LOCALLY ADVANCED PANCREATIC CANCER: BEYOND THE BORDERS MUSTAFA SUKER

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Locally Advanced Pancreatic Cancer: Beyond the borders

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Locally Advanced Pancreatic Cancer: Beyond the borders

Lokaal irresectabel pancreascarcinoom: Voorbij aan de grenzen

Thesis

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Aan mijn ouders

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Chapter 1
Introduction

M. Suker, C.H.J. van Eijck

Adapted from book chapter 'Pancreatic resection after neoadjuvant treatment'. Published in: 'Minimally Invasive Surgery for Upper Abdominal Cancer'. Springer International Publishing; 2017. p. 221-229.

Introduction

Pancreatic cancer has a very poor prognosis, with the projection to be the second leading cancer-related death in 2030.[1] Pancreatic cancer can be divided in three stages: resectable (15%), locally advanced (35%), and metastatic disease (50%).[2] The diagnosis of resectable and locally advanced pancreatic cancer is determined by the tumor invasion of critical structures, in particular the portal vein, superior mesenteric vein, coeliac artery, and superior mesenteric artery. This tumor invasion is usually assessed by contrast enhanced computed tomography (CT). There are several definitions for resectable and locally advanced disease, usually based on the tumor burden of the surrounding major vessels. This tumor burden can be defined as no invasion at all to the surrounding structures (resectable disease) or too much invasion in the surrounding structures to be deemed resectable (locally advanced disease). In between these two extremes, there is a diagnostic gap where a tumor has some vessel involvement but is still resectable, this gap is called borderline resectable disease. The two most commonly used definitions for (borderline) resectable disease and locally advanced disease are that of National Comprehensive Cancer (NCCN) and the combined definition of Americas Hepato-Pancreato-Biliary Association (AHPBA), the Society of Surgical Oncology (SSO), and the Society for Surgery of the Alimentary Tract (SSAT).[3, 4] In the Netherlands, the Dutch Pancreatic Cancer Group uses it owns definition to determine resectability.[5] The definitions of NCCN, AHPBA/SSO/SSAT, and DPCG for borderline resectable and locally advanced disease are summarized in **Table 1**. For decades, the primary treatment for borderline resectable pancreatic cancer was upfront surgery. However, neoadjuvant therapy is becoming more and more a valuable upfront therapy for borderline resectable disease. Although there is no clear level I evidence for this treatment.[6] The main purpose of neoadjuvant treatment is threefold: 1) improve probability of radical resection, 2) patient selection of patients with rapid disease progression that will undergo unnecessary surgery, 3) early treatment of occult metastasis. As a result, more patients receive systemic treatment, since a significant portion of patients are not eligible for adjuvant therapy due to morbidity.[7] In contrary, locally advanced pancreatic cancer is conventionally treated with induction chemotherapy and sometimes followed by local therapy such as (chemo)radiotherapy or local ablation. Surgery is not recommended as an upfront treatment in locally advanced unresectable pancreatic cancer and is only reserved for patients with disease response and after tumor downstaging with chemotherapy and or (chemo)radiotherapy.[8]

In this thesis, we focus on patients diagnosed with locally advanced pancreatic cancer and will be discussed in more depth in the next paragraph.

Table 1. NCCN, AHPBA/SSO/SSAT, and DPCG definitions of borderline resectable and locally advanced pancreatic cancer.

	NCCN	AHPBA/SSO/SSAT	DPCG
Borderline resectable	No distant metastases	No distant metastasis	No distant metastasis
	Solid tumor contact with SMA < 180 degrees	Solid tumor contact with SMA < 180 degrees	Solid tumor contact with SMA < 90 degrees
	Solid tumor contact with GA and/or CHA without involvement of CA	Solid tumor contact with GA and/or CHA without involvement of CA	Solid tumor contact with CA or CHA < 90 degrees
	Reconstructable SMV and/or PV despite tumor involvement or occlusion	Reconstructable SMV and/or PV despite tumor involvement or occlusion without tumor contact with surrounding arteries	Solid tumor contact with SMV or PV < 270 degrees
Locally advanced	No distant metastasis	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 CA or CHA ≥ 90 degrees
	Solid tumor contact with the first jejunal SMA branch and/or aortic involvement.	Abutment of CA due to tumor involvement	Solid tumor contact with SMV or PV ≥ 270 degrees
	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 jenjunal branch in to SMV.		

SMA: Superior Mesenteric Artery

GA: gastroduodenal artery

CA: Coeliac Axis

CHA: Common Hepatic Artery

SMV: Superior Mesenteric Vein
PV: Portal Vein

Locally advanced pancreatic cancer

The diagnosis of borderline resectable pancreatic cancer remains difficult. There are some consensus definitions **(Table 1)**. Bottom line, borderline resectable pancreatic cancer is diagnosed by the surgeon if he deems the tumor resectable despite vascular encasement on CT-scan with a possibility, that the resection is radical and resected vascular structures are reconstructable. The diagnosis of locally advanced pancreatic cancer (LAPC) is a more defined diagnosis. The tumor has a vascular invasive aspect on CT-scan, making it unresectable due to the high probability of micro- or macroscopically irradical resection. Unfortunately, there is no worldwide consensus on how much the vascular involvement is, to deem the tumor unresectable **(Table 1)**.

Part I: Staging of LAPC

The diagnostic approach of LAPC patients consists of a CT-scan of chest, abdomen, and pelvis to exclude metastatic disease.[7] Although, in (borderline) resectable pancreatic cancer chest CT-scans are recommended, many centers do no perform them routinely.[9] This is due to the limited influence of these scans on treatment management and survival.[10, 11] In LAPC, the clinical value of chest CT-scans is not yet defined as there is limited data available on this matter. Further staging of LAPC can be accomplished by staging laparoscopy. It is recommended to perform a staging laparoscopy in LAPC, if in any phase of the treatment a local therapy is considered (i.e. radiotherapy or surgery).[4] A staging laparoscopy has shown to upstage approximately one third of the patients with LAPC on CT-scan to a metastatic disease.[12, 13] However, these studies are more than a decade old and should be interpreted with caution, due to the more accurate imaging techniques nowadays. Therefore, contemporary studies are warranted.

Part II: Treatment of LAPC

Conventionally, LAPC is treated like metastatic disease with induction systemic chemotherapy. For decades, fluorouracil was the standard first-line treatment for LAPC. This changed after an RCT in 1997, including patients with metastatic and locally advanced pancreatic cancer, which showed a median overall survival (OS) of 5.6 months in the gemcitabine arm while fluorouracil arm gave a median OS of 4.4 months ($p=0.0025$).[14] More recently, an RCT was conducted by Conroy et al. in 2011 with FOLFIRINOX versus gemcitabine for patients with metastatic and LAPC.[15] The median OS in the FOLFIRINOX group was 11.1 versus 6.8 months in the gemcitabine group ($p<0.001$). Since this revolutionary paper, many case series with first-line FOLFIRINOX for LAPC are published. Recently, a phase II trial endorsed the potential survival benefit of first-line FOLFIRINOX for patients with LAPC. In 31 patients, the median OS was 26.6 months, where 42% of the patients underwent a resection, all being a radical resection.[16] Another systemic chemotherapy regimen is nab-paclitaxel–gemcitabine and is examined in a recent RCT from Von Hoff et al. Although including only patients with metastatic pancreatic cancer, this RCT showed a survival benefit for nab-paclitaxel–gemcitabine versus gemcitabine alone (median OS 8.5 vs. 6.7 months, $p <0.001$).[17] The benefit of systematic therapy above surgery-first approach in patients with LAPC was further underlined in an American nationwide database set which showed a median OS of 21 months ($n=377$) versus 14 months ($n=216$) in favor of the neoadjuvant group ($p<0.001$).[18]

Additional treatment after first-line chemotherapy is only advised if there is no clinical tumor progression. The optimal subsequent regimen has yet to be established, due to contradicting results. In the last decade, there were three randomized trials that

evaluated the effect of (chemo)radiotherapy versus chemotherapy alone in LAPC.[7] One study randomized gemcitabine (n=60) versus fluorouracil-cisplatin-radiotherapy followed by gemcitabine (n=59), and showed a median OS of 14.3 months versus 8.4 months in favor of the gemcitabine alone arm (p= 0.014). In the contrary, another study randomized between gemcitabine versus gemcitabine-radiotherapy, and reported a median OS of 9.2 months versus 11.1 months in favor of the gemcitabine-radiotherapy arm (p=0.017). The most recent study that was published showed no difference in subsequent treatment with radiotherapy. This study enrolled patients with LAPC for 4 months of gemcitabine with or without erlotinib. If no progression was seen, the patients were randomized between 2 months extension (n=136) of the chemotherapy or capecitabine-radiotherapy (n=133) (median OS 15.2 vs 16.5, p = 0.83). Less is known about the survival benefit of resection after induction chemotherapy and radiotherapy. Currently, there is no consensus in the literature on selection of patients with LAPC for resection after induction therapy.[19]

Outline of this thesis

The staging of LAPC remains essential, especially in the current expansion of local therapies.[20] As proper staging of LAPC allows for better understanding of new treatment protocols, since patients with understaged disease are excluded before diluting true outcomes. Furthermore, there are no definitive answers on which regimens should be used as treatment for LAPC. The role of FOLFIRINOX and radiotherapy in the treatment of LAPC is of interest, as they have shown promising results lately. This thesis is divided in two parts. The first part focuses on the staging of LAPC. The second part focuses on the treatment of patients with LAPC.

Part I: Staging of LAPC

Chapter 2 evaluates the clinical value of follow-up chest CT-scans in patients with LAPC.

Chapter 3 examines the yield of staging laparoscopy for occult metastasis in LAPC.

Part II: Treatment of LAPC

Chapter 4 is a systematic review and meta-analysis on survival data of FOLFIRINOX treatment in patients with LAPC.

Chapter 5 presents the results of a patient cohort with LAPC treated with FOLFIRINOX in Erasmus MC.

Chapter 6 outlines the findings of a multicenter phase II trial on FOLFIIRNOX and stereotactic body radiotherapy for LAPC patients.

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Part I
Staging of LAPC

Chapter 2

The yield of chest computed tomography in patients with locally advanced pancreatic cancer

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Submitted

Abstract

Objective:

To evaluate the incidence of pulmonary metastases on chest computed tomography (CT) in patients with locally advanced pancreatic cancer (LAPC).

Methods:

All patients diagnosed with LAPC in a single tertiary center (Erasmus MC) between October 2011 and December 2017 were reviewed. The staging chest CT-scan and follow-up chest CT-scans were evaluated. Pulmonary nodules were divided into three categories: apparent benign, too small to characterize, and apparent malignant.

Results:

In 124 consecutive patients diagnosed with LAPC, 119 (96%) patients underwent a staging chest CT-scan at initial presentation. In 88 (74%) patients no pulmonary nodules were found; in 16 patients (13%) an apparent benign pulmonary nodule was found, and in 15 patients (13%) a pulmonary nodule too small to characterize was found. Follow-up chest CT-scan(s) were performed in 111 (93%) patients. In one patient with either no pulmonary nodule or an apparent benign pulmonary nodule at initial staging, an apparent malignant pulmonary nodule was found on follow-up chest CT-scan. However, biopsy of the nodule was inconclusive. Of 15 patients in whom a pulmonary nodule too small to characterize was found at staging, 12 (80%) patients underwent a follow-up CT-scan; in four (33%) of these patients an apparent malignant pulmonary nodule was found.

Conclusion:

In patients with LAPC in whom at diagnosis a chest CT scan revealed either no pulmonary nodules or apparent benign pulmonary nodules, routine follow up chest CT scans is not recommended. Patients with pulmonary nodules too small to characterize are at risk to develop apparent malignant pulmonary nodules during follow-up.

Introduction

Projections indicate that pancreatic cancer will be the second leading cause of cancer-related death by 2030.[1] At the time of diagnosis, 15% of patients with pancreatic cancer have (borderline) resectable disease (stage I or II), whereas 35% of patients present with locally advanced pancreatic cancer (LAPC, stage III), and 50% of patients initially present with metastatic disease (stage IV).[2] The definition of LAPC is determined by the extent of tumor contact with the superior mesenteric artery, celiac artery, superior mesenteric vein, and portal vein.[3] Moreover, imaging should demonstrate no evidence of metastatic disease.

