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RESEARCH ARTICLE

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FOLFIRINOX and radiotherapy for locally advanced pancreatic cancer: A cohort study

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Abstract

Introduction: One-third of the patients with pancreatic cancer present with locally advanced unresectable pancreatic cancer (LAPC). Our aim was to determine survival outcomes and toxicity after FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) followed by radiotherapy (RT) in biopsy-proven patients with LAPC.

Methods: We analysed a cohort of biopsy-proven patients with LAPC, who were eligible for induction FOLFIRINOX (eight cycles) and subsequent RT (30 fractions, 60 Gy). Eligible patients underwent a staging laparoscopy to detect occult metastasis before the treatment. The primary outcome was overall survival (OS), and secondary outcomes were progression-free survival (PFS), treatment-related toxicity, and resection rate.

Results: Forty-four patients were diagnosed with biopsy-proven LAPC. Twenty-five patients were eligible and all underwent staging laparoscopy before the treatment. In three (12%) patients occult metastases were found. Twenty-two patients started induction FOLFIRINOX, 17 (77%) completed all cycles. Seventeen (77%) patients were treated with subsequent RT, with 16 (94%) receiving the full dosage. Three (14%) patients underwent a radical resection after the treatment. Median OS was 15.4 months (95% confidence interval [CI], 10.0-20.7), median PFS was 11 months (95% CI, 7.7-14.4).

Conclusions: Median OS after FOLFIRINOX and RT was 15 months in patients with LAPC. Toxicity remains severe, however, most patients completed all eight scheduled cycles of FOLFIRINOX and RT.

KEYWORDS
chemotherapy, locally advanced pancreatic cancer (LAPC), radiotherapy (RT)

1 | INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related deaths, with projections to be the second leading cause of cancer-related deaths in 2030.[1] Pancreatic cancer can be divided in three groups: resectable pancreatic cancer (stage I or II; 15%), locally advanced unresectable pancreatic cancer (LAPC) (stage III; 35%), and metastatic disease (stage IV; 50%).[2] Resectability of pancreatic cancer is determined by the extent of tumor contact with the superior mesenteric artery (SMA), coeliac artery, common hepatic artery, superior mesenteric vein, and portal vein. There are several definitions for resectability, which mainly differ in the extent of vascular tumor contact on computed tomography (CT). The Dutch Pancreatic Cancer Group has defined LAPC as venous tumor contact exceeding 270

TABLE 1 Baseline characteristics

	FOLFIRINOX (N = 22)	No FOLFIRINOX (N = 19)	*P* =
Age, median (IQR)	62 (52-67)	62 (53-67)	0.33
Sex			0.74
Male	6	7	
Female	16	12	
WHO			<0.001
0-1	22	9	
2-4	0	10	
Jaundice			0.76
Yes	9	9	
No	13	10	
Weight loss			0.74
Yes	15	14	
No	7	5	
Diabetes			1.00
Yes	4	4	
No	18	15	
Abdominal pain			0.59
Yes	21	17	
No	1	2	
BMI, median (IQR)	23 (22-25)	23 (20-28)	0.90
Tumor origin			0.23
Head	13	12	
Body	9	5	
Tail	0	2	
Median CA 19.9	309 (105-912)	560 (167-744)	0.88
Median CEA	3.5 (2.4-12.2)	3.4 (2.2-4.1)	0.50
Maximum tumor size (mm), median (IQR)	36 (30-43)	35 (23-40)	0.37
Locally advanced based on			
Only arterial	7	9	0.35
Only venous	5	4	1.00
Both arterial and venous	10	6	0.52

Abbreviations: BMI, body mass index; WHO, world health organization.

degrees or arterial contact exceeding 90 degrees (Table 1) without distant metastases.[3] The initial treatment for LAPC is a systemic chemotherapy.[4] FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) is the preferred treatment, based upon the results of a randomized study showing a significant and relevant improvement in overall survival (OS) compared with gemcitabine in patients with metastatic disease (median OS 11.1 vs 6.8 months; $P < 0.0001$).[5] No randomized trials have been published on FOLFIRINOX in patients with LAPC. However, several case series have shown favorable survival with a median OS ranging from 10.0 to 32.7 months.[6] Patients who do not develop the metastatic disease during FOLFIRINOX may benefit from subsequent radiotherapy (RT) for local control.[4]

The objective of this study was to assess survival outcomes and toxicity of FOLFIRINOX followed by RT in patients with LAPC.

