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## A patient-level meta-analysis of FOLFIRINOX for locally advanced pancreatic cancer

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### Declaration of interest statement

Dr. Marthey reports personal fees from ROCHE, outside the submitted work. Dr. Faris reports personal fees and other from Novartis, personal fees from N-of-One, personal fees from Merrimack Pharmaceuticals, outside the submitted work.

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## Summary

**Background**—Thirty-five percent of pancreatic cancer patients have unresectable locally advanced pancreatic cancer (LAPC) at diagnosis. Several studies have evaluated systemic chemotherapy with FOLFIRINOX for patients with LAPC. We report a patient-level meta-analysis of LAPC patients treated with FOLFIRINOX as first-line treatment.

**Methods**—A systematic literature search was performed in Embase, Medline (ovidSP), Web of Science, Scopus, PubMed Publisher, Cochrane, and Google Scholar. Studies evaluating FOLFIRINOX as first-line treatment for LAPC were included. The primary outcome was overall survival (OS) and secondary outcomes included progression free survival (PFS), and grade 3 or 4 adverse events. We collected patient-level data from all studies that reported survival outcomes. The Kaplan-Meier method was used for survival outcomes. Grade 3 or 4 adverse event rates and the percentage of subsequent (chemo)radiation or resection in eligible studies were pooled in a random effects model.

**Findings**—Thirteen eligible studies representing 689 patients were included of whom 355 had LAPC. Eleven studies, representing 315 LAPC patients, reported survival outcomes and were eligible for patient-level meta-analysis. The median OS ranged from 10.0 to 32.7 months across studies with a patient-level median OS of 24.2 months [95% CI: 21.6 - 26.8 months]. The median PFS ranged from 3.0 to 20.4 months across studies with a patient-level median PFS of 15.0 months [95% CI: 13.8 – 16.2 months]. In 10 studies representing 490 patients, 296 Grade 3 or 4 adverse events were reported (i.e. 60.4 events per 100 patients). No death was attributed to FOLFIRINOX toxicity. Subsequent treatments included (chemo)radiation (63.5%) and surgical resection (25.9%).

**Interpretation**—Patients with LAPC treated with FOLFIRINOX had a median OS of 24.2 months that is far superior to previously reported OS with gemcitabine. Future research should evaluate these promising results in a randomized controlled trial and determine which patients might benefit from (chemo)radiation or a resection after FOLFIRINOX.

## Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death with only a 6% survival at 5 years.(1, 2) At the time of diagnosis, about 15% of patients have resectable disease (stage I or II), 35% locally advanced pancreatic cancer (LAPC, stage III), and 50% metastatic disease (stage IV).(3) The diagnosis of resectable disease and LAPC is determined by the extent of tumor contact with the superior mesenteric artery, celiac artery, superior mesenteric vein, and portal vein. The risk of a positive resection margin increases with increasing tumor contact of the arteries and/or veins. LAPC is considered unresectable because patients who underwent a resection with positive margin had the same overall survival (OS) as patients who did not undergo a resection.(4) Several definitions for LAPC have been proposed that vary mainly in the extent of tumor contact. The two commonly used criteria are from the National Comprehensive Cancer Network (NCCN, USA) and from the joint consensus conference of the Americas Hepato-Pancreato-Biliary Association (AHPBA), the Society of Surgical Oncology (SSO), and the Society for Surgery of the Alimentary Tract (SSAT).(5, 6) The NCCN and AHPBA/SSO/SSAT definitions for LAPC are summarized in table 1.

Systemic chemotherapy is the main treatment for patients with LAPC or metastatic disease. For decades 5-fluorouracil (5-FU) was the standard palliative treatment for pancreatic cancer. In 1997, a randomized controlled trial (RCT) including metastatic and LAPC patients showed an improved survival of 5.6 months for patients treated with gemcitabine versus 4.4 months with 5-FU ( $p=0.0025$ ).(7) In 2011, an RCT (the PRODIGE 4/ACCORD 11 RCT) found a median OS of 11.1 months with FOLFIRINOX versus 6.8 months with gemcitabine ( $p<0.0001$ ) in patients with metastatic disease.(8) No RCT has been performed with FOLFIRINOX for LAPC patients. Many case series with FOLFIRINOX for LAPC patients have been published in the past four years, but the sample size of most studies was too small to draw definitive conclusions about efficacy and safety of FOLFIRINOX in LAPC patients. The aim of this paper was to perform a systematic review and patient-level meta-analysis to evaluate FOLFIRINOX as first-line treatment for patients diagnosed with LAPC.

## Method

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.(9, 10) It was registered at the University of York PROSPERO 2015 with registration number CRD42015017354.(11)

## Selection criteria and search strategy

Eligible studies included treatment naïve patients of any age who received FOLFIRINOX as first-line treatment for LAPC, regardless of subsequent other treatment. The regular FOLFIRINOX regimen as described in the PRODIGE 4 trial consisted of 2-h intravenous infusion of oxaliplatin (85 mg/m<sup>2</sup>) followed by a 2-h intravenous infusion of leucovorin (400 mg/m<sup>2</sup>) concomitantly with a 90-min intravenous infusion of irinotecan (180 mg/m<sup>2</sup>),

followed by a bolus (400 mg/m<sup>2</sup>) and a 46-h continuous infusion (2,400 mg/m<sup>2</sup>) of 5-FU. The duration of a cycle is 2 weeks.(12)

A systematic literature search was performed in Embase, Medline (ovidSP), Web of Science, Scopus, PubMed Publisher, Cochrane, and Google Scholar. The last search was run on July 2<sup>nd</sup>, 2015. Search terms included: FOLFIRINOX, folinic acid, fluorouracil, irinotecan, oxaliplatin, pancreas cancer, and relevant variants thereof. No language or publication date restrictions were imposed. The grey literature was not accessed (i.e. literature that has not been formally published).(13) See the webappendix, page 1 for the detailed search strategy.