Chest computed tomography (CT)-scan is more sensitive and specific in detecting pulmonary metastases than a conventional chest X-ray.[4] In patients with pancreatic cancer, the National Comprehensive Center Network (NCCN) guidelines recommend routine chest CT-scans.[5] Chest CT-scan in (borderline) resectable pancreatic cancer, nonetheless, was found to be of no influence on survival.[6-8] Chest CT-scans frequently reveal sub-centimeter pulmonary nodules that are often said to be too small to characterize. They impose a clinical dilemma, as these nodules of uncertain nature induce uncertainty with regard to their nature and as such carry a huge emotional burden to patients. These findings often lead to additional invasive diagnostic tests, which delays the start of treatment and can impose additional risks to the patients. For example, diagnostic transthoracic lung biopsies harbor a considerable risk of pneumothorax or intrathoracic bleeding and frequently are found to be non-diagnostic.[9]

Moreover, the clinical value of a chest CT-scan in LAPC could be questioned, because systemic chemotherapy is the first-line treatment for both LAPC and metastatic disease.[10] Detection of metastatic disease in LAPC patients is particularly relevant in the era of several locoregional treatments for pancreatic cancer, including radiofrequent ablation (RFA), irreversible electroporation (IRE), and stereotactic body radiotherapy (SBRT).[11] While the benefit of these treatments has not been shown definitively, even their strongest proponents agree that they are unlikely to benefit patients with metastatic disease. The aim of this study is to evaluate the yield of routine chest CT-scans in patients with LAPC at initial staging and during follow-up.

Methods

We retrospectively reviewed all consecutive patients diagnosed with LAPC between October 2011 to December 2017 seen at Erasmus MC, The Netherlands. The database used for this study was approved by the institutional review board, and an informed

consent was waived. A diagnostic CT-scan of chest and abdomen was performed at diagnosis and during follow-up. The CT-scan was done on a 128 slice CT scanner with 3 phases (unenhanced, late arterial (35 sec) and portal-venous (70 sec) of the upper abdomen after intravenous injection of contrast medium. In addition, the lower abdomen and chest were scanned in the last phase. The majority of the staging CT-scans were performed in our institute, however, some patients already underwent a staging CT-scan in the hospital of referral. If the quality of these CT-scans was up to the standard and scan were performed <4 weeks before therapy, these scans were added in our imaging archive and formally reassessed. Otherwise, the patient underwent a new CT-scan in our institute following the guidelines as described above. Diagnosis of LAPC was according to the Dutch guidelines. [12]

All patients with LAPC were offered a treatment consisting of 8 cycles of FOLFIRINOX followed by either conventional or stereotactic body radiotherapy when no disease progression was observed on follow-up scanning. Usually, follow-up CT-scans were performed after 4 and 8 cycles of FOLFIRINOX, and 3 months after radiotherapy. In the case of SBRT an additional CT-scan was performed after 6 months. After this, patients underwent CT-scans only on indication.

Pulmonary nodules observed during initial and follow-up CT scans were divided into three categories: apparent benign, too small to characterize, and apparent malignant, whereby an apparent benign nodule was defined as a lesion with homogenous calcification. A nodules was considered too small to characterize was a noncalcified nodule under 1 cm, or pleural effusion.[8]

Comparisons of patient's characteristic between patients without pulmonary nodule or benign nodules versus patients with nodules too small to characterize were analyzed using Fisher exact test for categorical variables, and a nonparametric median test for continuous variables. Overall survival (OS) was calculated from date of first staging CT-scan until death of any cause. The survival outcome is presented using Kaplan-Maier and compared log-rank in SPSS (version 21). A p-value < 0.05 was considered as statistically significant.

Results

In total 124 consecutive patients diagnosed with LAPC between December 2011 and December 2017 were identified. In 119 (96%) patients (45% male, median age 64 years [IRQ 56 -70]) a staging chest CT-scan was available. The World Health Organization performance score was 0 or 1 in 85 (71%) patients. The tumor was located in the pancreatic head in 73 (61%) of the patients, in the body in 40 (34%) patients, and in six (5%) in the tail. LAPC diagnosis was based on arterial contact in 74 (62%) patients,

venous contact in 18 (15%) patients, and both venous and arterial contact in 27 (23%) patients. The median baseline serum level of CA19-9 was 233 [IQR 61 - 974] and of CEA 6.3 [IQR 3.0 – 18.3]. All baseline characteristics are shown in table 1.

Table 1. Baseline characteristics.

Baseline characteristics	N=119 (% or IQR)
Age, median	64 [56-70]
Gender	
Male	53 (45)
Female	66 (55)
WHO PS*	
0-1	85 (71)
2-4	34 (29)
Smoking	
Yes	33 (28)
Never	38 (32)
Former	42 (35)
Missing	6 (5)
BMI, median	24 [21-27]
Tumor origin	
Head	73 (61)
Body	40 (34)
Tail	6 (5)
Maximum tumor size (mm)	37 [30-44]
LAPC based on	
Only arterial	74 (62)
Only venous	18 (15)
Both arterial and venous	27 (23)
Median CA 19.9 (µg/L)	233 [61-966]
Median CEA (kU/L)	6.3 [3.0-18.3]

* PS: performance status

Best supportive care was initiated in 35 (29%) after initial diagnosis of LAPC. The reason for initiating best supportive care was patients' condition in 20 (57%), and patients' request in 15 (43%) patients. FOLFIRINOX was given as first-line treatment in 81 (68%) patients; Nab-paclitaxel and gemcitabine in two (2%) patients, and gemcitabine alone in one (1%) patient. Subsequent radiotherapy was given in 56 (68%) patients after induction chemotherapy. The reason for not receiving radiotherapy after chemotherapy was progression after chemotherapy in 13 (50%) patients, and toxicity in 13 (50%) patients. Conventional radiotherapy was given to 19 (34%) patients, while stereotactic body radiotherapy was given to 37 (66%) patients.

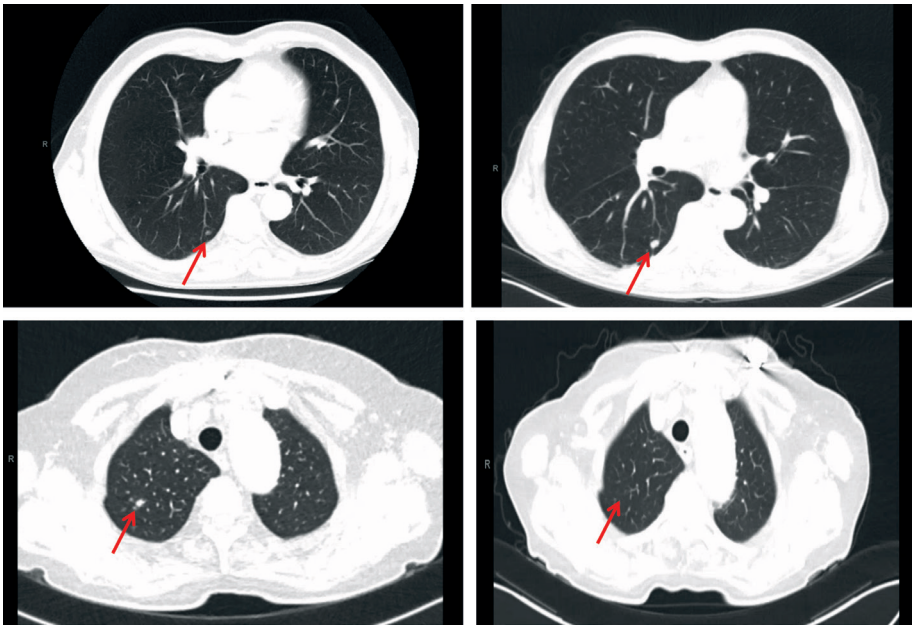

Figure 1. Staging (left) and follow-up (right) CT-scans of patients with nodule too small to characterize (up), and benign nodule (under).

In 31 (26%) patients a pulmonary nodules was found on the initial staging CT-scan. In 15 (13%) patients the nodules were classified as too small to characterize, whereas in 16 (13%) patients the nodules were classified as apparent benign. The baseline characteristics gender, age, tumor diameter, tumor location, smoking history, and baseline serum CA 19-9 and CEA were not associated with the presence of nodules too small to characterize on staging chest CT-scan (table 2). A follow-up chest CT-scan was performed in 111 (93%) patients (figure 2), median time between staging and follow-up CT-scan was 7 months [IQR 2 – 15]. The median number of follow-up chest CT-scans was 2 [IQR 1 – 4]. In one (1%) patient in whom the initial CT-scan no pulmonary nodule was seen, malignant appearing pulmonary nodules were seen during follow-up . The follow-up chest CT-scan was performed for restaging purposes before start of treatment one month after first chest CT-scan. However, biopsy of one of the nodules was inconclusive. Of the 15 patients in whom the initial CT-scan revealed a pulmonary nodule too small to characterize on staging imaging, 12 (80%) patients underwent a follow-up chest CT-scan after a median time of 4 months [IRQ 2 – 20]. In four (33%) of these patients an apparent malignant pulmonary nodules was observed, which coincided in one patient with the development of a liver metastasis. Whereas, in five (42%) patients no apparent malignant nodule on follow-up chest CT-scan was found, while three (25%) patients had unchanged nodule. In these patients,

Table 2. Comparing clinical characteristics for patients with and without nodules too small to characterize on staging CT-scan.

	Patients with nodules too small to characterize (N=15)	Patients with benign or without pulmonary nodules (N=104)	p-value
Age, median [IQR]	68.5 [60.7 – 70.1]	63.5 [55.6 – 69.8]	0.09
Male gender	54%	43%	0.58
Smoking (current)	23%	30%	0.75
Tumor origin (head)	40%	39%	1.00
Maximum tumor size (mm) [IQR]	37 [35 – 47]	37 [30 – 44]	0.81
Median CA 19.9 (µg/L)) [IQR]	244 [169 – 1392]	231 [56 – 966]	0.97
Median CEA (kU/L)) [IQR]	5.7 [3.0 – 50.5]	6.5 [3.1 – 18.0]	0.96
Chemotherapy	60%	73%	0.36
Radiotherapy	40%	49%	0.59
Survival (mo) (95% CI)	13 (10 – 15)	11 (3 – 18)	0.88

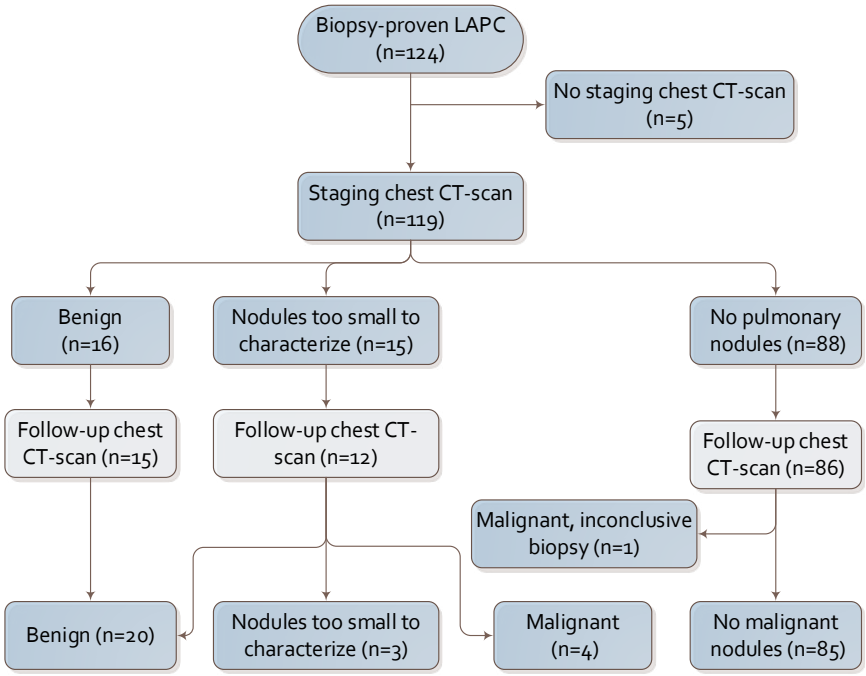

Figure 2. Flowchart of the study population.