2 | METHODS

Between January 2012 and December 2014, all consecutive patients diagnosed with biopsy-proven LAPC who received induction FOLFIRINOX at the Erasmus MC Cancer Institute were enrolled in a local database. No informed consent was obtained from the patients during this period as the standard local treatment was induction FOLFIRINOX followed by RT. Furthermore, all patients who had biopsy-proven LAPC but did not receive the FOLFIRINOX treatment in the same period were retrospectively identified by searching the local review board meeting reports. LAPC was defined as tumor contact with the SMA, coeliac artery, or common hepatic artery exceeding 90 degrees, or contact with the superior mesenteric vein or portal vein exceeding 270 degrees on CT scan, in the absence of metastatic disease.[3]

Patients were eligible for FOLFIRINOX and RT if they had a World Health Organization (WHO) performance status of 0 or 1, and were not older than 75 years. The diagnostic workup of patients with suspicion of LAPC consists of a CT scan of the thorax, abdomen, and pelvis.[4] Histopathological diagnosis of pancreatic cancer was confirmed with biopsy by endoscopic ultrasound in all patients. After confirmation of the diagnosis, a staging laparoscopy was performed to exclude occult metastases. FOLFIRINOX treatment was started within 4 weeks after staging laparoscopy in all patients. The dose of FOLFIRINOX was according to the PRODIGE 4 trial, consisting of a 2 hour intravenous infusion of oxaliplatin (85 mg/m^2) followed by a 2 hour intravenous infusion of leucovorin (400 mg/m^2) concomitantly with a 90 minute intravenous infusion of irinotecan (180 mg/m^2), followed by a bolus (400 mg/m^2) and a 46 hour continuous infusion (2400 mg/m^2) of fluorouracil.[5] The duration of a cycle was 2 weeks.[7] Patients were scheduled for eight cycles of FOLFIRINOX. Surveillance imaging was performed after four and eight cycles of FOLFIRINOX with a tri-phase abdominal CT scan. Treatment was terminated if progression (according to RECIST 1.1) was seen.[8] Patients who had stable disease or partial response received RT after eight cycles of FOLFIRINOX or earlier if the FOLFIRINOX treatment was discontinued because of toxicity. Dose reduction of 25% was applied if there were serious adverse events related to one of the components of FOLFIRINOX. Chemotherapy was discontinued if toxicity persisted after the second dose reductions. Radiotherapy consisted of 2 Gy per fraction to a total dose of 60 Gy. After RT, again a tri-phase CT scan was performed and patients were considered in a multidisciplinary review board for curative-intent resection. Adverse events were graded using the National Cancer Institute Common Toxicity Criteria 4.0.

OS was calculated from the start of the FOLFIRINOX treatment to the date of death. Progression-free survival (PFS) was calculated from the start of FOLFIRINOX treatment to the date of progression or death. For the patients who did not receive FOLFIRINOX, OS was calculated from the date of histopathological confirmation of LAPC until progression or death. Survival functions were estimated using the Kaplan-Meier method in the SPSS (version 21).

3 | RESULTS

During the study period, 44 patients presented with biopsy-proven LAPC (Figure 1). Nineteen patients (12 [60%] female, median age 62 years) were not included due to either poor condition (WHO performance status 2-4 condition) (n = 10), patient preference (n = 6), or no staging laparoscopy performed before the treatment (n = 4). These four patients received the chemotherapy treatment in other hospitals. A total of 25 patients were enrolled and underwent a staging laparoscopy. In three patients (12%), occult peritoneal metastases were identified. In total, 22 patients were scheduled for FOLFIRINOX and RT; the remaining 19 patients received FOLFIRINOX in other hospitals, gemcitabine, and best supportive care. Baseline patient and tumor characteristics were similar between the FOLFIRINOX with RT group vs other LAPC patients, except for the high rate of poor performance status in the latter (Table 1).