After removing duplicates, abstracts were independently reviewed by two authors (MS and BRB). Differences between authors were resolved by discussion. Abstracts were excluded if the record type was a case report, review, letter to the editor, or a conference abstract without full text. When eligibility criteria appeared to be met, the full text was retrieved for further evaluation. Full text studies were excluded if the study used a regimen other than FOLFIRINOX, used FOLFIRINOX in combination with other chemotherapy at the same time, investigated FOLFIRINOX not as first-line treatment, did not include LAPC patients, was a review, or if the same patient cohort was presented in another study.

## Outcome

The primary outcome measure was OS. Secondary outcomes were progression free survival (PFS), grade 3 or 4 adverse events, percentage of (chemo)radiation, percentage of resection after FOLFIRINOX, and percentage of R0 resection.

Two authors (MS and BRB) independently extracted information from the full texts using a predefined data extraction sheet. Disagreements were resolved by discussion.

The following study details were extracted: study characteristics (first author, year of publication, study design), study population (total number of patients analyzed, patient groups, tumor stage, location, and local extend of the disease), diagnostic work-up (staging laparoscopy), type of intervention (FOLFIRINOX regimen and number of administered cycles, percentage of (chemo)radiation, resection, and R0 resection), and outcome (duration of follow-up, OS, PFS, grade 3 or 4 adverse events). Updated patient-level data on OS and PFS were obtained from the authors of all studies presenting survival outcomes. Percentage of (chemo)radiation and resection were obtained from the studies and are not patient-level data.

## Patient-level data collection

Patient-level data on OS and PFS were obtained from the authors of all studies presenting survival outcomes. The authors of the original studies updated and checked their patient-level data. No patient-level data was missing on survival outcomes. Results other than survival outcomes (e.g., toxicity data or percentage of (chemo)radiation and resection) are not based on patient-level data.

Statistical analysis To ascertain the risk of bias, each study was assessed (MS) using the scoring system developed by the Critical Appraisal Skill Program (CASP). The CASP tool is

a critical appraisal tool for observational studies to assess the methodological quality of the individual studies.(14) Publication bias was assessed with a funnel plot.(15)

Survival outcomes (OS and PFS) were evaluated with the Kaplan-Meier method using patient-level data in SPSS version 21.(16) Studies presenting only LAPC patients who underwent a resection after FOLFIRINOX were excluded from survival analysis to avoid selection bias. A post hoc subgroup analysis of the (patient-level) median OS of studies with at least 20 LAPC patients was conducted.

Grade 3 or 4 adverse events were calculated as number of events per 100 patients and pooled in random effects models using the statistical MedCalc package (version 16.2).(17) Pooled percentages of (chemo)radiation, resection, and R0 were calculated in random effects models using the statistical MedCalc package (version 16.2).(17) Random (instead of fixed) effects models were used because of anticipated heterogeneity in LAPC definitions across studies.(18) We tested for heterogeneity with visual inspection of the forest plots and used  $I^2$  as measure of consistency across studies. A Spearman's correlation was calculated (as post hoc analyses) across studies between (chemo)radiation and OS, resection and OS, and the median number of administered FOLFIRINOX cycles and OS.

No funding has been received for this work. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

## Results

### Studies

The search criteria resulted in 840 potentially eligible studies. After screening of the abstracts, 30 studies were selected for full text assessment, of which 13 studies fulfilled the inclusion criteria.(12, 19-30) The excluded studies are presented in the webappendix, pages 2 and 3. Figure 1 presents the flowchart.

### Study characteristics

One study was a prospective non-randomized phase II study,(12) one was a prospective cohort study,(26) and the other eleven studies were retrospective cohort studies.(19-25, 27-30) Three studies used the NCCN criteria(22, 29, 30), and three studies used the AHPBA/SSO/SSAT criteria(23, 24, 28) to define LAPC. The other seven studies determined LAPC based on multidisciplinary review board or retrospective evaluation of pretreatment imaging.(12, 19-21, 25-27) Only three studies presented a patient cohort including only LAPC patients.(22, 26, 30) None of the studies described a staging laparoscopy as part of the diagnostic work-up. Study characteristics are presented in Table 2. The study quality assessments and funnel plot are presented in the webappendix, pages 4 and 5.

### Patient characteristics

The thirteen studies included a total of 689 patients, of whom 355 patients had LAPC. All other patients had (borderline) resectable, metastatic, or recurrent disease. The total population consisted of 53% male patients and the median age ranged from 56 to 66 years (Table 2).

## Survival

Eleven studies representing 315 LAPC patients were available for patient-level survival analysis. One study with 25 LAPC patients was excluded from survival analyses because only patients who underwent a resection after FOLFIRINOX were included.(28) Another study with 10 LAPC patients did not report survival outcomes.(23) One study included 5 patients who received FOLFIRINOX not as first-line treatment and these patients were excluded from the survival analysis.(27) All studies defined survival as the time from the start of FOLFIRINOX. The median OS ranged from 10.0 to 32.7 months across studies with a patient-level median OS of 24.2 months [95% CI 21.6 - 26.8 months]. OS at 1 year was 80.0% [95% CI: 74.7 – 84.4] and at 2 years 50.2% [95% CI: 42.9 – 57.5]. A post hoc analysis including only the five studies with at least 20 LAPC patients found a median OS ranging from 21.1 to 26.0 months.(20, 22, 26, 29, 30) The median PFS ranged from 3.0 to 20.4 months across studies with a patient-level median PFS of 15.0 months [95% CI: 13.8 – 16.2 months]. Figure 2 presents the survival curves of all individual studies as well as the pooled survival curves for OS and PFS.