Table 3. Clinical characteristic of the patients with nodules too small to characterize on first staging chest CT-scan.

Patient	Gender	Age (years)	Tumor location in pancreas	Baseline CA19-9	Baseline CEA	First-line treatment	Radiotherapy	CA19.9 difference	CEA difference	Pulmonary nodule on follow-up CT	Progression site	Alive	Survival (months)
1	Female	73	Head	2675	8,0	FOLFIRINOX	SBRT	-2568	-3.29	Unchanged	No	Yes	18
2	Female	74	Head	169	-	BSC	No	-	-	-	-	No	5
3	Male	67	Body	13674	113,0	FOLFIRINOX	No	-	-	Benign	-	No	6
4	Female	64	Head	1392	50,5	BSC	No	-	-	Unchanged	-	No	8
5	Male	68	Tail	11	103,0	FOLFIRINOX	SBRT	+19	-20.3	Malignant	Liver Lung	No	25
6	Female	70	Head	931	4,4	BSC	No	-	-	Benign	-	No	3
7	Male	54	Body	921	5,7	FOLFIRINOX	SBRT	-710	-2.1	Malignant	Lung	Yes	34
8	Male	69	Head	227	-	FOLFIRINOX	No	-	-	Malignant	Lung Local	No	8
9	Male	70	Head	244	1,4	BSC	No	+769	+0.5	Unchanged	Liver	No	6
10	Male	53	Head	-	-	BSC	No	-	-	-	Local	No	13
11	Female	69	Body	-	-	Nab-paclitaxel + gemcitabine	SBRT	-	-	Malignant	Lung	No	34
12	Female	68	Head	201	2,4	FOLFIRINOX	Conventional	-144	-1.0	Benign	Liver Peritoneum	No	25
13	Female	73	Head	-	-	BSC	No	-	-	-	-	No	11
14	Male	61	Body	150	3,0	FOLFIRINOX	SBRT	+1742	+1.4	Benign	Liver Peritoneum	No	14
15	Male	60	Body	-	-	FOLFIRINOX	SBRT	-	-	Benign	Liver	No	7

- = Missing data

BSC = Best supportive care

SBRT = Stereotactic Body Radiotherapy

no biopsies or resections were performed to obtain a pathological confirmation in any of the radiologically apparent malignant pulmonary nodules. The indication for these follow-up scans was restaging in 9 (75%) patients, and deterioration of condition in 3 (25%) patients. The CT-scan of the three patients with deterioration of condition showed local progression in one (33%) patients, liver metastases in one (33%) patients, and liver and peritoneal metastases in one (33%) patient. Clinical characteristics of the patients with nodules too small to characterize on first staging chest CT-scan are shown in table 3.

Median follow-up time for all 119 patients was 36 months (95% CI 31 – 40), while median OS after first chest CT-scan was 12 months (95% CI 10 – 14). There was no difference between patients with benign or without pulmonary nodules versus patients with nodules too small to characterize for receiving chemotherapy (72% vs 60%; p=0.49) or radiotherapy (49% vs. 40%; p=0.59). The median OS for patients with pulmonary nodule too small to characterize was 11 months (95% CI 4 – 18) versus 13 months (95% CI 10 – 15) in patients without these nodules (p=0.88) (figure 3).

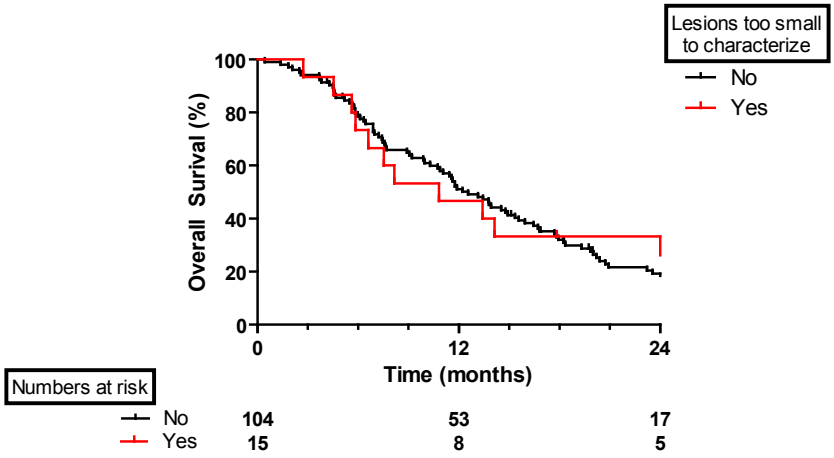

Figure 3. Kaplan-Meier of patients with and without nodules too small to characterize on first staging chest CT-scan (p= 0.88).

Discussion

Staging and restaging chest CT-scans are routinely performed in patients with LAPC. To our knowledge, this is the first study to, retrospectively though, assess and valuate the clinical value of these CT-scans, dividing any observed pulmonary nodule into any of three categories: apparent benign, too small to characterize, and apparent malignant pulmonary nodules too small to characterize were seen on first staging chest CT-scan in fifteen (13%) patients with LAPC. In this group of patients, follow-up chest CT-scan revealed a subsequent apparent malignant nodule in four patients. Of these four patients, one patient had simultaneous a liver metastasis. Thereby, staging and follow-up chest CT-scan performed in 111 patients gave additional information only in three (3%) patients. All the malignant nodules found on follow-up CT-scans were first seen on the staging CT-scan as nodules too small to characterize. These findings suggest that follow-up CT-scans are only of clinical value if there is a pulmonary nodule too small to characterize on the first staging CT-scan.

In the group with no pulmonary nodules on first staging CT-scan, one (1%) patient showed a possible malignant appearing nodule. However, there was radiological uncertainty about this diagnosis. Therefore, the patient underwent a transthoracic biopsy which yielded no confirmation of a malignancy. The patient started with systemic chemotherapy, but stopped after two cycles due to deterioration of condition. No other follow-up chest CT-scan were performed after the restaging CT-scan. The patient died eventually 5 months after first chest CT-scan, and 2 months after last cycle of FOLFIRINOX . This case gives more insight about the clinical dilemmas of follow-up chest CT-scans in LAPC patients.

The NCCN guidelines advise a staging chest CT-scan in all pancreatic cancer patients.[12] In addition to these guidelines, or maybe to challenge the evidence of them, retrospective observational studies have assessed the added value of chest CT-scans in patients with resectable pancreatic cancer.[7, 8, 13] Poruk et al. showed that in 183 patients with resectable pancreatic cancer and nodules too small to characterize on the staging CT-scan, 16% of the patients subsequently developed apparent malignant pulmonary nodules during routine follow-up chest CT-scans.[13] Nonetheless, there was no difference in median OS between patients with and without these nodules too small to characterize. More recently, Mehtsun et al. showed that in 451 patients with resectable pancreatic cancer with pulmonary nodules too small to characterize, subsequent apparent malignant nodules in was found in only 19 (4%) patients.[7] In this study, there was also no difference in median OS between patients with and without pulmonary nodules too small to characterize. In the LAPC setting, exclusion of metastatic disease is of the essence. Therefore, staging chest CT-scan seems reasonable, especially in the era of local therapies emerging as possible

new treatment for LAPC.[14] For treatment monitoring purposes restaging chest CT-scans are recommended.[12] Nonetheless, our study shows that patients without any pulmonary nodule on staging CT-scan only 1 patient developed malignant appearing nodules evidence during follow-up chest CT-scans, without any histopathological proof. Furthermore, only 4% of the patients showed metastatic pulmonary nodules in follow-up CT-scans. These restaging chest scans could be an extra burden for patients, as small nodules could be seen. This could impose additional stress to these patients, as it could also implicate the clinical management. Physicians face the decision to do diagnostics on these nodules or ignore them, keeping in mind that local therapy could be a futile treatment strategy for these patients. In the current study, there was no difference in initial treatment management between patients with and without pulmonary nodules

The main limitation of our study is its retrospective design, which implicates that patients who were deemed as metastasized pancreatic cancer due to pulmonary metastasis are missed in this study. Furthermore, the data is obtained from only one institute. Nonetheless, our institute is the biggest academic hospital in the Netherlands where most of the patients are referred from non-academic hospitals. However, more studies are needed to confirm our findings.

In conclusion, follow-up chest CT-scans added information on pulmonary metastasis only in 4% of the patients. However, these nodules were first seen as too small to characterize on staging chest CT-scans. The management and survival of patients with nodules too small to characterize on staging CT-scan did not significantly differ from patients without these nodules. Routinely follow-up chest CT-should be questioned, unless undefined pulmonary nodules are found on staging chest CT-scan.

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Chapter 3

Yield of staging laparoscopy before treatment of locally advanced pancreatic cancer to detect occult metastases

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Abstract

Introduction:

Locally advanced pancreatic cancer (LAPC) is found in 35% of patients with pancreatic cancer. However, these patients often have occult metastatic disease. Patients with occult metastases are unlikely to benefit from locoregional treatments. This study evaluated the yield of occult metastases during staging laparoscopy in patients with LAPC.

Methods:

Between January 2013 and January 2017 all patients with LAPC underwent a staging laparoscopy after a recent tri-phasic CT-scan of the chest and abdomen. Data were retrospectively reviewed from a prospectively maintained database. Univariate and multivariable logistic regression analysis was conducted to predict metastasis found at laparoscopy.

Results:

A total of 91 (41% male, median age 64 years) LAPC patients were included. The median time between CT-scan and staging laparoscopy was 21 days. During staging laparoscopy metastases were found in 17 patients (19%, 95% CI: 12% - 28%). Seven (8%) patients had liver-only, 9 (10%) patients peritoneal-only, and 1 (1%) patient both liver and peritoneal metastases. Univariate logistic regression analysis showed that CEA (OR 1.056, 95% CI 1.007-1.107, p=0.02) was the only preoperative predictor for occult metastases. In a multivariable logistic regression analysis of the preoperative risk factors again only CEA was an independent predictor for occult metastatic disease (p=0.03). Patients with a CEA above 5 µg/L had a risk of occult metastasis of 91%. FOLFIRINOX was given to 69 (76%) of the patients with a median number of cycles of 8. Subsequent radiotherapy was given to 44 (48%) patients after the FOLFIRINOX treatment. Six (14%) patients underwent a resection after FOLFIRINOX and radiotherapy. The overall 1-year survival was 53% in patients without occult metastasis versus 29% with occult metastasis (p=0.11). The 1-year OS for patients that completed FOLFIRINOX and radiotherapy was 84%.

Conclusion:

The yield of staging laparoscopy for occult intrahepatic or peritoneal metastases in patients with locally advanced pancreatic cancer was 19%. Staging laparoscopy is recommended for patients with LAPC for accurate staging to determine optimal treatment.

Introduction

Projections indicate that pancreatic cancer will be the second leading causes of cancer-related death by 2030.[1] At the time of diagnosis, about 15% of patients has (borderline) resectable disease (stage I or II), 35% locally advanced pancreatic cancer (LAPC, stage III), and 50% metastatic disease (stage IV).[2] 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.[3] Several definitions for LAPC vary mainly in the extent of tumor contact.

Neoadjuvant treatment is becoming the standard treatment in patients with LAPC, where induction chemotherapy followed by locoregional therapy is often used.[4] Patients with dramatic response after neoadjuvant treatment, identified by clinical and radiological response without evidence for metastatic disease, are considered for surgery.[5] Therefore, detection of occult metastatic disease in LAPC patients is particularly relevant in the era of several locoregional treatments for PDAC, including radiofrequent ablation (RFA), irreversible electroporation (IRE), and stereotact body radiotherapy (SBRT).[4, 6] The assumption is that locoregional treatments are not or at least less effective in the presence of occult metastatic disease.

