6%); CRT: 33/169 (19.5 %) terminated therapy before receiving 80% of the planned chemotherapy and radiotherapy dose. The reasons for withdrawal from the study during CRT or CT are listed in the CONSORT diagram.

In the chemotherapy arm, 3 patients died during continued chemotherapy due to toxicity (CMV infection, pulmonary embolism, peripheral arterial disease); in the radiochemotherapy arm, no patients died due to treatment related toxicities.

9/122 patients died perioperatively within 30 days after surgery; 4/62 in the radiochemotherapy arm and 5/60 in the chemotherapy arm. There were no differences between the two arms in terms of the duration of surgery (CT: 343±133 min, N=55; CRT: 323±140 min, N=56; p=0.492, 11 patient data missing); postsurgical hospitalization time was longer following CRT (CT: 14.5±7.4 days, N=58; CRT: 19,1±14.9 days, N=53; p=0.04; 11 patient data missing).

Table 3. Most common grade 3 or 4 adverse events by treatment regimen

Patients with grade 3 and 4 toxicity post randomization	CT (n = 167)	CRT (n = 169)	*p* Value
Hematologic toxicity, No. (%)			
Anemia	3 (2)	8 (5)	0.22
Leukopenia	**12 (7)**	**50 (30)**	**>.001**
Neutropenia	6 (4)	3 (2)	0.34
GGT increased	8 (5)	4 (1)	0.26
Thrombocytopenia	**14 (8)**	**43 (25)**	**>.001**
Nonhematologic toxicity, No. (%)			
Alkaline phosphatase	7 (4)	6 (4)	0.79
Bilirubin	3 (2)	3 (2)	1
Bleeding	0	1 (1)	1
Diarrhea	7 (4)	5 (3)	0.57
Vomiting	3 (2)	4 (2)	1
Fatigue	2 (1)	5 (3)	0.45
Fever	1 (1)	1 (1)	1
Weight loss	1 (1)	2 (1)	1
GOT/GPT	10 (6)	5 (3)	0.20
Infection	4 (2)	5 (3)	1
Cardiac disorders	1 (1)	0	0.50
Motor neuropathy	3 (2)	0	0.12
Mucositis	3 (2)	0	0.12
Pain	2 (1)	1 (1)	0.62
Sensory neuropathy	5 (3)	1 (1)	0.12
Nausea	8 (5)	11 (7)	0.64
Cholangitis	9 (5)	3 (2)	0.09
Hypokalemia	4 (2)	5 (3)	1

Therapy-related death	CT	CRT	*p* Value
Therapy-related death, No. of patients (%)	3/167 (2)	0/169 (0)	0.12
Death following surgery (within 30 days), No. of patients (%)	5/60 (8)	4*/62 (8)	0.74

CT: chemotherapy; CRT: chemoradiotherapy; GOT: Glutamate oxaloacetate transaminase; GPT: Glutamate pyruvate transaminase; GGT: γ-glutamyl transferases
*A further patient died 37 days post-surgery, due to multiple surgeries following primary surgery.

19 **Statistical methods**

Sample Size Calculation

In 2011, the study was planned with the primary endpoint overall survival (OS), for which the inclusion of 830 patients was required to guarantee randomization of 590 patients (log rank test, power 80%, significance level 5%; $\alpha = 0.05$). The primary hypothesis was that CRT increases survival from 11.7 months with CT to 15 months *(*Huguet et al*,* **Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies.** *J Clin Oncol 25:326-31, 2007).*

Interim Analysis 2018

The scheduled interim analysis without unblinding in 12/2017 revealed that the sample size of 830 patients could not be achieved within an acceptable time period due to slow accrual. Therefore, the Protocol Committee decided to **change the endpoint to R0 resection rate**. With no reference data found in the literature, we used unblinded data from 180 patients enrolled in the study from 2013-2015 as basis of the analysis. At that time, 126/180 patients (70%) were randomized, and documentation was complete for 106 patients. Of these 106 patients, 35 patients were surgically treated with 25 patients achieving R0 resection (R0 resection rate: 25/106 = 23.6%). The R0 resection rate was nearly twice as high in one arm (30.2%) than in the other arm (17.0%). The overall survival following R0 resection was significantly better compared to no resection. It was estimated that a sample size of 525 patients, which should include 350 randomizable subjects, was needed for the new hypothesis, and that a significant difference in R0 resection rates between the two treatment arms (Fisher's exact test, power 80%, significance level 5%, dropout rate 5%; R0 rate 30.2% versus 17%) could be found. Secondary endpoints were specified as overall survival (OS), disease-free survival (DFS), locoregional control (LRC), distant metastasis (DM), toxicity and resection quality.