Two studies used a dose modification of the FOLFIRINOX dose described in the PRODIGE-4 trial.(12) Median OS was 21.2 months in the study that did not give a bolus of 5-FU (20) and median OS was 26.0 months in the study with 80% dose intensity.(30) The median number of administered cycles was reported in nine of eleven studies and ranged from 3 to 11 cycles, where each cycle was 2 weeks.(12, 20-22, 24-27, 30) No significant correlation was found across studies between the median number of cycles and median OS ( $p=0.95$ ) (webappendix , page 6).

## Toxicity data

In eight studies, the adverse events were reported using the Common Terminology Criteria for Adverse Events (CTCAE). Two studies did not state which criteria were used.(19, 22) Three studies did not report toxicity data.(19, 28, 29) A total of 490 patients in 10 studies were analyzed for grade 3 or 4 adverse events. Of these ten studies, eight studies used the full dose of FOLFIRINOX as described in the PRODIGE-4 trial.(12) Two studies had a modification of this dose with one study not giving a bolus of 5-FU (20) and another study with 80% dose intensity.(30) No deaths attributed to FOLFIRINOX were reported. In 10 studies representing 490 patients, 296 Grade 3 or 4 adverse events were reported (i.e. 60.4 events per 100 patients). All grade 3 or 4 adverse events are presented in table 4. The pooled event rates per 100 patients for grade 3 or 4 adverse events are presented in forest plots (Figure 4). The pooled rates per 100 patients were 19.6 (95% CI: 10.9–29.9,  $I^2 = 83\%$ ) for neutropenia, 5.9 (95% CI: 2.9–9.8,  $I^2 = 53\%$ ) for thrombocytopenia, 8.2 (95% CI: 5.0 –12.1,  $I^2 = 36\%$ ) for diarrhea, 8.8 (95% CI: 5.0 – 13.5,  $I^2 = 36\%$ ) for vomiting, and 11.7 (95% CI: 7.3 – 17.0,  $I^2 = 51\%$ ) for fatigue.

The use of granulocyte-colony stimulating factor (G-CSF) was reported in eight studies representing 368 patients.(12, 20-22, 24-27) Of those 368 patients, 269 (73.1%) received G-CSF. Four studies gave G-CSF as primary prophylaxis.(20, 22, 25, 26) one study as secondary prophylaxis(12), and three studies left it to the discretion of the treating physician. (21, 24, 27)



## Subsequent treatment

Results on subsequent treatments were not based on patient-level data. The percentage of (chemo)radiation ranged from 31.2% to 100.0% across studies. (Chemo)radiation was reported in eight studies representing 271 patients of whom 154 patients received (chemo)radiation (56.8%) after FOLFIRINOX.(19, 20, 22-24, 26, 29, 30) The pooled percentage of (chemo)radiation in a random effects model was 63.5% (95% CI: 43.3% – 81.6%,  $I^2=90\%$ ). The modalities were stereotactic body radiotherapy (SBTR) in three studies(20, 23, 29), chemoradiation in three studies(22, 24, 30), and conventional radiation therapy in two studies.(19, 26) No significant association was found across studies between the percentage of (chemo)radiation and OS ( $p=0.12$ ) (webappendix, page 6).

The percentage of resection for LAPC ranged from 0.0% to 42.9% across studies. The percentage of margin negative (i.e. R0) resection of patients who underwent a resection ranged from 50% to 100% (Table 5). Four studies did not report the percentage of an R0 resection.(19, 21, 25, 27) One study only presented those patients that underwent a resection after FOLFIRINOX and was not included in the analysis for the percentage of resection.(28) In twelve studies, 91 of 325 patients (28.0%) underwent a resection after FOLFIRINOX for LAPC. The pooled percentage of resection in a random effects model was 25.9% (95% CI: 20.2% – 31.9%,  $I^2=24\%$ ). Resection margin status was missing in 10 patients. An R0 resection was reported in 60 out of 81 patients (74.1%). The pooled percentage of R0 resection in a random effects model was 78.4% (95% CI: 60.2% – 92.2%,  $I^2=64\%$ ) (Figure 4). No significant correlation was found across studies between percentage of resection and OS ( $p=0.39$ ) (webappendix, page 7).

## DISCUSSION

We found thirteen studies that assessed FOLFIRINOX as first-line treatment for LAPC. The patient-level meta-analysis of eleven studies representing 315 patients found a median PFS of 15.0 months and a median OS of 24.2 months.

In 2005, Conroy et al. first reported a nonrandomized phase II trial that evaluated FOLFIRINOX in patients with LAPC or metastatic pancreatic cancer.(12) In this study, 11 out of 46 patients (23.9%) had LAPC with a median OS of 15.7 months. In 2011, a phase III trial (PRODIGE 4/ACCORD 11 trial) demonstrated the effectiveness of FOLFIRINOX in the setting of metastatic pancreatic cancer.(8) Since then many case series evaluating FOLFIRINOX for LAPC have been published, with recently the largest series of Sadot et al. with 101 patients.(28) All studies with at least 20 patients found a similar median OS ranging from 21.1 to 26.0 months.(20, 22, 26, 29, 30) The median OS of 24.2 months after FOLFIRINOX in patients with LAPC compares favorably to a median OS of 6 to 13 months that was found for gemcitabine in patients with LAPC.(31, 32) However, the present meta-analysis included only non-randomized studies and the favorable OS after FOLFIRINOX may be partly attributable to patient selection. A phase III trial comparing gemcitabine with FOLFIRINOX in patients with LAPC is currently recruiting patients (PRODIGE 29-NEOPAN).(33)