Staging consists of a tri-phasic CT-scan of chest, abdomen, and pelvis to detect metastatic disease. [5] Most guidelines advice that the most recent CT scan should be less than 4-6 weeks old prior to start of treatment. A consensus report by the American Hepato-Pancreato-Biliary Association recommended staging laparoscopy in patients with LAPC.[7] Several studies have estimated the yield of staging laparoscopy in patients with LAPC at about 35%, but imaging has improved considerably in recent years.[8, 9]

The aim of this study was to assess the yield of staging laparoscopy in patients with LAPC after recent and high-quality tri-phasic computed tomography (CT).

Methods

Between January 2013 and January 2017 all patients with biopsy-proven LAPC and eligible for FOLFIRINOX were included from four hospitals. The diagnostic work-up included a tri-phasic CT scan and EUS with fine needle aspiration (FNA). CT-scan was performed on a 128 slice CT scanner with 3 phases (unenhanced, late arterial (35 sec) and portal-venous (70 sec) of the upper abdomen after intravenous injection of contrast material. In addition, the lower abdomen and thorax were scanned in the last phase. LAPC was defined according to the Dutch guidelines as tumor contact with the superior mesenteric artery (SMA), coeliac artery, or common hepatic artery

exceeding 90 degrees or contact with the superior mesenteric vein or portal vein exceeding 270 degrees (Table 1).[10] Only patients eligible for protocolled systemic chemotherapy with FOLFIRINOX and subsequent radiotherapy were included.[11] All patients underwent a staging laparoscopy to exclude occult metastases. The institutional review board waived an informed consent.

Table 1. Definition of resectability according to the Dutch Pancreatic Cancer Group.

	SMA	Celiac axis	CHA	SMV-PV
Resectable (all four required)	no contact	no contact	no contact	≤90° contact
Borderline resectable (minimally one required)	≤90° contact	≤90° contact	≤90° contact	≤90°-270° contact, and no occlusion
Irresectable (minimally one required)	contact > 90°	contact > 90°	contact > 90°	contact > 270° or occlusion

The staging laparoscopy was standardized in all patients and done under general anesthesia. The procedure started with open introduction of a 10mm trocar through an infraumbilical incision. The 30 degrees endoscope was inserted and the entire abdominal cavity was inspected. A second (and sometimes third) 5 mm trocar was placed in the right or left upper abdominal quadrant to evaluate the posterior aspect of segments 2, 3, 4, 5, and 6 of the liver, the omentum majus and minus, Douglas, the mesentery of the transverse colon, and Treitz' ligament. Any suspicious lesion was biopsied and submitted for pathological evaluation. If occult metastasis was found during staging laparoscopy only systemic FOLFIRINOX chemotherapy was given, without radiotherapy. For the patients that did not show occult metastasis during staging laparoscopy, patients were re-staged by CT scan after 4 and 8 cycles of FOLFIRINOX chemotherapy. If no metastatic disease was found on imaging, patients received radiotherapy. In the period 2013 to 2015 conventional radiotherapy with 30 fractions of 2 Gray was given, whereas between 2015 and 2017 five fractions of 8 Gray stereotactic body radiotherapy (SBRT) was given. After FOLFIRINOX and radiotherapy patients were considered for exploration and a possible resection based on the local extent of disease and performance status.

Data were collected in a prospectively maintained database, and were retrospectively reviewed. Additional data were collected retrospectively. The following parameters were retrieved: baseline characteristics including serum tumor markers (CEA (µg/L) and CA 19-9 (kU/L), date of CT-scan prior to laparoscopy, date of staging laparoscopy, length of stay, and findings during staging laparoscopy. If an abdominal metastasis was found in the first two months post-laparoscopy on follow-up imaging this was calculated as a false negative rate of the staging laparoscopy.

Univariate and multivariable logistic regression analysis was conducted to predict the presence of occult metastasis found at laparoscopy. Potential preoperative risk factors for occult metastatic disease included gender, age, smoking, tumor size, and serum tumor markers (CEA (µg/L) and CA 19-9 (kU/L)). Conventional cut-off values were used for both tumor markers: serum CA19-9 ≥ 35 and CEA value ≥ 5. The 1-year overall survival (OS) was calculated from date of histology to date of death. The survival outcomes will be presented using Kaplan-Maier and compared log-rank in SPSS (version 21).

Results

From January 2013 to January 2017, 91 (41% male, median age 64 years) consecutive patients with biopsy-proven LAPC staged on tri-phasic CT-scan underwent a staging laparoscopy to exclude occult metastasis. Symptoms found at presentation were obstructive jaundice in 44 (48%) patients, diabetes in 24 (26%) patients, weight loss in 74 (81%) patients, and pain in 71 (78%) patients. The tumor location was in the pancreatic head in 56 (62%) patients, and pancreatic tail in 36 (38%) patients. Median tumor size was 37 mm [IQR 30-46]. The median time between CT-scan and staging laparoscopy was 21 days [IQR 12 - 32, 95% range 3 - 63]. All baseline characteristics of the included patients are shown in table 2.

During staging laparoscopy, a biopsy was performed in 36 (40%) patients. In 17 (19%) patients the biopsy was consistent with pancreatic adenocarcinoma. In nine (53%) patients the malignant lesions were peritoneal, in seven (41%) patients hepatogenic, and in one (6%) patient both peritoneal and hepatic. A flowchart of staging laparoscopy findings is shown in figure 1. Of the 74 patients that did not show occult metastasis during staging laparoscopy, seven (8%) patients showed a new intra-abdominal metastatic lesion on CT-scan within two months from the staging laparoscopy. All these new lesions were found in the liver, with five lesions being superficial and two lesions found deeper in liver parenchyma.

In univariate logistic regression of preoperative parameters, serum CEA (µg/L) was the only statistically significant risk factor (OR 1.06, 95% CI 1.01-1.11, p=0.02) for occult metastasis found at staging laparoscopy. Whereas, gender, age, smoking, tumor size and CA 19-9 (kU/L) were not statistically significant predictors. In a multivariate logistic regression CEA (µg/L) was the only independent predictor (OR 1.07, 95% CI 1.01 – 1.14, p=0.03). A CEA (µg/L) ≥ 5 gave a 91% risk for occult metastatic disease during staging laparoscopy, while CEA <5 gave a 4% risk for occult metastasis (p=0.04).The serum CA19-9 (kU/L) ≥ 35 gave a 79% risk for occult metastasis, while CA19-9 <35 gave a 19% risk for occult metastasis (p=1.00). All preoperative parameters are shown in table 3 and 4.

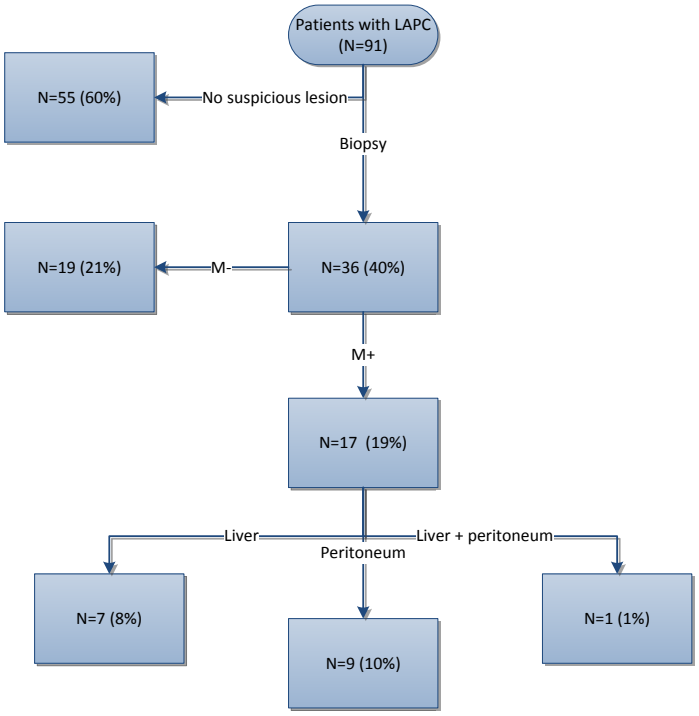

Figure 1 Flowchart of the staging laparoscopy findings.

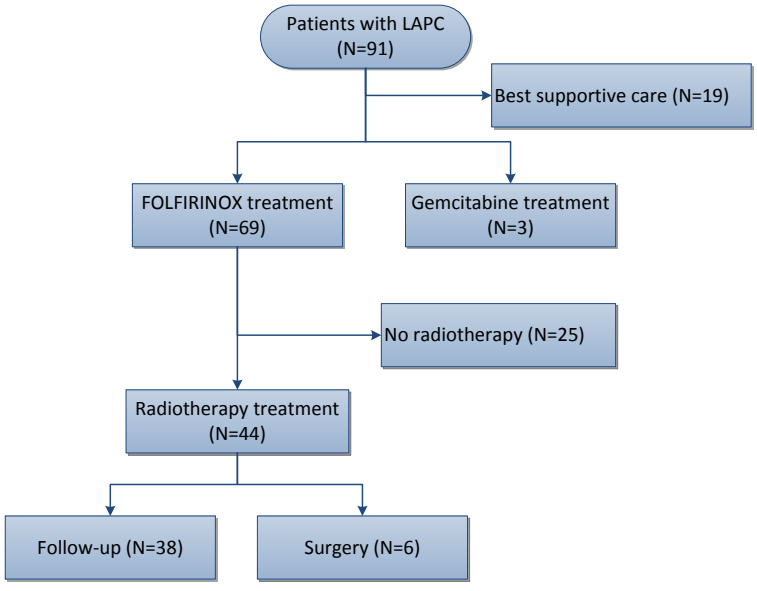

Figure 2. Flowchart of the treatment modalities given to the patients.

Table 2. Baseline characteristics.

Baseline characteristics	N=91 (% or IQR)
Age, median [IQR]	64 [56-69]
Gender	
Male	37 (41)
Female	54 (59)
WHO PS	
0	14 (15)
1	74 (81)
2	3 (3)
Jaundice	44 (48)
Weight loss*	74 (81)
Diabetes	24 (26)
Abdominal pain	71 (78)
BMI, median	24 [21-27]
Smoking	
Yes	27 (30)
Never	34 (37)
Former	27 (30)
Missing	3 (3)
Tumor origin	
Head	56 (62)
Distal	35 (38)
Median CA 19.9 (µg/L)	253 [50-1003]
Median CEA (kU/L)	5 [3-11]
Maximum tumor size (mm), median	37 [30-46]
Time between CT-scan and staging laparoscopy (days), median	21 days [12 – 32]

*Subjectively assessed by patient

IRQ: Interquartile range

WHO PS: World Health Organization Performance Status

CA 19.9: Cancer antigen 19.9

CEA: Carcino-embryonaal antigen

FOLFIRINOX was given to 69 (76%) patients, while 19 (21%) patients received best supportive care and three (3%) patients underwent gemcitabine chemotherapy. The reasons for patients to receive best supportive care after staging laparoscopy was due deterioration of condition (n=9), and patients preference (n=10). The median number cycles of FOLFIRINOX was 8 [IQR 4 – 8], with 55% of patients completing the scheduled 8 cycles of FOLFIRINOX. There were 35 (51%) adverse events of grade

3 or 4 during the FOLFIRINOX treatment. Of the patients that received FOLFIRINOX eventually 13 (14%) received conventional radiotherapy, another 31 (34%) patients underwent SBRT. Eventually, six (14%) patients underwent a radical resection after the FOLFIRINOX and radiotherapy treatment (figure 2).

The 1-year OS of all 91 patients was 51% (95% CI 40-61) with a median follow-up time of 32 months (95% CI 22 - 46), as shown in figure 3. The 1-year survival for patients without occult metastasis found on staging laparoscopy was 53% (95% CI 41% - 64%), while patients with occult metastasis found with occult metastasis on staging laparoscopy was 29% (95% CI 47% - 87%) (p=0.11), as shown in figure 4. The 1-year OS for patients that completed both FOLFIRINOX and radiotherapy was 84%(95% CI 69 - 92).

Table 3. Univariate and multivariate logistic regression for predictive preoperative parameters.