Statistical analysis

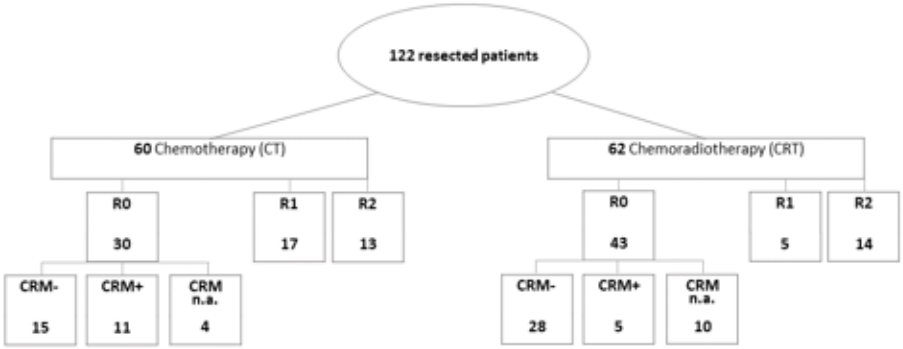
The results observed in the different groups were compared using the chi-square, Fisher exact test and t-tests, as appropriate. Kaplan-Meier estimates were used to examine differences in overall survival and disease-free survival, with induction therapy, randomization, resectability (R0; R1; R2 or non-resectability), and CRM status as grouping factors. Observations were censored at 60 months follow-up time, and T0 was set to the date of randomization. Median survival and 1-, 2-, and 5-year survival rates were calculated for each group, and median follow-up was calculated following Schemper and Smith methodology *(Schemper et al, A note on quantifying follow-up in studies of failure time. Control Clin Trials 17:343-6, 1996)*. Cox regression models were used to estimate hazard ratios (HR) between chemotherapy and chemoradiotherapy in relevant subgroups and presented as forest plots. With the significance level set at 0.05. All statistical analyses were performed using R Version 4.2.2 using the intention-to-treat (ITT) population *(Team RC: R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria., 2022)*.

Results

Resection rate

60/167 patients (35.9%) underwent surgery after CT compared to 62/169 (36.6%) after CRT. Final central histopathological assessment of CRM status was unknown in 14 patients (4 in CT group; 10 in CRT group) due to missing resection margin of the specimen or impossible CRM evaluation; malignant histology and tumor staging were confirmed by the local pathologist. (Supplement Fig. 2)

Supplement Figure 2. CONSORT diagram for pathological outcome after resection



CRM: circumferential resection margin; CT: chemotherapy; CRT: chemoradiotherapy; CRM-positive: R0 resection, but tumor within ≤ 1 mm of resection margin; CRM-negative: R0 resection, with no tumor within 1mm of resection margin; online only

The proportion of R0 resection, the primary endpoint of the study, was not statistically significant in the randomized intention-to-treat (ITT) population: R0 resection rate (CRT: 43/169 pts = 25% versus CT: 30/167 pts = 18%; p= 0.113).

However, a significant difference in the quality of resections (R0/R1/R2) was seen between the 2 treatment groups in the ITT randomized population. In the CRT arm, the resection rates were 43/169 (25.4%) R0, 5/169 (3.0%) R1 resections; 14/169 (8.3%) R2 resections, and 107/169 (63.3%) who did not undergo surgery. In the CT arm, there were 30/167 (18.0%) R0 resections; 17/167 (10.2%) R1 resections; 13/167 (7.8%) with R2 resections and 107/167 (64.1%) without surgery (p=0.03). The same was true for the complete remission rate (p=0.01) (Table 2).

In the surgical-treated group the ratio of R0/R1/R2 resections (p=0.02); the CRM-negative status (p=0.04) and complete remission rate (p=0.004) were all significantly higher in the CRT arm compared to CT (Table 2). Moreover, the pathological nodal status was different between the two arms (p=0.03): CRT pN0 35/47 (74,5%); pN1 12/47 (25.5%) and CT pN0 23/45 (51.1%); pN1 22/47 (48.9%).