The median OS of 24.2 months that we found in patients with LAPC (stage III) treated with FOLFIRINOX is the same as the median OS for patients with resected pancreatic cancer (stage I or II) followed by adjuvant gemcitabine in the ESPAC-3 trial.(34) This raises the question whether neoadjuvant FOLFIRINOX could also benefit patients with resectable pancreatic cancer. Neoadjuvant chemotherapy with FOLFIRINOX is attractive for several reasons: pancreatic cancer is a systemic disease at diagnosis in almost all patients,(35) the percentage of an R0 resection is expected to be higher with FOLFIRINOX, and a futile resection is avoided in patients who develop metastatic disease during chemotherapy. At least four phase II trials are ongoing to investigate neoadjuvant FOLFIRINOX in patients with resectable pancreatic cancer.(36-39)

No mortality attributed to FOLFIRINOX was reported. The pooled grade 3 or 4 adverse event rates per 100 patients were 60.4 for all grade 3 or 4 adverse events, 19.6 for neutropenia, 5.9 for thrombocytopenia, 8.2 for diarrhea, 8.8 for vomiting, and 11.7 for fatigue. The only prospective study in this meta-analysis found considerably higher rates of grade 3 or 4 adverse events, almost certainly due to more accurate ascertainment of adverse events in prospective studies.(12) Thus the pooled adverse event rates are likely an underestimate of the actual adverse event rate of FOLFIRINOX. The PRODIGE-4 trial also showed a better safety profile for gemcitabine compared to FOLFIRINOX in patients with metastatic pancreatic cancer.(8) In the same study, however, a definitive degradation of quality of life at 6 months was reported in 31% in the FOLFIRINOX group versus 66% in the gemcitabine group ( $p < 0.001$ ). Future studies should focus on predictive factors for the efficacy of FOLFIRINOX to minimize toxicity in nonresponsive patients.

We found that 63.5% of patients received (chemo)radiation after FOLFIRINOX. Across studies no significant correlation was found between the use of (chemo)radiation and OS. However, this analysis was not performed at the patient-level. The rationale of (chemo)radiation is that about 30% of pancreatic cancer patients die from local progression in the absence of metastatic disease.(40) LAPC patients who do not develop metastatic disease during systemic treatment might benefit from local control of the tumor with (chemo)radiation. The role of (chemo)radiation in LAPC is still unclear due to conflicting results.(41) In a phase III trial (LAP 07), 442 patients were randomized to receive 4 months of gemcitabine with or without erlotinib. Patients with controlled disease after 4 months were then randomized to either continued systemic chemotherapy or chemoradiation. The median survival was 16.4 months for continuing chemotherapy and 15.3 months for proceeding to chemoradiation (HR: 1.03; 95% CI: 0.79-1.34;  $p=0.83$ ).(42) Two ongoing RCTs are evaluating the benefit of (chemo)radiation after induction chemotherapy.(43, 44) Stereotactic body radiation therapy (SBRT) has shown promising results in tumor control in patients with LAPC.(45, 46) The feasibility and efficacy of SBRT following induction FOLFIRINOX is being evaluated in clinical trials.(47, 48)

We found that in 25.9% of LAPC patients underwent a resection after FOLFIRINOX, of whom 78.4% had an R0 resection. Considerable heterogeneity across studies in the percentage of resection is explained by lack of consensus in the literature on selecting patients for resection after FOLFIRINOX.(49) No significant correlation was found across studies between the percentage of resection and OS. However, this analysis was not



performed at the patient level. Future studies should evaluate whether resection after FOLFIRINOX improves OS or quality of life, and how to select patients for resection.

The main limitation of this patient-level meta-analysis is that all studies were nonrandomized and most studies had a retrospective design. Retrospective studies are known to underreport toxicity outcomes. Moreover, PFS may be biased due to the lack of standardized on-treatment imaging in retrospective studies. Secondly, the results of this meta-analysis may be biased because studies used different definitions for LAPC; three studies used the NCCN criteria(22, 29, 30), three studies used the AHPBA/SSO/SSAT criteria,(23, 24, 28) and the other seven studies diagnosed LAPC based on multidisciplinary review board or retrospective evaluation of pretreatment imaging.(12, 19-21, 25-27) The NCCN and AHPBA/SSO/SSAT definitions for LAPC vary mainly in the extent of vascular involvement (Table 1); definitions for LAPC were ambiguous in the other seven studies. Consensus on the definition of LAPC is required to improve comparison across future studies. Thirdly, it was not reported how eligibility for FOLFIRINOX was determined: did nearly all patients with LAPC receive FOLFIRINOX, or only a small subgroup of the fittest patients? Consequently, it is unclear which LAPC patients can anticipate a median OS of 24.2 months with FOLFIRINOX. Fourthly, after first-line FOLFIRINOX many patients had additional cancer-directed treatments including chemotherapy, targeted treatment, (chemo)radiation, and surgical resection. These additional treatments varied within and across studies. Insufficient data was available to evaluate the impact of these additional treatments on survival outcomes. However, despite the large variation in additional treatments, the median OS was very consistent across the studies with at least 20 LAPC patients. Finally, no study reported standard pretreatment staging laparoscopy, as recommended by a consensus statement.(6) Staging laparoscopy has been demonstrated to upstage patients to metastatic disease in up to a third of patients in two studies.(50, 51) Better staging may yield OS beyond 24 months for LAPC patients treated with FOLFIRINOX.