	Univariate, p-value	OR (95% CI)	Multivariate, p-value	OR (95% CI)
Age	0.35	1.03 (0.97 – 1.11)	0.83	0.99 (0.84 - 1.18)
Gender (male)	0.55	0.73 (0.25 – 2.09)	0.72	0.78 (0.04 - 14.88)
Smoking	0.96	1.03 (0.03 – 3.33)	0.34	2.38 (0.22 – 25.98)
Tumor size	0.75	1.01 (0.96 – 1.05)	0.65	0.98 (0.87 – 1.09)
CA 19.9 (µg/L)	0.06	1.00 (1.00 – 1.00)	0.37	1.00 (0.998 - 1.001)
CEA (kU/L)	0.02	1.06 (1.01 – 1.10)	0.03	1.07 (1.01 – 1.14)

Table 4. The number of patients with occult metastasis found with staging laparoscopy and CEA value higher than 5.

		CEA≥5		
		No	**Yes**	**Total**
Occult metastasis	**No**	25	32	**57**
	Yes	1	10	**11**
Total		26	42	68*

*Preoperative CEA values of 23 patients were unknown before staging laparoscopy.

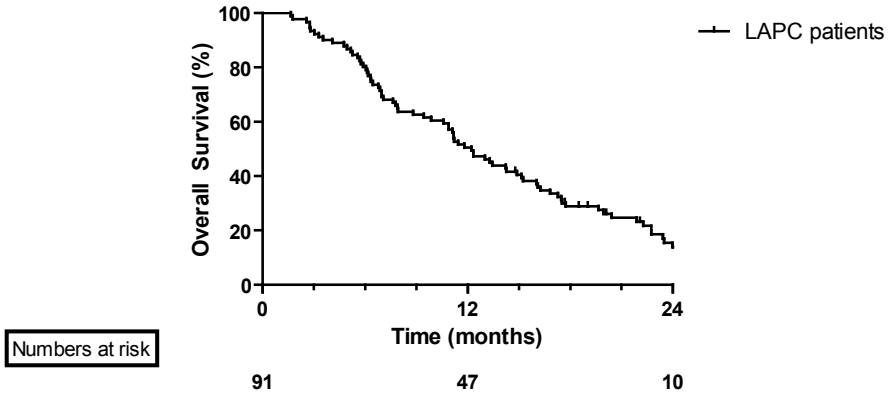

Figure 3. Overall survival of the included patients in this cohort.

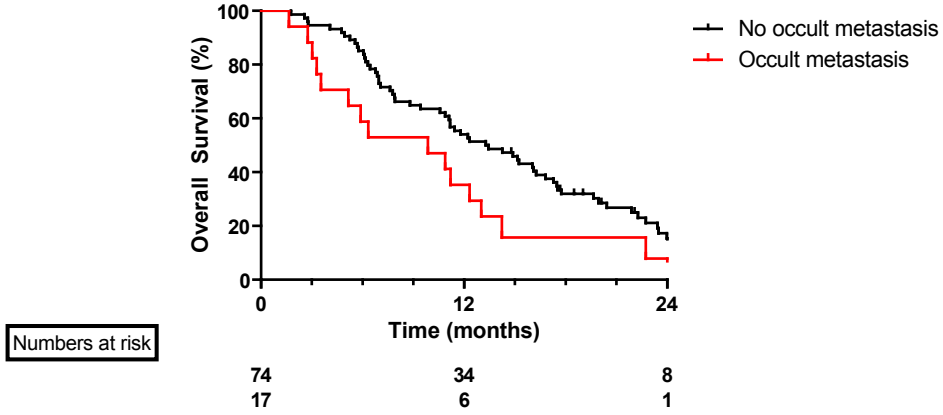

Figure 4. Overall survival of patients with and without occult metastasis found at staging laparoscopy.

Discussion

The yield of staging laparoscopy in 91 patients with LAPC was 19%. LAPC patients with occult metastasis had peritoneal and/or liver metastases that were too small for detection by state of the art tri-phasic CT of the chest and abdomen. Our study includes the largest cohort of patients with LAPC that underwent staging laparoscopy. Two studies (representing 74 and 68 LAPC patients) and published almost a decade ago also evaluated the yield of staging laparoscopy in LAPC patients.[8, 9] They found a yield of 34% (95% CI: 24% – 45%) and 35% (95% CI: 25% – 47%) for occult metastatic disease detected at staging laparoscopy.[8, 9] A Cochrane meta-analysis of seven studies (representing 1015 patients) for staging laparoscopy in (borderline) resectable pancreatic cancer showed a yield of 22%[12] The higher yield of about 1 in 3 LAPC patients found in the previous studies versus 19% in the present study could be explained by improvement in the quality of CT scans.[8, 9] Furthermore, a specialized radiologist reviewing the CT-scans could also improve the detection of occult metastasis found on CT-scan. In addition, multidisciplinary approach of LAPC in recent years have resulted in more multidisciplinary board review of these patients. This could influence the yield of CT-scan for occult metastatic disease in LAPC setting. [13] In our study, all CT-scans were reviewed by a specialized radiologist, and all patients were reviewed by a multidisciplinary team. This also could have led to a lower yield for staging laparoscopy for LAPC compared to earlier studies.

Systemic chemotherapy with FOLFIRINOX has become the standard initial treatment for LAPC patients with a good performance status. While no randomized controlled trial (RCT) has been published, a patient-level meta-analysis of FOLFIRINOX for LAPC found a median OS of 24 months.[14] In this meta-analysis, 64% received additional radiotherapy, and 62% eventually underwent a curative-intent resection. A systematic review found no RCT to evaluate the benefit of ablative treatments, such as radiofrequency ablation (RFA) and irreversible electroporation (IRE), for LAPC patients.[15] A more recent RCT randomized 269 LAPC patients with progression-free disease after 4 months of systemic treatment to continuation of systemic treatment or chemoradiotherapy. No difference in OS could be demonstrated with a hazard ratio of 1.03 [95% CI: 0.79-1.34; p=0.83].[16] All ablative treatments have a small but real risk of mortality.[14, 15, 17] While an OS benefit of ablative treatment has not been definitively shown for LAPC patients, it is even less likely that LAPC patients with occult metastatic disease benefit from ablative treatments. Staging laparoscopy in patients with LAPC could improve patient selection in clinical trials. A risk of occult metastatic disease of about 20% in LAPC patients seems to justify a staging laparoscopy prior to consideration of ablative treatments. In the Netherlands, several local ablative therapies are studied as subsequent treatment after systemic chemotherapy for LAPC

patients. Currently, three ongoing clinical trials examine the safety and potential survival benefit of SBRT (ClinicalTrials.gov Identifier: NCT02292745), IRE (ClinicalTrials.gov Identifier: NCT02791503), and RFA ClinicalTrials.gov Identifier: NCT03690323).

Radiological imaging is advancing fast with more modalities that aim to detect occult metastasis not visible on tri-phasic CT. MRI, 18FDG-PET/CT scan, and contrast-enhanced ultrasonography all have their benefits and pitfalls for detecting occult metastasis in pancreatic cancer. However, superior diagnostic accuracy over CT-scan has not been definitively shown for any of these modalities.[18] Furthermore, if these new modalities raise the suspicion of metastatic disease, a biopsy with pathological confirmation is still required. A biopsy of subcentimeter lesions in the liver or lung can be challenging. The advantage of staging laparoscopy over additional imaging is that pathological confirmation of occult metastatic disease can be obtained. Circulating tumor cells are being examined as a staging parameter in pancreatic cancer.[19-21] However, the results are still not definitive for clinical use.

Serum CEA was the only independent predictive factor for occult metastasis found with staging laparoscopy. Patients with a CEA above 5 µg/L had a risk of occult metastasis of 91%. Although these patients have a particularly high risk of the presence of occult metastases, this risk is still 4% in patients with a CEA below 5. We believe that a staging laparoscopy is justified even in LAPC patients with a somewhat lower risk of occult metastases, as a low CEA level does not exclude the presence of occult metastasis.[22, 23] Despite higher CEA levels have been associated with metastatic disease in pancreatic cancer, no definite conclusions on which CEA cutoff level should be used.[24]

The 1-year OS in patients without occult metastases was 51% . This was similar to a recent patient-level meta-analysis, in which 1-year OS ranged from 33 to 96% across studies.[14] The 1-year OS for patients that completed FOLFIRINOX and radiotherapy was 84%. Although FOLFIRINOX is currently the most effective treatment for patients with LAPC, better treatments are clearly needed.

The main limitation of our study is that some data (e.g., tumor markers) were collected retrospectively, and therefore sometimes missing. Secondly, we used the Dutch Pancreatic Cancer Group definition for LAPC; some of the included patients would have been classified as borderline resectable when using the NCCN and AHPBA/SSO/SSAT classifications.[10, 25, 26] This could have led to an underestimation of the yield of staging laparoscopy in LAPC patients. Furthermore, the management for borderline resectable pancreatic cancer in the Netherlands is upfront surgery or in a trial setting neoadjuvant chemoradiotherapy followed by surgery. Therefore, the definitions are of influence on the treatment strategy.[10] In addition, we included only patients with a good performance who were eligible for FOLFIRINOX and subsequent radiotherapy. We performed staging laparoscopy prior to systemic

treatment, since we offer all patients without progressive disease SBRT in order to improve the R0 resection rate. Although only 14% of patients in our study underwent a resection, the resection margins were negative in all patients. The drawback of this approach is that initial treatment with systemic chemotherapy remains the same whether or not occult metastases are found. However, about 35% of patients respond to FOLFIRINOX with the risk that small peritoneal and liver lesions disappear and are not found at staging laparoscopy after FOLFIRINOX. These patients would not benefit from SBRT, as in the treatment of metastatic disease there are no studies supporting radiotherapy for metastatic pancreatic cancer.[27]

In conclusion, staging laparoscopy upstages 19% of patients with LAPC to metastatic disease. Patients with (occult) metastatic disease are less likely to benefit from local therapy. Therefore, staging laparoscopy should be included in the pretreatment work-up for patients with LAPC if local therapy is considered.

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Part II
Treatment of LAPC

Chapter 4

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

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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.

Funding

No funding has been received for this work.

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).

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.

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

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.

Methods

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/m2) followed by a 2-h intravenous infusion of leucovorin (400 mg/m2) concomitantly with a 90-min intravenous infusion of irinotecan (180 mg/m2), followed by a bolus (400 mg/m2) and a 46-h continuous infusion (2,400 mg/m2) 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 2nd, 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 appendix A, 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 appendix B. Figure 1 presents the flowchart.

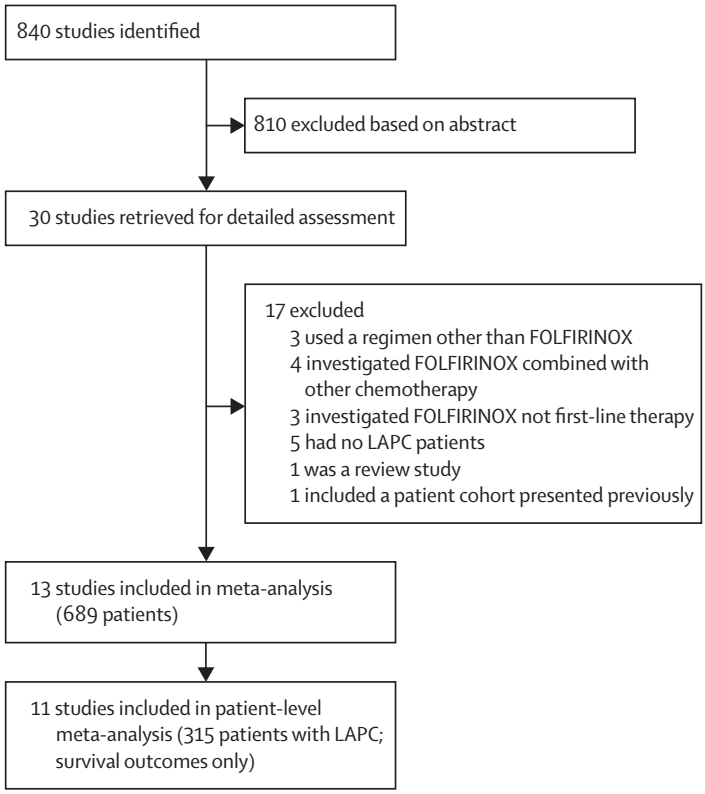

Figure 1. Flowchart of the included studies.