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Survival and treatment failure

450 patients died within the median follow-up time of 55.1 months. Following CRT, 151 (33.6%) patients and 151 (33.6%) patients in the CT arm, respectively, had died. In the patient population excluded from randomization, 148 (32.9%) patients had died. Median survival from study enrolment was 15 months (5-year survival rate: 5.3%, SE:1.2%) for all patients (n=495), 9 months (5-year survival rate: 0.0%) for non-randomized patients (n=159) and 18 months (5-year survival rate: 7.0%, SE: 1.6%) for randomized patients (n=336).

There was no significant difference in overall ITT survival between the two arms (p=0.57; HR 0.94; CI 0.747-1.174). Median survival was 14 months (CT) compared to 15 months (CRT). The 5-year survival rate was 10.1%, (SE: 2.5%) in the CRT group and 3.8% (SE: 1.8% in the CT group (95% CI: 1.7-10.5%) (Figure 1A). There was no difference in DFS between the two groups (p=0.48; HR 0.92; CI 0.736-1.156). Median DFS was 8 months in the CT arm compared to 9 months in the CRT group.

There were fewer locoregional recurrences after CRT than with CT. Locoregional recurrences as first event within 5 years were 29.9%, SE: 10.5% (CT) versus 40.9%, SE: 9.2% (CRT), HR 0.41; CI 0.227-0.746; p=0.004) and for all locoregional recurrences 5-year rate 46.9%, SE: 12.7% (CT) versus 63.2%, SE: 8.5% (CRT), HR 0.33; CI 0.206-0.530; p< 0.001 (Fig. 2). The prevalence of distant metastases (including peritoneal metastases) was comparable in both arms: 5-year rate in CRT 82.7%, SE: 4.3% versus 84.7%, SE: 5.4% in CT (HR 1.09; CI 0.833-1.433; p=0.52).