In conclusion, this patient-level meta-analysis found a median OS of 24.2 months after FOLFIRINOX in patients with LAPC. This is superior to the median OS reported for gemcitabine in LAPC patients of 6 to 13 months.(31, 32) An ongoing phase III trial will provide level I evidence regarding FOLFIRINOX in LAPC patients.(33)

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Research in context

### Evidence before this study

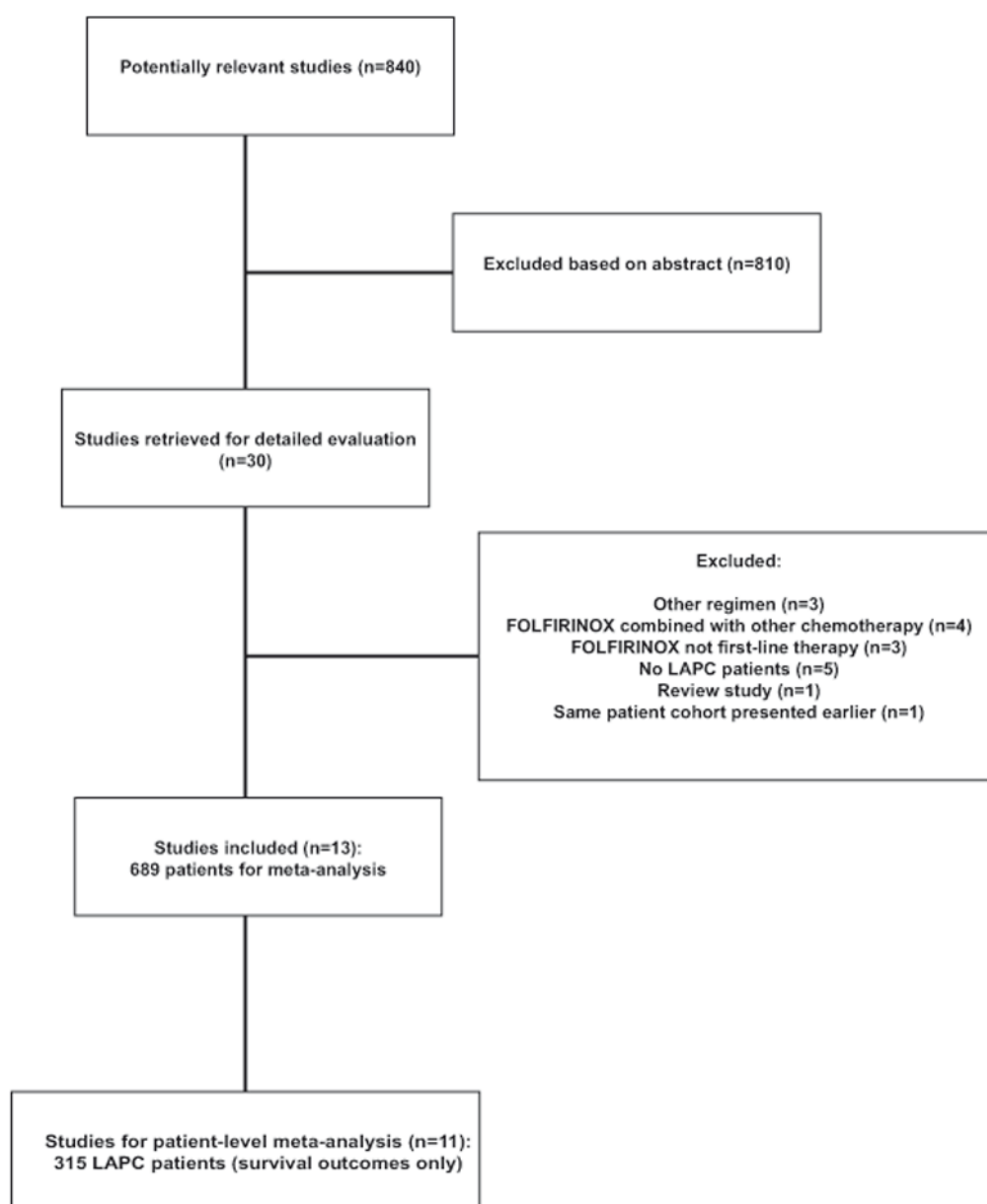
Pancreatic cancer is the fourth most common cause of cancer death. Thirty-five percent of all pancreatic cancer patients present with locally advanced pancreatic cancer (LAPC). Palliative gemcitabine has been the standard of care for LAPC patients for over a decade with a modest survival benefit of about 3 months compared to best supportive care. In patients with metastatic pancreatic cancer, FOLFIRINOX was shown to improve the median overall survival (OS) to 11 months compared to 7 months with gemcitabine. Recently, several studies have evaluated FOLFIRINOX for LAPC patients.

### Added value of this study

This is the first meta-analysis combining patient-level data of 11 studies with 315 LAPC patients treated with FOLFIRINOX. We found a pooled median OS of 24 months in LAPC patients after treatment with FOLFIRINOX.