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 appendix C.

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]

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	15
Hosein (24)	2012	USA	2008-2011	18	58 (41-73)	-	4	14	-	-
Mahaseth (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	-	-
Total				689		87	49	355	183	15

* Median age of patients who received FOLFIRINOX.

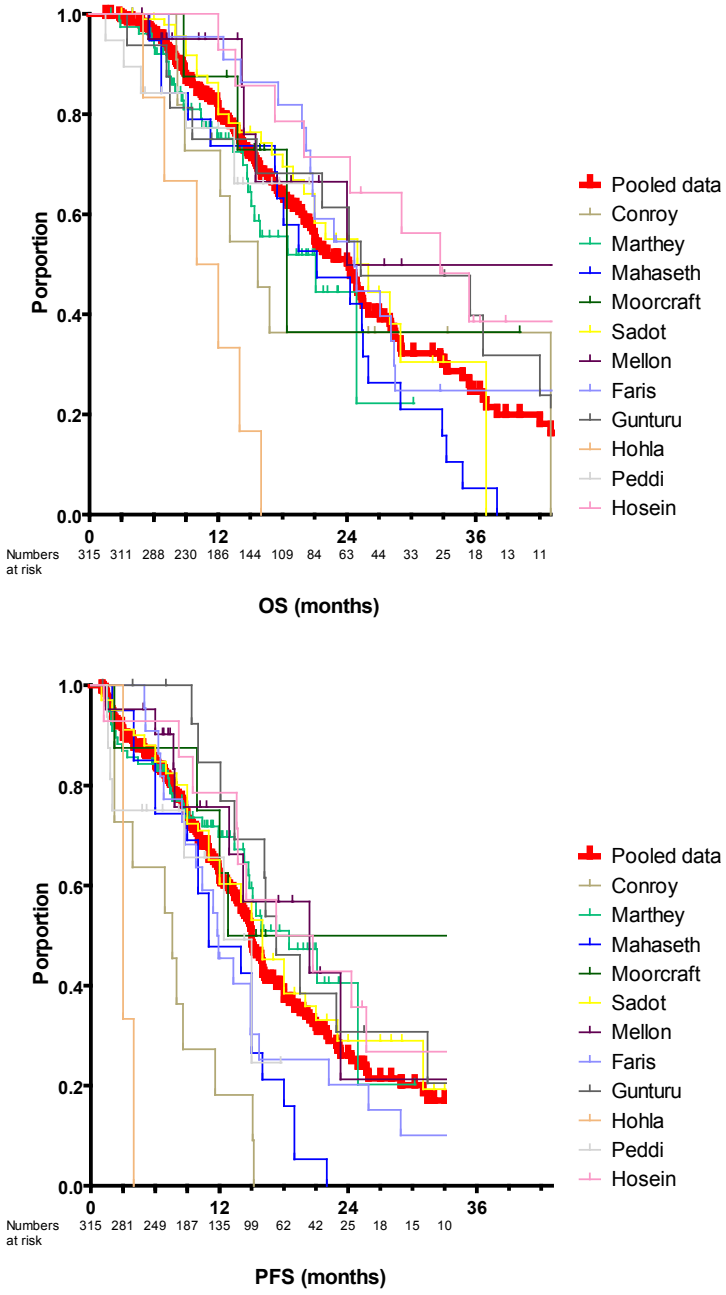

Figure 2. Kaplan-Meier survival curves for PFS and OS. Numbers at risk at x-axis are the number of patients at risk for the pooled data.

No significant correlation was found across studies between the median number of cycles and median OS (p=0·95) (appendix D).

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
Pooled patient-level data	**315**	**12,3 (8,0-20,5)**	**15,0**	**24,2**

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

IQR: Interquartile range

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.

Table 4. Grade 3 or 4 adverse events.

Author	Patients	Grade 3 or 4 AE	Neutropenia	Fatigue	Diarrhea	Vomiting	Thrombocytopenia	Neuro-pathy	Febrile neutropenia	Unspe-cified	Anemia	Nausea	Thromboembolism	Abdominal pain	Mucositis	Infection	Leukopenia	Allergic reaction	Elevated ALT, AST	Anorexia	Hypoalbuminia	Alopecia	Hand-foot syndrome
Boone (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	
Faris (22)	22	8	4				1		0				1						2				
Gunturu (25)	35	9	4	2	1	1	1	0	0		0												
Hosein (24)	18	16	4	2	2		3	0	3		2	0			0					0		0	
Mahaseth (20)	60	35	2	8	8	5	3	3	0						1	3		2					
Marthey (26)	77	30	9	5	5	7	0	3			1				0							0	0
Moorcraft (27)	49	59	14	9	2	2	5	2	7	7	2	1	6		2								
Sadot (30)	101	14																					
Peddi (21)	61	34	12	3	2		2		3	7	0			5									
Total (number of events/100 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.

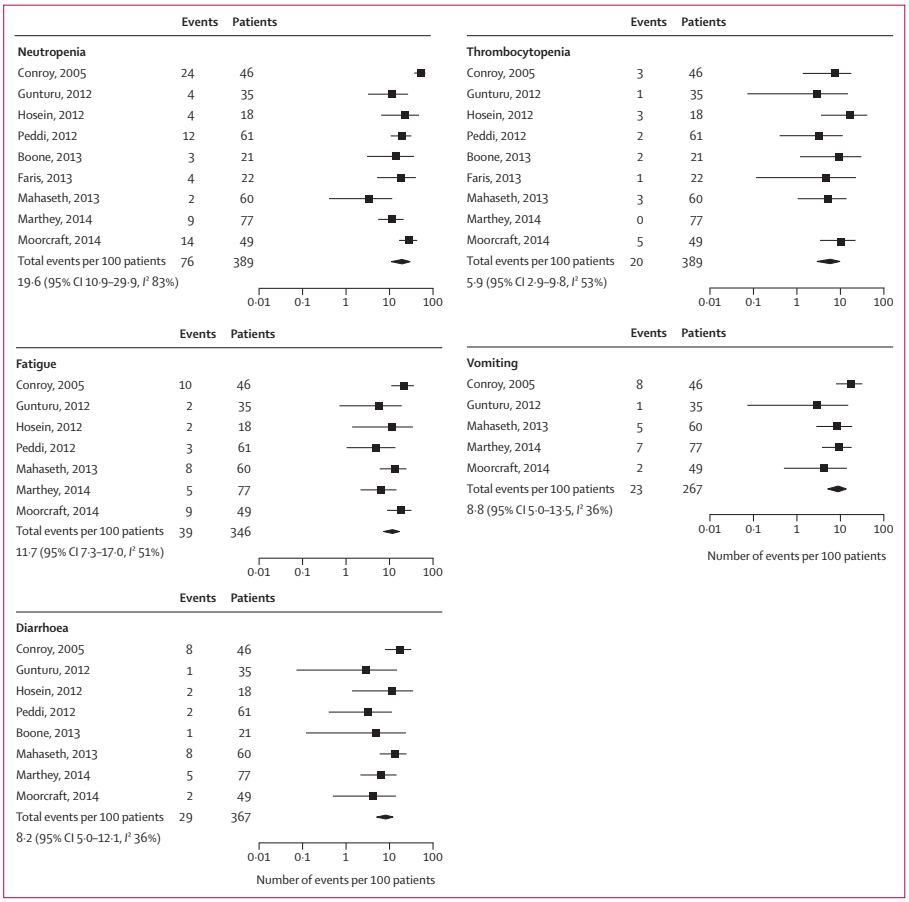

Figure 3. Forest plots of reported grade 3 or 4 adverse event rates.

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.

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]

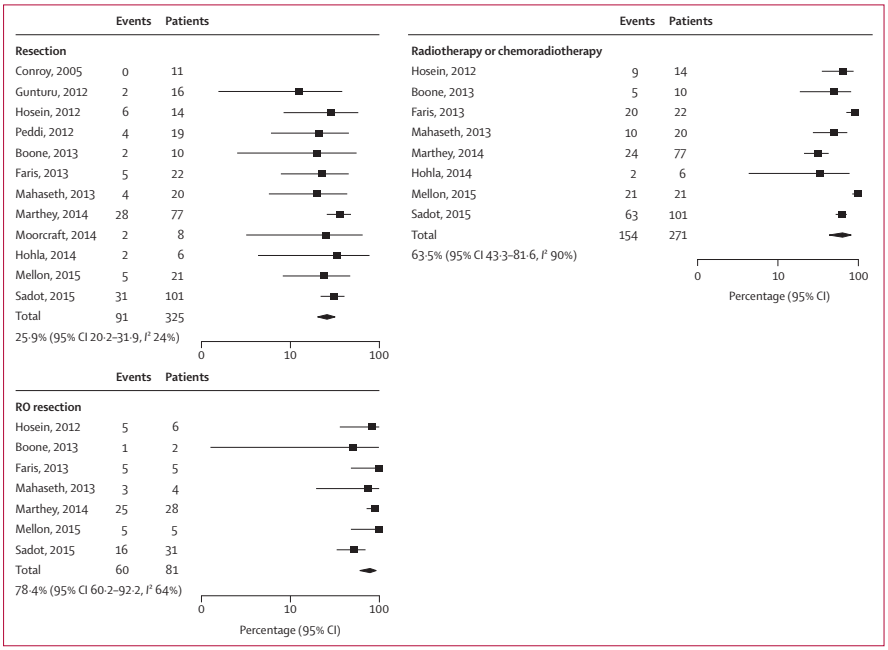

Figure 4. Forest plots of the percentage of (chemo)radiation, resection, and R0 resection.

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 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%)
Total	**325**	**154 (57%)**	**91 (28%)**	**60 (74%)**

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

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) (appendix D).

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) (appendix D).

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]

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.

Dr. Mellon reports personal fees from Elekta, outside the submitted work.

Dr. Taieb reports personal fees from Roche, personal fees from AMGEN, personal fees from Merck, personal fees from Calgene, personal fees from Lilly, personal fees from Sanofi, outside the submitted work.Dr. El-Rayes reports personal fees from Genentech/Roche, personal fees from Merrimack, grants from Taiho Pharmaceutical, grants from Bristol-Myers Suibb, grants from Boston Biomedical, grants from Cleave Bioscinies, grants from Genentech, grants from AVEO, grants from Pfizer, outside the submitted work; .Dr. Lacy reports personal fees from Sirtex Medical, outside the submitted work.

Dr. Allen reports grants from Novartis, personal fees from Sanofi, outside the submitted work.

The other authors declared no conflicts of interest.

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Appendix A

Table 1. Articles retrieved from different electronic databases.

Electronic database	Retrieved	Unique studies
Embase.com	741	730
Medline (OvidSP)	163	14
Web-of-science	199	43
Scopus	194	12
PubMed publisher	7	3
Cochrane central	12	0
Google scholar	100	38
Total	**1416**	**840**

Last search in electronic databases performed on the 2nd of July 2015.

Detailed search strategy

Embase.com

((‘folinic acid’/exp AND fluorouracil/exp AND irinotecan/exp AND oxaliplatin/exp AND ‘drug combination’/exp AND (‘pancreas cancer’/de OR ‘pancreas tumor’/de OR ‘pancreas adenoma’/de OR ‘pancreas adenocarcinoma’/de OR ‘pancreas carcinoma’/de OR ‘pancreas islet cell carcinoma’/de OR (pancrea* NEAR/3 (cancer* OR neoplas* OR tumo* OR adenocarcinom* OR carcinom* OR adenom*)):ab,ti)) OR (Folfirinox):ab,ti)

Medline (OvidSP)

((Leucovorin/ AND fluorouracil/ AND irinotecan.mp. AND oxaliplatin.mp. AND Drug Combinations/ AND (expPancreatic Neoplasms/ OR (pancrea* ADJ3 (cancer* OR neoplas* OR tumo* OR adenocarcinom* OR carcinom* OR adenom*)).ab,ti.)) OR (Folfirinox).ab,ti.)