Table 2. Surgical and pathologic outcomes by treatment regimen

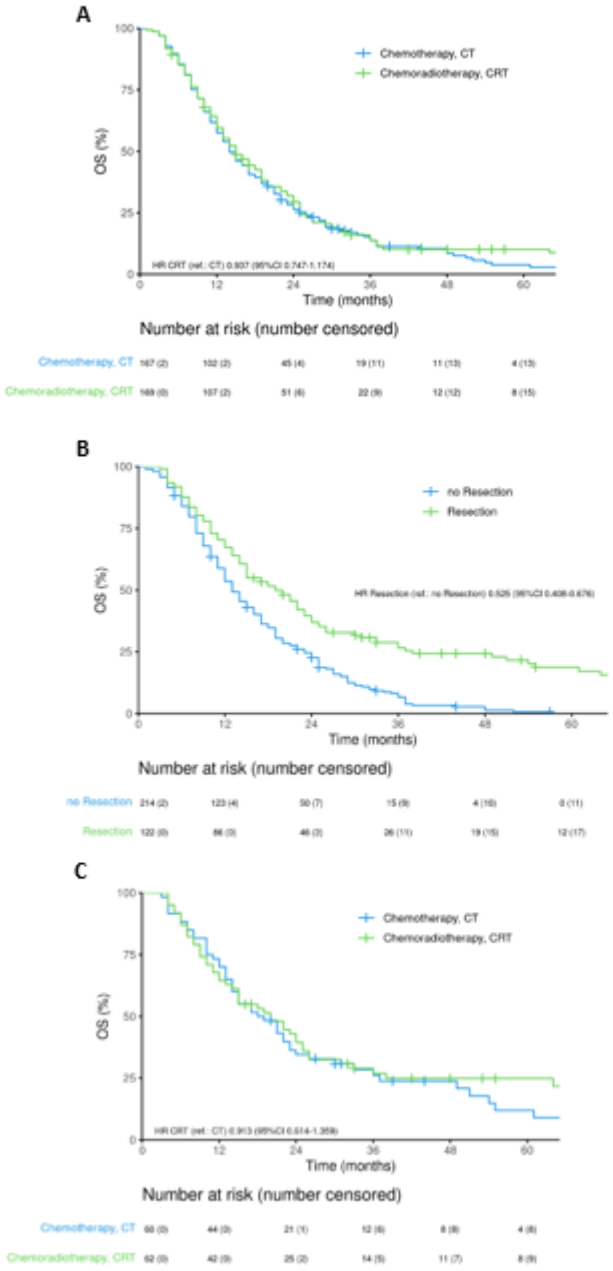
Randomized Patients	**CT (n=167)**	**CRT (n=169)**	**p**
Surgery, No. (%)			0.91
Yes	60/167 (36)	62/169 (37)	
No	107/167 (64)	107/169 (63)	
Surgery following FOLFIRINOX, No. (%)			0.81
Yes	56/140 (40)	56/147 (38)	
No	84/140 (60)	91/147(62)	
R0 Resection*	30/167 (18)	43/169 (25)	0.113
Resection Status, No.#			***0.03***
R0	30/167 (18)	43/169 (25)	
R1	17/167 (10)	5/169 (3)	
R2	13/167 (8)	14/169 (8)	
no surgery	107/167 (64)	107/169 (63)	
Pathological Complete Remission, No. (%)			***0.01***
Yes	1/167 (1)	11/169 (7)	
No	166/167 (99)	158/169 (93)	
Surgically treated Patients	**CT (n=60)**	**CRT (n=62)**	
R0 Resection*	30/60 (50)	43/62 (69)	***0.04***
Resection Status, No. (%) #			***0.02***
R0	30/60 (50)	43/62 (69)	
R1	17/60 (28)	5/62 (8)	
R2	13/60 (22)	14/62 (23)	
CRM Status, No. (%) (Basis R0 resection; patients with pCR were counted as CRM negative)			***0.04***
negative	15/26 (58)	28/33 (85)	
patients with pCR	1	11	
positive	11/26 (42)	5/33 (15)	
unknown or not available	4	10	
Pathological Complete Remission, No. (%)			***0.004***
Yes	1/60 (2)	11/62 (18)	
No	59/60 (98)	51/62 (82)	
Pathological Nodal status (pN), No. (%)			***0.03***
0	23/45 (51)	35/47 (74)	
1	22/45 (49)	12/47 (23)	
missing, No.	15	15	
Pathological Perineural Invasion (Pn), No. (%)			0.07
0	16/48 (33)	26/49 (53)	
1	32/48 (67)	23/49 (47)	
missing, No.	12	13	
Pathological Vascular Invasion (V), No. (%)			0.21
0	35/48 (73)	38/45 (84)	
1	13/48 (27)	7/45 (16)	
missing, No.	12	17	
Pathological Lymphatic vessel invasion (L), No. (%)			0.10
0	31/47 (66)	39/47 (83)	
1	16/47 (34)	8/47 (17)	
missing, No.	3	15	

CT: chemotherapy; CRT: chemoradiotherapy; CRM: Circumferential resection margin

* R0 Resection: only the rate of R0 resection was compared between the two arms

Resection Status: the resection parameters R0, R1, R2, or no resection were compared overall

Fig 1. Kaplan-Meier estimates of overall survival (A) by treatment group, (B) in patients with and without surgery and (C) in patients with surgery and treatment group



CT: chemotherapy; CRT: chemoradiotherapy; HR: hazard ratio; CI: confidence interval; OS: overall survival; T=0 refers to the time of randomization