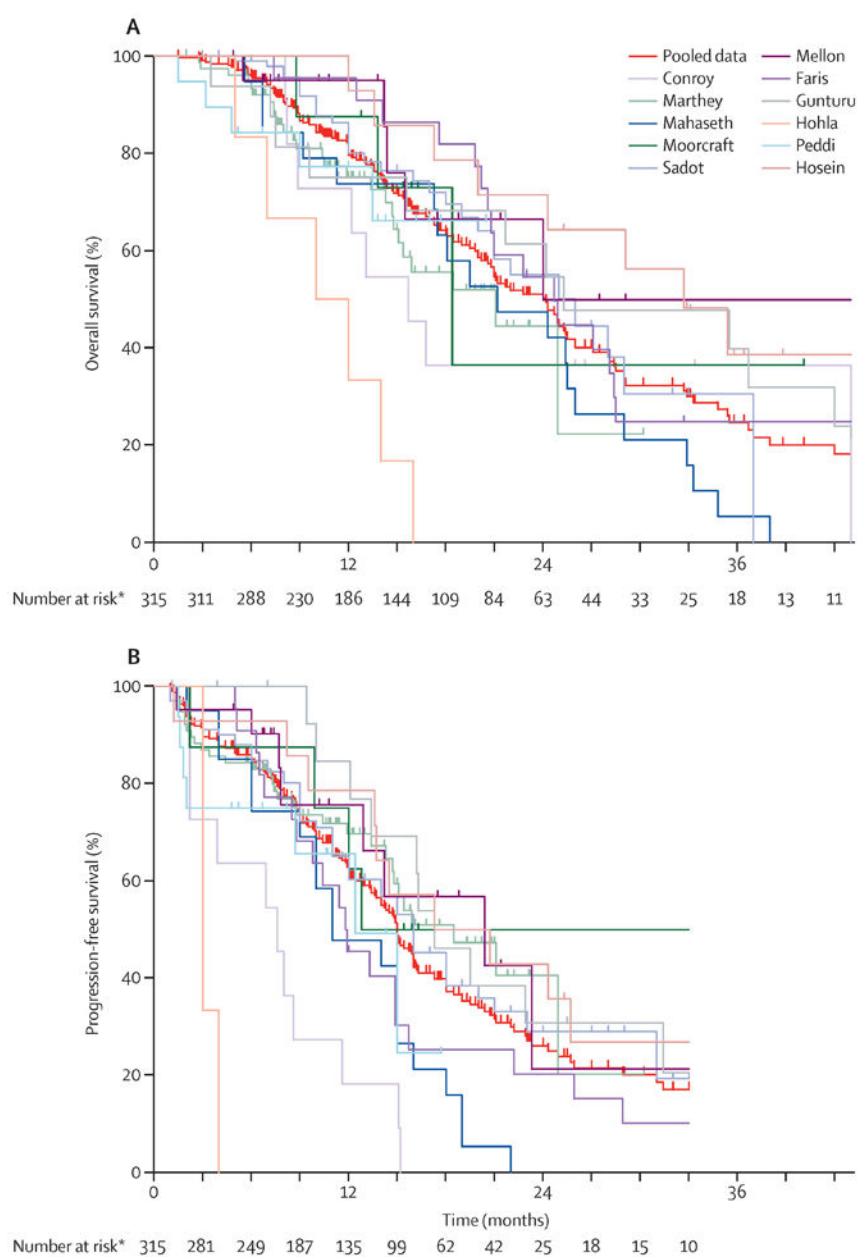
### Implications of all the available evidence

We found a median OS of 24 months in LAPC patients treated with FOLFIRINOX appears that is far superior to the previously reported OS with gemcitabine of 6 to 13 months. However, confirmation of these results in a randomized controlled trial is needed. Meanwhile, the observed favorable survival after FOLFIRINOX should be discussed with LAPC patients with a good performance status (ECOG 0-1).