Patients who were eligible for the standard care received a median of eight cycles of FOLFIRINOX (range 2-9), with 4 (18%) patients receiving less than five cycles and 18 (82%) patients receiving at least seven cycles. The reasons for termination of the FOLFIRINOX after less than five cycles were toxicity in 3 (14%) patients and distant progressive disease in 1 (5%) patient. A dose reduction was required for 8 (36%) patients, with 7 patients receiving 75%, and 1 patient 50% of the prescribed dose. No recombinant human granulocyte colony-stimulating factor analogs were prescribed for any patient during the treatment. One patient (5%) had a partial radiological response, 19 (83%) stable disease, and 2 (9%) patients progressive disease after FOLFIRINOX treatment.

Five (23%) patients of the 22 did not receive RT due to deterioration of patients' condition (n = 3), distant progressive disease under FOLFIRINOX (n = 2). The remaining 17 (77%) patients received RT; 16 (94%) received the full dose of 60 Gy and only 1 (6%) patient received 52 Gy due to the patient's condition. One (6%) patient had a partial response, 11 (65%) patients stable disease, and 5 (29%) patients progressive disease. The progression was seen both local and distant in three (60%) patients, and only distant in two (40%) patients.

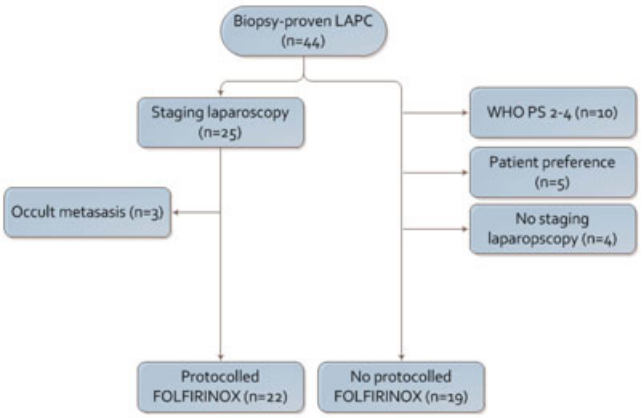

FIGURE 1 Flowchart of the study population [Color figure can be viewed at wileyonlinelibrary.com]

At last follow-up, all 22 patients died of progressive disease. The median PFS and OS of the group "protocolled FOLFIRINOX" (n = 22) was 11 months (95% confidence interval [CI], 7.7-14.4) and 15.4 months (95% CI, 10.0-20.7), respectively (Figure 2). The actual 1-year survival rate was 68% (95% CI, 47%-84%), and the actual 2-years survival rate was 14% (95% CI, 5%-33%). The median OS after completion of both FOLFIRINOX and RT (n = 17) was 18.7 months (95% CI, 13.4 -23.9). The median OS of "protocolled FOLFIRINOX" (n = 22) from the date of histopathological confirmation until the date of death was 16.3 months (95% CI, 11.4-21.2). In comparison, the patients who did not receive protocolled FOLFIRINOX and RT (n = 19) all died, and had a median OS of 6.2 months (95% CI, 3.8–8.5) with actual 1-year OS of 37% (95% CI, 19%-59%) and actual 2-year OS of 5% (95% CI, 9%-25%).

There were 13 (59%) grade 3 or 4 adverse events seen in 13 patients, including diarrhea (n = 4), elevated liver enzymes (n = 3), neutropenic fever (n = 1), nausea (n = 1), mucositis (n = 1), fatigue