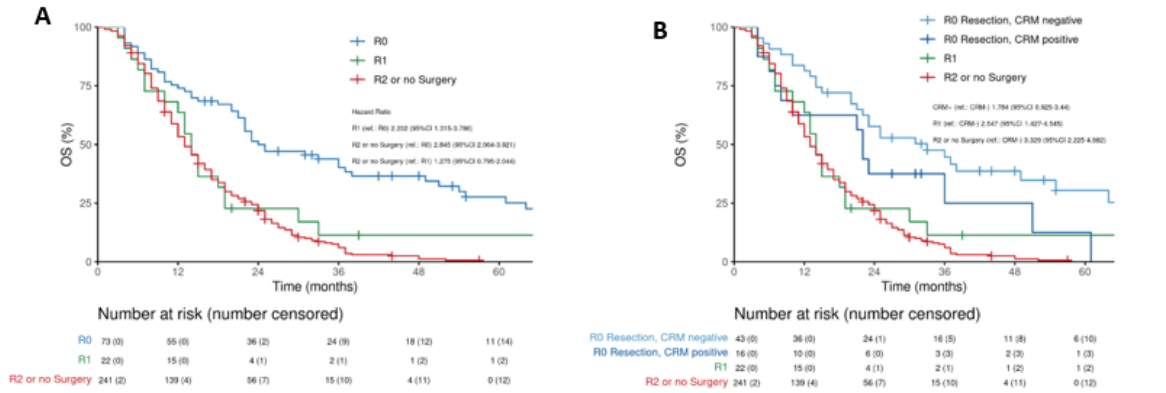
Surgery

Overall, 122/336 patients of both arms underwent surgery, which was associated with a longer survival compared to patients who did not underwent surgery (p<0.001, HR: 0.53, 95% CI: 0.408-0.676). Median survival: 19 months with surgery compared to 13 months without surgery (5-year survival rates: 18.7%, SE: 4.0% (95% CI: 11.1%-27.7%;) versus 0% (p<0.001) (Figure 1B).

There was a correlation between the quality of resection margins and survival.

Patients whose resection status was CRM-negative had a median survival of 33 months; patients with R0 resection had a median survival of 24 months. The respective 5-year survival rates were 30.4%, SE: 8.1% (95% CI: 18.1% - 51.1%) for CRM-negative status and 27.6%, SE: 6.0% (95% CI: 17.4%-42.4%) for R0 resection status, respectively. Patients with either a R1 resection status, R2 or no surgery had significantly worse overall survival (Supplement Fig. 3)

Supplement Figure 3. Kaplan-Meier estimates of overall survival by resection status (A) and CRM status (B)



HR: hazard ratio; CI: confidence interval; OS: overall survival; CRM: circumferential resection margin; T=0 refers to the time of randomization; **B**: HR R1 (ref.: CRM+) 1.428 (95%CI 0.702-2.905); HR R2 or no surgery (ref.: CRM+) 1.867 (95%CI 1.063-3.278); HR R2 or no surgery (ref.: R1) 1.307 (95%CI 0.813-2.103); online only

Subgroup analysis

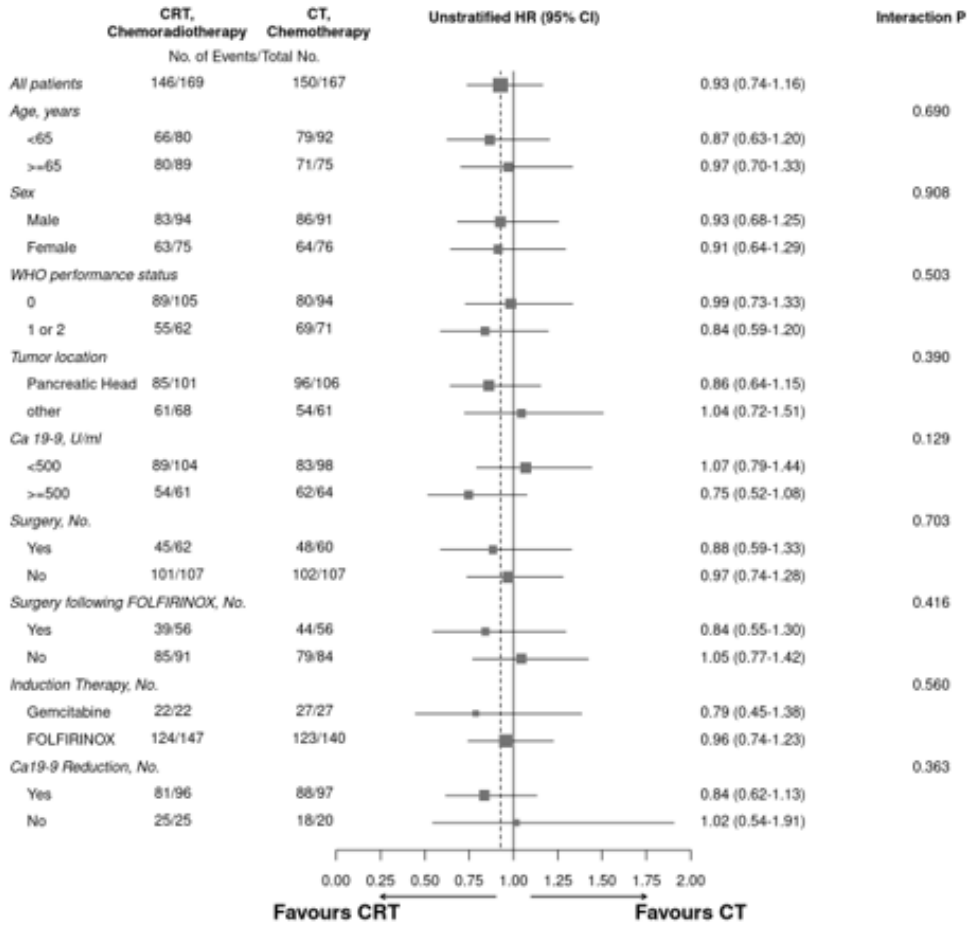
Subgroup analysis of sex, age, performance status, and tumor location showed no difference between the two arms (Supplement Fig. 4) concerning survival.