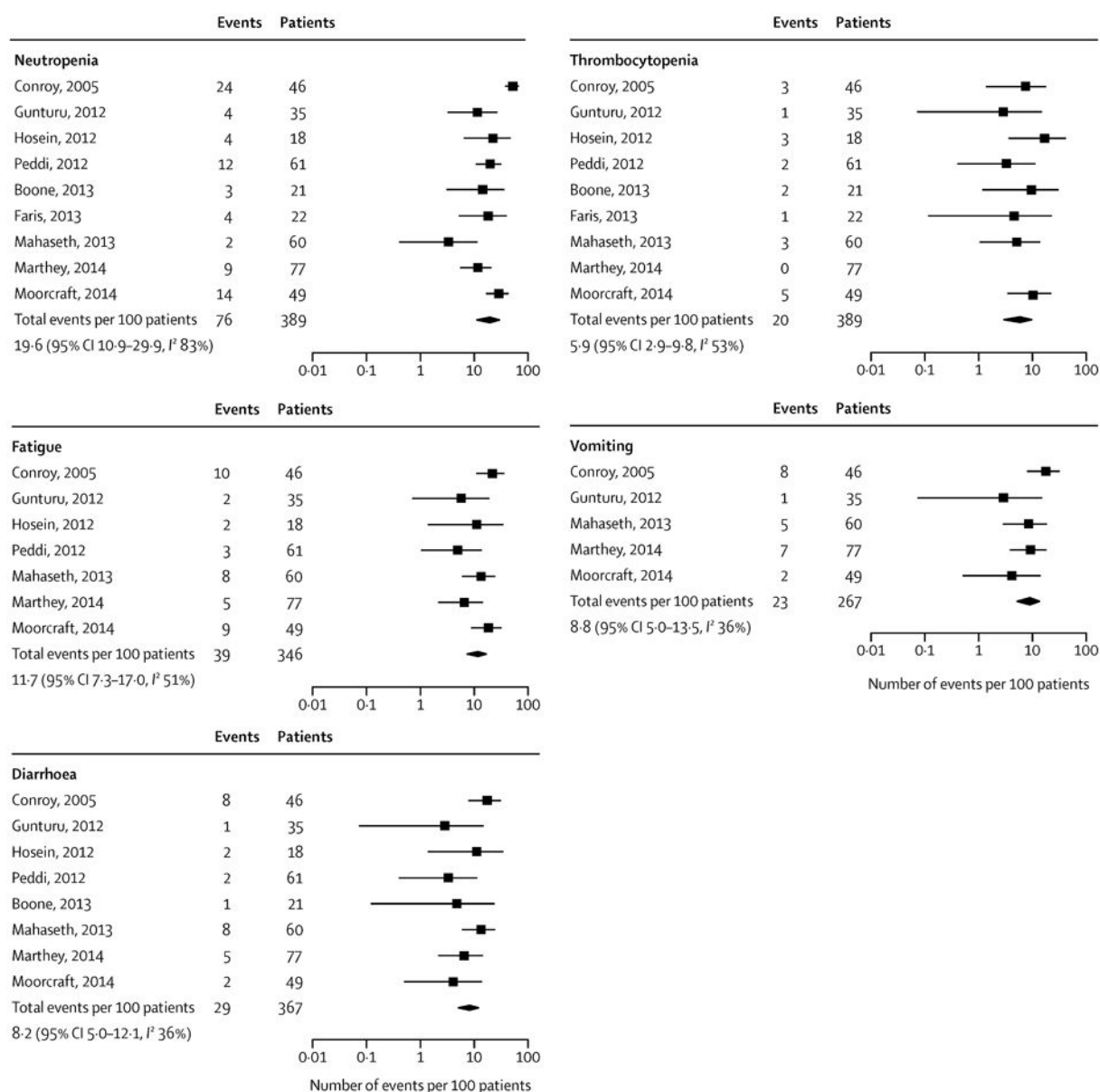


**Figure 1. Flowchart of the included studies**



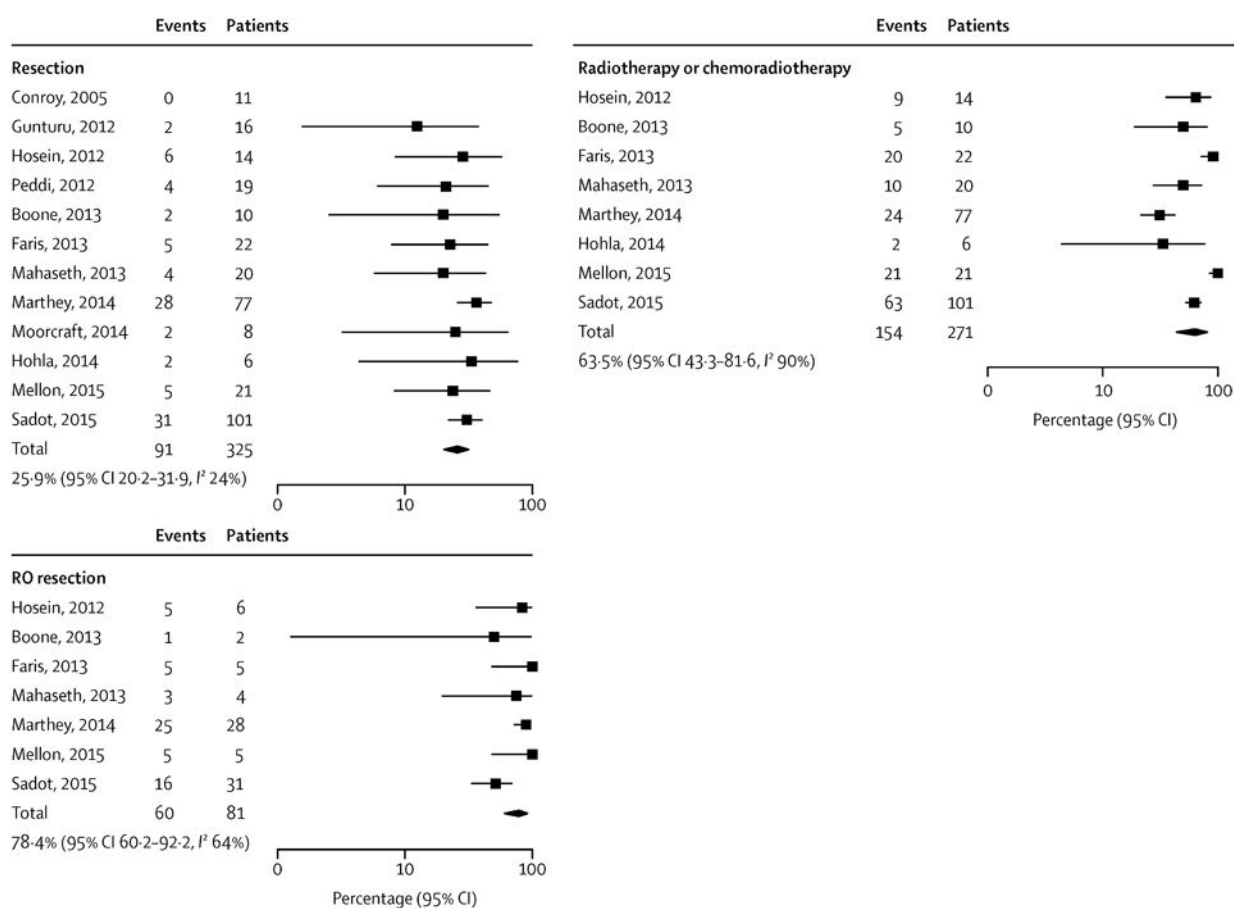


**Figure 2. Kaplan-Meier survival curves for PFS and OS. Numbers at risk at x-axis are the number of patients at risk for the pooled data**



**Figure 3. Forest plots of reported grade 3 or 4 adverse event rates**

Totals (i.e. pooled rates) are expressed as the number of events per 100 patients. Totals were calculated using random effects modeling and differ slightly from table 4.



**Figure 4. Forest plots of the percentage of (chemo)radiation, resection, and R0 resection**  
 Totals (i.e. pooled percentages) were calculated using random effects modeling and differ slightly from table 3 were totals were calculated as overall proportions.

**Table 1**

NCCN and AHPBA/SSO/SSAT definitions for LAPC.

NCCN	AHPBA/SSO/SSAT
No distant metastasis	No distant metastasis
Solid tumor contact with SMA and/or CA >180 degrees	Circumferential encasement of SMA and/or CHA
Solid tumor contact with the first jejunal SMA branch and/or aortic involvement.	Abutment of CA due to tumor involvement
Unreconstructable SMV and/or PV due to tumor involvement or occlusion	Unreconstructable SMV and/or PV due to tumor involvement or occlusion
Contact with most proximal draining jejunal branch into SMV.	