Cochrane

(Folfirinox):ab,ti

PubMed publisher

Folfirinox[tiab] AND publisher[sb]

Web-of-science

TS=(Folfirinox)

Google scholar

Folfirinox

Scopus

TITLE-ABS-KEY(Folfirinox)

Appendix B

Excluded studies after full text assessment

1. Paniccia A, Edil BH, Schulick RD, et al: Neoadjuvant FOLFIRINOX application in borderline resectable pancreatic adenocarcinoma. Medicine 93, 2014
2. Conroy T, Gavoille C, Samalin E, et al: The role of the FOLFIRINOX regimen for advanced pancreatic cancer. Curr Oncol Rep 15:182-189, 2013
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Appendix C

Table 1. Quality assessment according to Critical Appraisal Skill Program.

CASP factors	Boone	Conroy	Faris	Ferrone	Gunturu	Hohla	Hosein	Mahaseth	Marthey	Mellon	Moorcraft	Peddi	Sadot
Clearly focused question	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Appropriate design	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Appropriate recruitment	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Operation clearly defined	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Appropriate outcomes used	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Confounding factors identified	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Confounding factors accounted	Yes	Yes	NR	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Follow-up complete enough	No	Yes	No	Yes	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Suitable duration of follow-up	No	Yes	No	No	No	NR	No	NR	Yes	Yes	Yes	No	Yes
Precise statistical results presented	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Appropriate interpretation	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Possible bias acknowledged	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ability to generalise results	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Interpretation related to the existing evidence	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

NR = Not Reported

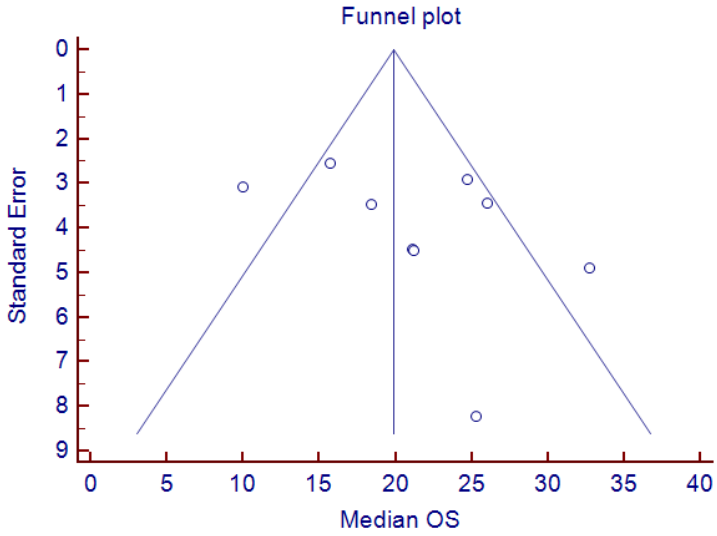


Figure 1. Funnel plot of the survival studies.

Two studies are not shown in this funnel plot as Peddi et al. did not reach the median OS and Mellon et al. did not have a sufficient number of events to calculate the standard error. Therefore the median OS in this funnel plot differ slightly from the pooled analysis.

Appendix D

Figure 1. Median number of FOLFIRINOX cycles and median OS across studies (p=0·95).

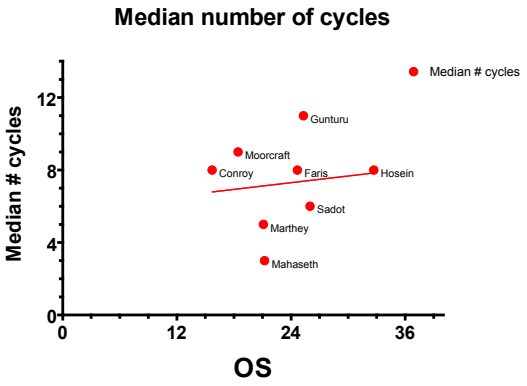


Figure 2. Percentage of (chemo)radiation and median OS across studies (p=0·12).

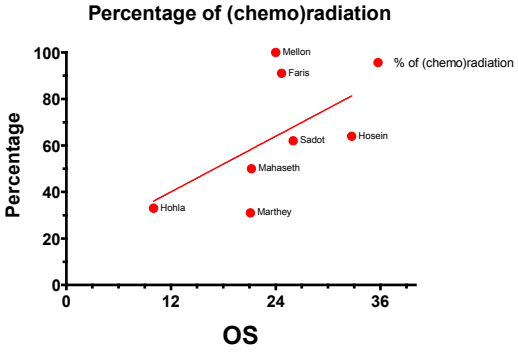
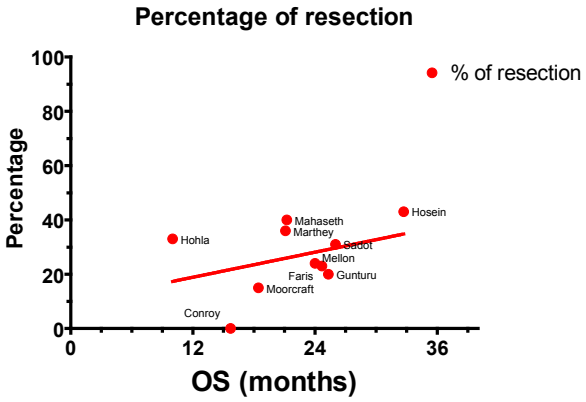


Figure 3. Percentage of resection and median OS across studies (p=0·39).



Chapter 5

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

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Abstract

Introduction:

One-third of patients with pancreatic cancer present with locally advanced unresectable pancreatic cancer (LAPC). Our aim was to determine survival outcomes and toxicity after FOLFIRINOX followed by radiotherapy in biopsy-proven LAPC patients.

Methods:

We analyzed a cohort of biopsy-proven LAPC patients, who were eligible for induction FOLFIRINOX (8 cycles) and subsequent radiotherapy (30 fractions, 60 Gray). Eligible patients underwent a staging laparoscopy to detect occult metastasis prior to 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 prior to 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 radiotherapy, with 16 (94%) receiving the full dosage. Three (14%) patients underwent a radical resection after treatment. Median OS was 15.4 months (95% CI 10.0-20.7), median PFS was 11.0 months (95% CI 7.7 – 14.4).

Conclusions:

Median OS after FOLFIRINOX and radiotherapy was 15 months in patients with LAPC. Toxicity remains severe, however most patients completed all 8 scheduled cycles of FOLFIRINOX and radiotherapy.

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death, with projections to be the second leading cause of cancer-related death 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, 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. The Dutch Pancreatic Cancer Group has defined LAPC as venous tumor contact exceeding 270 degrees or arterial contact exceeding 90 degrees (table 1) without distant metastases.[3] The initial treatment for LAPC is 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 OS compared to gemcitabine in patients with metastatic disease (median OS 11.1 versus 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 metastatic disease during FOLFIRINOX may benefit from subsequent radiotherapy for local control.[4]

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

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 (EMC) 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 radiotherapy. Furthermore, all patients that 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 superior mesenteric artery (SMA), coeliac artery, or common hepatic artery exceeding 90 degrees or contact with the superior mesenteric vein or portal vein exceeding 270 degrees on computed tomography (CT) scan, in the absence of metastatic disease.[3]

Table 1. Baseline characteristics.

	FOLFIRINOX (N=22)	No FOLFIRINOX (N=19)	p=
Age, median [IQR]	62 [52-67]	62 [53-67]	0.33
Gender			0.74
Male	6	7	
Female	16	12	
WHO			<0.001
0-1	22	9	
2-4	0	10	
Jaundice			
Yes	9	9	0.76
No	13	10	
Weight loss			
Yes	15	14	0.74
No	7	5	
Diabetes			
Yes	4	4	1.00
No	18	15	
Abdominal pain			
Yes	21	17	0.59
No	1	2	
BMI, median [IQR]	23 [22-25]	23 [20-28]	0.90
Tumor origin			
Head	13	12	0.23
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

Patients were eligible for FOLFIRINOX and radiotherapy if they had a World Health Organization (WHO) Performance status of 0 or 1, and were not older than 75 years old. The diagnostic work-up of patients with suspicion of LAPC consists of a computed tomography (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-h intravenous infusion of oxaliplatin (85 mg/m^2) followed by a 2-h intravenous infusion of leucovorin (400 mg/m^2) concomitantly with a 90-min intravenous infusion of irinotecan (180 mg/m^2), followed by a bolus (400 mg/m^2) and a 46-h continuous infusion (2400 mg/m^2) of fluorouracil.[5] The duration of a cycle was 2 weeks.(7) Patients were scheduled for 8 cycles of FOLFIRINOX. Surveillance imaging was performed after 4 and 8 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 radiotherapy after 8 cycles of FOLFIRINOX or earlier if the FOLFIRINOX treatment was discontinued because of toxicity. Dose reduction of 25% were 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 radiotherapy, 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 National Cancer Institute (NCI) Common Toxicity Criteria (CTC 4.0).

Overall survival (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 SPSS (version 21).

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), and no staging laparoscopy performed prior to treatment (n=4). These four patients received 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 or best supportive care. Baseline patient and tumor characteristics were similar between the FOLFIRINOX with RT group versus other LAPC patients, except for the high rate of poor performance status in the latter (table 1).

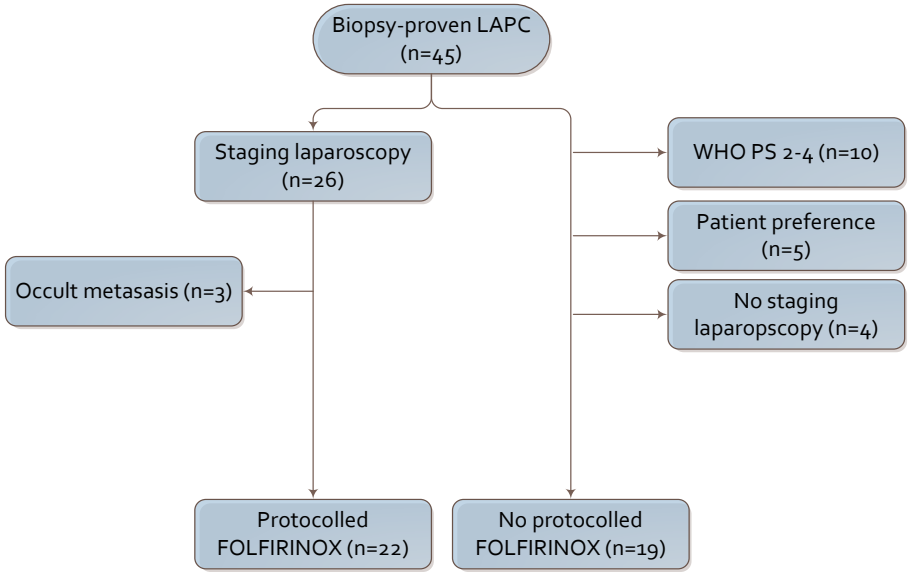

Figure 1. Flowchart of the study population.

Patients that were eligible for the standard care received a median of 8 cycles of FOLFIRINOX (range 2-9), with 4 (18%) patients receiving less than 5 cycles and 18 (82%) patients receiving at least 7 cycles. The reasons for termination of the FOLFIRINOX after less than 5 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 (GCSF) analogs were prescribed for any patients 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 radiotherapy due to deterioration of patients' condition(n=3), distant progressive disease under FOLFIRINOX (n=2). The remaining 17 (77%) patients received radiotherapy; 16 (94%) received the full dose of 60 Gray and only 1 (6%) patient received 52 Gray 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.

At last follow-up, all 22 patients died of progressive disease. The median PFS and OS of the group "protocolled FOLFIRINOX" (n=22) was 11.0 months (95% 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 radiotherapy (n=17) was 18.7 months (95% CI 13.4 -23.9). The median OS of "protocolled FOLFIRINOX" (n=22) from date of histopathological confirmation until date of death was 16.3 months (95% CI 11.4 – 21.2). In comparison, the patients that did not receive protocolled FOLFIRINOX and radiotherapy (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%).