5-year survival rate of 24.8%, SE: 5.7% following CRT and surgery was twice as high as for CT and surgery (11.9%, SE: 5.1%) (Fig. 3, Supplement Fig. 4); HR of 0.88 (0.59-1.33, p=0.70). In patients without surgery, no detrimental effect regarding survival was found for patients treated with CRT as compared to CT (HR of 0.97 (0.74-1.28, p=0.70)).

Patients whose Ca19-9 levels dropped between the start and end of the induction therapy (in absolute terms) had a five-year survival with CRT (12.7%, SE: 3.6%) versus 2.8%, SE: 1.9% (CT; HR of 0.84 (0.62-1.13; p=0.27)). (Figure 3)

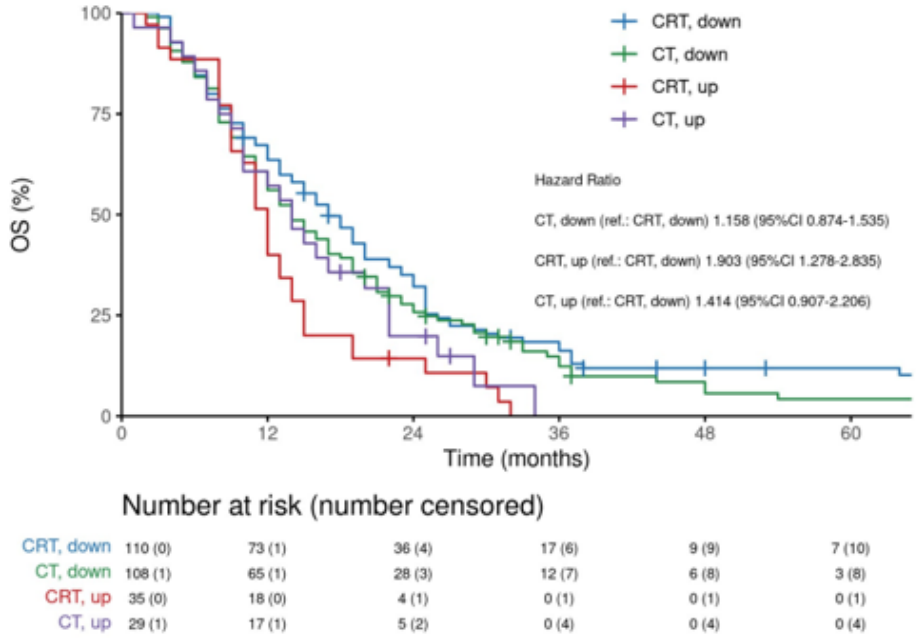
A multivariate analysis (Supplement table 2) showed R0 resection; and type of induction therapy (Gemcitabine vs. FOLFIRINOX) as independent parameters.