SMA: Superior Mesenteric Artery

CA: Coeliac Axis

CHA: Common Hepatic Artery

SMV: Superior Mesenteric Vein

PV: Portal Vein

Table 2

## Study characteristics

First author	Year of publication	Country	Period of inclusion	Number of patients	Age, median years (range)	Stage of disease			
						Resectable	Borderline resectable	Locally advanced	Metastatic
Recurrence									
Boone (23)	2013	USA	2011-2012	21	59 (42-73)	-	11	10	-
Conroy (12)	2005	France	2000-2002	46	56 (40-69)	-	-	11	35
Faris (22)	2013	USA	2010-2012	22	63 (45-78)	-	-	22	-
Ferrone (28)	2015	USA	2011-2014	127	62* (38-77)	87	15	25	-
Gunturu (25)	2012	USA	2010-2011	35	61 (48-77)	-	-	16	19
Hohla (19)	2013	Austria	2010-2012	49	62 (42-76)	-	-	6	28
Hosein (24)	2012	USA	2008-2011	18	58 (41-73)	-	4	14	-
Mahaseh (20)	2013	USA	2010-2012	60	63 (36-78)	-	4	20	36
Marthey (26)	2014	France	2010-2012	77	61 (37-79)	-	-	77	-
Mellon (29)	2015	USA	2009-2014	23	66 (45-85)	-	2	21	-
Moorcraft (27)	2014	UK	2010-2013	49	60 (34-76)	-	9	13	27
Peddi (21)	2012	USA	2009-2012	61	58 (37-72)	-	4	19	38
Sadot (30)	2015	USA	2010-2013	101	64 (37-81)	-	-	101	-
<b>Total</b>				<b>689</b>		<b>87</b>	<b>49</b>	<b>355</b>	<b>183</b>
									<b>15</b>

\* Median age of patients who received FOLFIRINOX.

**Table 3**

Median PFS and OS for patients with LAPC.

Author	N patients	Median follow-up, months (IQR)	Median PFS, months	Median OS, months
Conroy (12)	11	26,6 (26,0-33,4)	7,6	15,7
Faris (22)	22	54,0 (32,7-55,3)	11,8	24,7
Gunturu (25)	16	33,1 (11,4-49,3)	17,3	25,3
Hohla (19)	6	Not applicable	3,0	10,0
Hosein (24)	14	36,1 (32,9-38,8)	17,3	32,7
Mahaseth (20)	20	4,0 (4,0-4,0)	11,0	21,2
Marthey (26)	77	11,3 (7,8-17,6)	18,5	21,1
Mellon (29)	21	10,5 (7,3-20,1)	20,4	24,0
Moorcraft (27)	8	15,9 (15,4-16,3)	12,8	18,4
Peddi (21)	19	11,4 (8,2-16,2)	12,4	Not reached
Sadot (30)	101	12,0 (8,0-18,0)	16,0	26,0
<b>Pooled patient-level data</b>	<b>315</b>	<b>12,3 (8,0-20,5)</b>	<b>15,0</b>	<b>24,2</b>

Median follow-up of patients alive at last follow-up.

IQR: Interquartile range



Table 4

Grade 3 or 4 adverse events

Author	Patients	Grade 3 or 4 AE	Neutropenia	Fatigue	Diarrhea	Vomiting	Thrombocytopenia	Neuropathy	Fever/ neutropenia	Unspecified	Anemia	Nausea	Thrombocytoidia	Abdominal pain	Mucositis	Infection	Leukopenia	Allergic reaction	Elevated ALT/AST	Anorexia	Hypothalamic	Alopecia	Hand-foot syndrome
Boss (23)	21	12	3		1		2	1					1				2			1	1		
Conroy (12)	46	79	24	10	8	8	3	7	2		8	9										0	
Foris (22)	22	8	4				1		0				1						2				
Gautam (25)	35	9	4	2	1	1	1	0	0		0												
Hosain (24)	18	16	4	2	2		3	0	3		2	0			0					0			
Malshech (26)	60	35	2	8	8	5	3	3	0						1	3		2					
Markey (26)	77	30	9	5	5	7	0	3		1					0							0	
Moscarelli (27)	49	59	14	9	2	2	5	2	7		2	1	6		2								
Solar (30)	101	14																					
Pedati (21)	61	34	12	3	2		2		3		0			5									
Total (number of events/10.0 patients):	490	296 (60)	79 (27)	39 (14)	29 (10)	23 (8)	20 (7)	16 (6)	15 (5)	14 (5)	13 (5)	10 (4)	8 (3)	5 (2)	3 (1)	3 (1)	2 (1)	2 (1)	2 (1)	1 (0)	1 (0)	0 (0)	0 (0)

Cells were left empty when a study did not report on an adverse event.

Totals differ slightly from pooled rates in Figure 4 that were calculated using random effects modeling.

**Table 5**

Percentages of (chemo)radiation and resection and R0 resection for LAPC patients.

Author	N patients analyzed	(Chemo)radiation (%)	N Resected (%)	N R0 resected (%)
Boone (23)	10	5 (50,0%)	2 (20,0%)	1 (50,0%)
Conroy (12)	11	NR	0,0%	NA
Faris (22)	22	20 (90,9%)	5 (22,7%)	5 (100,0%)
Gunturu (25)	16	NR	2 (12,5%)	NR
Hohla (19)	6	2 (33,3%)	2 (33,3%)	NR
Hosein (24)	14	9 (64,3%)	6 (42,9%)	5 (83,3%)
Mahaseth (20)	20	10 (50,5%)	4 (20,0%)	3 (75,0%)
Marthey (26)	77	24 (31,2%)	28 (36,4%)	25 (89,3%)
Mellon (29)	21	21 (100,0%)	5 (23,8%)	5 (100,0%)
Moorcraft (27)	8	NR	2 (25,0%)	NR
Peddi (21)	19	NR	4 (21,1%)	NR
Sadot (30)	101	63 (62,4%)	31 (30,7%)	16 (51,6%)
<b>Total</b>	<b>325</b>	<b>154 (57%)</b>	<b>91 (28%)</b>	<b>60 (74%)</b>

Totals were calculated as overall proportions and differ slightly from pooled percentages in Figure 3 that were calculated using random effects modeling.

NA: not applicable, NR: not reported