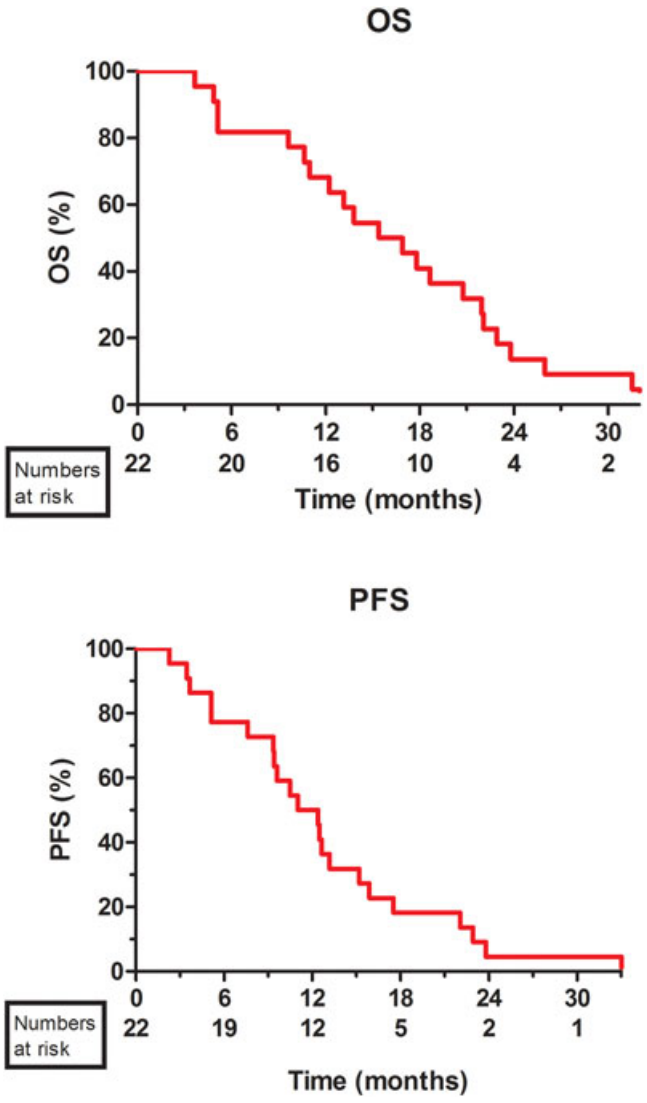

FIGURE 2 Kaplan-Meier curves of OS and PFS for the patients treated with FOLFIRINOX. OS, overall survival; PFS, progression-free survival [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Serious adverse events during FOLFIRINOX, n = 13

Description	Grade 3	Grade 4
Diarrhea	4	0
Elevated ALT/AST	1	2
Neutropenic fever	1	0
Ascites	1	0
Fatigue	1	0
GI bleeding	0	1
Mucositis	1	0
Nausea	1	0
Paresthesia	0	0
Total	10	3

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; GI, gastrointestinal.

(n = 1), gastrointestinal bleeding (n = 1), and ascites (n = 1). All serious adverse events of the FOLFIRINOX treatment are summarized in Table 2. No deaths were attributed to FOLFIRINOX. Only one (6%) patient had a serious adverse event of grade 3 of diarrhea during RT.

Three (14%) patients underwent an exploratory laparotomy after FOLFIRINOX and RT. One (5%) patient was found to have peritoneal metastasis at exploratory laparotomy and underwent a gastric bypass. Two (9%) patients underwent a curative-intent resection; modified Appleby resection, and one a distal pancreatectomy. Both (100%) resections were radical (R0, closest margin >1 mm). Survival time after resection was 16 and 10 months in two patients with a partial response in histopathological examination.

4 | DISCUSSION

In this cohort study, 22 patients with LAPC received FOLFIRINOX with subsequent conventional RT. The median OS was 15 months and the PFS 11 months. Most patients (77%) completed both chemotherapy and RT. No mortality was attributed to the treatment, but 64% had at least one grade 3 or 4 toxicity. Nineteen patients with LAPC did not receive the protocolled care for various reasons resulting in a median OS of 6.2 months.

Since the randomized controlled trial conducted by Conroy et al[5] showed a survival benefit for FOLFIRINOX vs gemcitabine for metastatic pancreatic cancer, many case series were published that evaluated the survival effect of FOLFIRINOX for patients with LAPC.[9-20] However, no randomized controlled trials have been published that confirm the survival benefit of FOLFIRINOX in LAPC patients. A recent patient-level meta-analysis of 315 LAPC patients treated with first-line FOLFIRINOX showed a median OS of 24.2 months and PFS of 15 months.[6]

Our median OS and PFS is lower than found in the meta-analysis. However, most studies in the meta-analysis were retrospective, which may cause selection bias. On the other hand, we used a staging laparoscopy before the treatment to rule out the occult metastatic disease. This approach is based upon two studies that have shown that 34% and 35% of patients with LAPC are found to have clinically and radiographically-undetermined metastatic disease during staging laparoscopy.[21,22]