Supplement Figure 4. Subgroup analysis of the effects of CT and CRT on overall survival (forest plot)



HR: hazard ratio; CI: confidence interval; CT: chemotherapy; CRT: chemoradiotherapy; T=0 refers to the time of randomization, online only

Fig 3. Kaplan-Meier estimates of overall survival based on CA 19-9 change between diagnosis (enrolment) and induction therapy (randomization)



CT: chemotherapy; CRT: chemoradiotherapy; HR: hazard ratio; CI: confidence interval; T=0 refers to the time of randomization; downregulation was defined as absolute downregulation of CA 19-9 values; median survival was 18 months in CRT and 15 months in CT; 5-year survival was 12.7% (±3.6%) in CRT and 2.8% (±1.9%) in CT

Supplement Table 2. Multivariate Analysis

Multivariate Analysis including the parameters chemotherapy (Folfirinox versus gemcitabine), surgery (Surgery versus no surgery), treatment arm (chemotherapy versus chemoradiotherapy), age, sex, decrease of CA-19-9 value after induction chemotherapy (comparison of values before induction chemotherapy with values after induction chemotherapy)

	HR	95% CI	p Value
Induction therapy Gemcitabine (ref.: Folfirinox)	1.675	1.137; 2.467	***0.009***
Randomization CRT (ref.: CT)	0.899	0.704; 1.146	0.389
Gender female (ref.: male)	0.964	0.754; 1.232	0.770
Age	1.012	0.996; 1.028	0.131
CA19-9 decrease yes (ref.: no)	0.808	0.615; 1.062	0.127
Surgery performed yes (ref.: no)	0.583	0.445; 0.764	***<0.001***

HR: Hazard ratio; CI: confidence interval, CT: chemotherapy; CRT: chemoradiotherapy; T=0 refers to the time of randomization; online only

20	**Summary – Conclusions**
	From April 2013 to February 2021, 525 patients were enrolled. The trial ended in November 2023 according to protocol. A panel of five experienced surgeons reviewed each case for resectability and only unresectable patients were included. Depending on their general health, patients received either gemcitabine or FOLFIRINOX as induction chemotherapy at the discretion of their attending physician. Following randomization into the chemotherapy arm (CT) the induction chemotherapy regimen was continued. In the chemoradiotherapy arm (CRT), intensity-modulated radiation therapy (IMRT) or three-dimensional radiotherapy (3DRT) techniques were used and patients received gemcitabine. In summary, for the treatment of LAPC, the study provides evidence that 1. Induction chemotherapy followed by chemoradiotherapy is feasible and equivalent in survival to chemotherapy alone in a multicenter setting. 2. Secondary surgery is associated with a significantly better prognosis than conservative therapy alone, especially if R0 resections can be achieved. 3. Chemoradiotherapy can improve the ratio of R0/R1/R2 resection in secondary surgery without increasing the postsurgical mortality. 4. Induction chemotherapy enables biological selection of patients with a favorable prognosis who benefit the most from chemoradiotherapy. Safety: Toxicities were comparable between the two arms except that grade 3 and 4 leucopenia and thrombocytopenia rates were higher with CRT. In the study context, the chemoradiotherapy did not increase surgical mortality and the duration of surgery; only the duration of postoperative hospitalization was longer. Efficacy: There was no significant difference between the 2 treatment arms in the randomized patient population regarding the primary endpoint of overall R0 resection rate, with 25% (43/169) in the chemoradiotherapy arm vs. 18% in the chemotherapy arm (30/167; p=0.113). Among the surgically treated patients, the R0 resection rate was higher after chemoradiotherapy 69.4% (43/62) compared to chemotherapy alone: 50.0% (30/60 pts, p=0.017). Other parameters of resection (ratio of R0, R1, R2 vs no resection) also favored CRT. No difference in overall survival was seen (HR 0.937, 95% CI 0.747-1.174, p=0.57), but surgery was associated with longer overall survival (p<0.001, hazard ratio: 0.525, 95%CI 0.408-0.676). There was no difference in 30-day postsurgical mortality (chemotherapy n=5/60; chemoradiotherapy n=4/62). Conclusions: Although not improving R0 resection rate or survival, there was a significant difference comparing all resection parameters (R0, R1, R2 or no resection) in favor of chemoradiotherapy.

	This multi-center CONKO-007 trial showed that chemoradiotherapy (CRT) is at least equally effective compared to chemotherapy alone in the treatment of inoperable LAPD, with an acceptable toxicity profile.
21	**Date of report**
	28.10.2024

Erlangen, 28.10.2024
Date

Prof. Dr. med. Rainer Fietkau