The FOLFIRINOX treatment toxicity of 59% serious adverse events is comparable to the other studies published about this treatment regimen, with the meta-analysis showing a 60% of serious adverse events during the treatment. Despite this high toxicity profile, FOLFIRINOX showed a better quality of life than gemcitabine in the PRODIGE 4 trial, probably by deferring definitive deterioration.[23]

RT had a very low rate of serious adverse events (6%) in our study and therefore is safe to give as the subsequent treatment after the first-line FOLFIRNOX. However, whether conventional RT improves survival for LAPC patients has not been evaluated in a randomized controlled trial.[4] In regard of chemoradiotherapy, in 2016 Hammel et al[24] published the LAP07 randomized controlled trial which randomized patients with LAPC for induction chemotherapy (gemcitabine vs gemcitabine and erlotinib), followed by a second randomization of continuing chemotherapy vs chemoradiotherapy (54 Gy plus capecitabine). During the interim analysis, the study was stopped as it reached the early stopping boundaries for futility. However, the study did not show a significant median OS benefit between continuing chemotherapy or subsequent chemoradiotherapy after induction chemotherapy with a median survival of 16.5 vs 15.2 months, respectively. The major disadvantage of conventional fractionated RT for pancreatic cancer is that although the pancreas is relatively radioresistant, the surrounding organs are highly radiosensitive.[25] In the last years, stereotactic body RT (SBRT) has emerged as the preferred RT after the systemic chemotherapy for LAPC. SBRT allows for a higher dose of RT to the pancreatic tumor with less radiation to the surrounding organs.[26] A low rate of serious adverse events (7%) was also seen by Mellon et al[27] when SBRT was given as therapy for borderline resectable and locally advanced pancreatic cancer after induction chemotherapy.

In our study, two patients (9%) underwent a resection with, both being a radical resection. This rate was lower than the pooled resection rate of 28% as shown in the meta-analysis.[6] In our clinic, the decision to do an exploration after induction therapy is based on the same definitions for LAPC. So arterial tumor encasement should not exceed 90 degrees and venous encasement should not exceed 270 degrees. These more conservative criteria for exploration could have led to a lower resection rate than given in other studies. Furthermore, the meta-analysis did not detect an association between a studied resection rate and survival. Some studies report remarkable survival outcomes in LAPC patients after induction FOLFIRINOX and resection. However, these patients are highly selective and the favorable outcomes may be largely attributable to guaranteed-time bias.[28,29] The most recent American Society of Clinical Oncology guideline advises that all patients with LAPC should receive first-line chemotherapy with or without RT, and surgery should be only considered if a dramatic response to induction

therapy was achieved.[4] In our clinic, the decision to do an exploration after induction therapy is based on the same definitions for LAPC. So arterial tumor encasement should not exceed 90 degrees and venous encasement should not exceed 270 degrees. These more conservative criteria for exploration could have led to a lower resection rate than given in other studies. Future studies should determine which patients could potentially benefit from a resection after induction chemotherapy.

Our study has several limitations. The main limitation is that the sample size of patients who received the full treatment is small to draw definitive conclusions. However, despite the small sample size, this study gives an overview of how many patients eventually receive induction chemotherapy after the diagnosis of LAPC. Furthermore, there is no general consensus in the definition for LAPC that can help generalize the interpretation of different treatment regimens. Although the Dutch Pancreatic Cancer Group definitions for LAPC are more conservative than the most commonly used definitions such as NCCN and AHPBA/SSO/SSAT definitions,[30,31] there is no evidence that there is a difference in survival because of these criteria. In addition, conventional RT was used in this study while SBRT can maybe induce a better local control as mentioned above.

In conclusion, this study gives an overview of the current practice and strategy of patients with LAPC in the Netherlands. FOLFIRINOX followed by RT can be offered to a limited number of patients, but it could be considered safe and shows promising survival results for patients with LAPC. Randomized controlled trials are needed to determine the value of RT, and resection in addition to FOLFIRINOX in patients with LAPC.

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