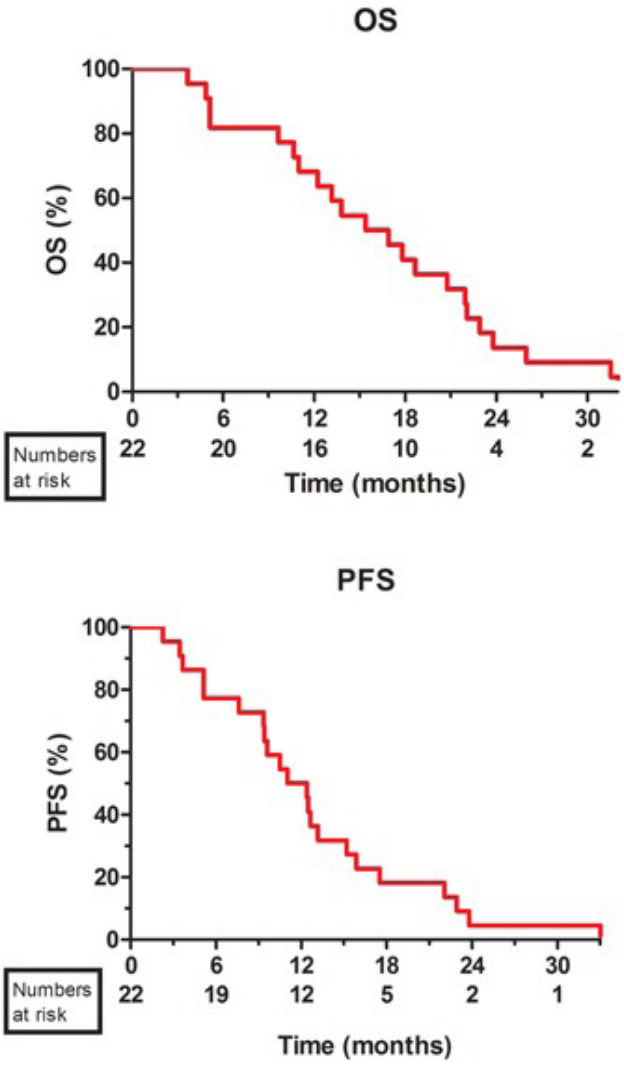

Figure 2. Kaplan-Meier curves of OS and PFS for the patients treated with FOLFIRINOX.

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 (n = 1), gastro-intestinal bleeding (n=1), and ascites (n = 1). All serious adverse events of the FOLFIRINOX treatment are summarized in table 3. No deaths were attributed to FOLFIRINOX. Only 1 (6%) patient had a serious adverse event of grade 3 of diarrhea during radiotherapy.

Three (14%) patients underwent an exploratory laparotomy patients after FOLFIRINOX and radiotherapy. 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. All two (100%) resections were radical (R0, closest margin > 1mm). Survival time after resection was 16 and 10 months in two patients with a partial response in histopathological examination.

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

GI: gastro-intestinal, ALT: alanine transaminase, AST: aspartate transaminase

Discussion

In this cohort study, 22 patients with LAPC received FOLFIRINOX with subsequent conventional radiotherapy. The median OS was 15 months and the PFS 11 months. Most patients (77%) completed both chemotherapy and radiotherapy. 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 versus 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 are published that confirmed a 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 15.0 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 staging laparoscopy prior to treatment to rule out 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]

Radiotherapy had a very low rate of serious adverse events (6%) in our study and therefore is safe to give as subsequent treatment after first-line FOLFIRNOX. However, whether conventional radiotherapy improves survival for LAPC patients has not been evaluated in a randomized controlled trial.[4] In regard of chemoradiotherapy, in 2016 Hammel et al. 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 versus chemoradiotherapy (54 Gy plus capecitabine).[24] 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 overall survival benefit between continuing chemotherapy or subsequent chemoradiotherapy after induction chemotherapy with a median survival of 16.5 versus 15.2 months respectively. The major disadvantage of conventional fractionated radiotherapy for pancreatic cancer is that although the pancreas is relatively radioresistant the surrounding organs are highly radiosensitive.[25] In the last years stereotactic body radiotherapy (SBRT) has emerged as the preferred radiotherapy after systemic chemotherapy for LAPC. SBRT allows for a higher dose of radiotherapy 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 and colleagues when SBRT was given as therapy for borderline resectable and locally advanced pancreatic cancer after induction chemotherapy.[27]

In our study, two (9%) patients underwent a resection with, both being a radical resection. This rate was lower than the pooled resection rate of 28% 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 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 studies resection rate and survival. Some studies report remarkable survival outcomes in LAPC patients after induction FOLFIRINOX and resection. However, these patients are highly selected and the favorable outcomes may be largely attributable to guaranteed-time bias.[28, 29] The most recent ASCO guideline advices that all patients with LAPC should receive first-line chemotherapy with or without radiotherapy and surgery should be only considered if 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 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 that received 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. Additionally, conventional radiotherapy 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 radiotherapy can be offered to a limited number of patients but it could be considered as safe and shows promising survival results for patients with LAPC. Randomized controlled trials are needed to determine the value of radiotherapy, and resection in addition to FOLFIRINOX in patients with LAPC.

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Chapter 6

Efficacy and feasibility of stereotactic radiotherapy after FOLFIRINOX in patients with locally advanced pancreatic cancer (LAPC-1 trial)

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Submitted

Abstract

Purpose:

Patients with locally advanced pancreatic cancer (LAPC) benefit from a standardized treatment regimen of systemic therapy followed by local therapy. We conducted a multicenter phase II trial to investigate feasibility and antitumor activity of sequential FOLFIRINOX and Stereotactic Body Radiotherapy (SBRT) in patients with LAPC (LAPC-1 trial).

Methods:

A single-arm, open-label multicenter phase 2 trial. Patients with biopsy-proven LAPC treated in four hospitals in the Netherlands between December 2014 and June 2017. Inclusion criteria consisted of World Health Organization performance status 0-1 and adequate hematologic, renal, and hepatic function. All patients underwent a staging laparoscopy prior to treatment and a restaging CT-scan after FOLFIRINOX was finished prior to SBRT. Patients were followed with CT scans to consider potential resectability. Patients received 8 cycles of FOLFIRINOX followed by SBRT (5 fractions/8Gy) if no tumor progression after the FOLFIRINOX treatment was observed. Following SBRT, resection was considered in case tumor downstaging was seen on restaging CT scans. Primary outcome was the 1-year overall survival (OS) rate. Secondary outcomes were median OS, 1-year progression-free survival (PFS) rate, treatment-related toxicity, and resection rate.

Results:

Fifty patients were included. Nineteen (38%) patients did not receive all 8 cycles of FOLFIRINOX, due to toxicity (n=12), disease progression (n=6), or patients' preference (n=1). Thirty-nine (78%) patients received the assigned dose of SBRT . The 1-year OS and PFS rates were 64% (95% CI: 50%-76%) and 34% (95% CI: 22%-48%), respectively. Thirty grade 3 or 4 adverse events were observed during FOLFIRINOX. Two (5%) grade 3 or 4 adverse events after SBRT were observed. Two (5%) grade 5 adverse events consisting of gastro-intestinal bleeding within three months after SBRT were observed. Six (12%) patients underwent exploratory laparotomy, all resulting in a complete (R0) resection. Two patients had a complete pathological response.

Conclusions:

FOLFIRINOX followed by SBRT in patients with LAPC is feasible and shows relevant antitumor activity. In 6 (12%) patients a potentially curative resection could be pursued following this combined treatment, with a complete histological response being observed in two patients.

Trial registration:
ClinicalTrials.gov Identifier: NCT02292745

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death with an estimated 5 year survival rate of approximately 5%.[1] At the time of diagnosis, approximately 15% of patients have (borderline) resectable disease (stage I or II), while 35% and 50% of patients present with irresectable locally advanced pancreatic cancer (LAPC, stage III)or metastatic disease (stage IV), respectively.[2] LAPC is determined by the extent of tumor contact with the superior mesenteric artery (SMA), celiac artery (CA), common hepatic artery (CHA), superior mesenteric vein (SMV), and portal vein (PV).[3] The risk of a positive resection margin increases with increasing tumor contact with arteries and/or veins. Several definitions for LAPC vary in defining the extent of tumor contact with the surrounding blood vessels.[4]

As part of current standards, LAPC is usually treated with induction chemotherapy followed by local therapies such as (chemo)radiotherapy or local ablation.[5] Surgery can be considered as salvage option following (chemo)radiotherapy in the absence of disease progression.[6]

Based upon the observed activity of FOLFIRINOX in patients with metastatic pancreatic cancer [7], several case series of FOLFIRINOX in patients with LAPC have been published.[8] These case series have shown a potential survival benefit of FOLFIRINOX treatment for patients with LAPC.[9]

In patients with LAPC, subsequent consolidation treatment after first-line chemotherapy is often considered in the absence of tumor progression.[6] Conventional (chemo)radiotherapy is most frequently used .[8] However, there is a disadvantage to conventional radiation due to its lack of selective tumor targeting .[6] Stereotactic Body Radiotherapy (SBRT) could possibly improve antitumor activity while limiting scattering to surrounding organs.[10] No prospective phase II trials investigating the role of sequential FOLFIRINOX and SBRT in patients with LAPC have been published to date.[11]

We conducted a multicenter phase II trial to investigate feasibility and antitumor activity of sequential FOLFIRINOX and Stereotactic Body Radiotherapy (SBRT) in patients with LAPC (LAPC-1 trial).

Methods

Between December 2014 and June 2017 all consecutive patients with biopsy-proven LAPC from four participating hospitals were enrolled in this study . The diagnostic work-up included a tri-phasic CT-scan of abdomen and thorax followed by staging laparoscopy. LAPC was defined according to the Dutch guidelines as tumor contact

with the SMA, CA, or CHA exceeding 90 degrees or contact with the SMV or PV exceeding 270 degrees.[12] All patients gave written informed consent prior to any study-related procedure (ClinicalTrials.gov Identifier: NCT02292745).

The inclusion criteria were biopsy-proven LAPC, age 18-75 years, World Health Organization (WHO) performance status ≤1, ASA classification ≤1, no evidence of metastatic disease, largest diameter of tumor ≤7 centimeter, normal renal, bone marrow, and liver function. Exclusion criteria were prior abdominal radiotherapy, lymph node metastasis outside the radiation field, tumor ingrowth into stomach, other invasive malignancies diagnosed within 3-years, pregnancy or breastfeeding, serious concomitant disorders that comprise the safety of the patient.

FOLFIRINOX was started within one month after CT-scan and staging laparoscopy in all patients. Standard FOLFIRINOX (2-h intravenous infusion of oxaliplatin (85 mg/m^2) followed by a 2-h intravenous infusion of leucovorin (400 mg/m^2) concomitantly with a 90-min intravenous infusion of irinotecan (180 mg/m^2), followed by a bolus (400 mg/m^2) and a 46-h continuous infusion (2400 mg/m^2) of fluorouracil) was given once every two weeks for up to 8 cycles. Dose reductions and delays were according to local practice. In cases of persisting toxicity following two dose reductions, FOLFIRINOX was discontinued.

Routine CT scans were performed after 4 and 8 cycles FOLFIRINOX. Patients in whom no disease progression was observed after the completion of FOLFIRINOX received SBRT consisting of daily fractions of 8 Gray, for a total dose of 40 Gray . Endoscopy was performed to implant three fiducials close to or within the tumor prior to the SBRT. A CT-scan was performed 3 and 6 months after SBRT. If the tumor was deemed resectable and no metastatic lesions were seen, an exploratory laparotomy was performed. Resectability was defined as arterial tumor contact less than 90 degrees and venous tumor contact less than 270 degrees.

The primary outcome of this study was the 1-year OS rate. The secondary objectives were 1-year progression free survival (PFS) rate, treatment related toxicity, locoregional PFS, metastatic PFS, and resection rate. OS was calculated from the start of the FOLFIRINOX to the date of death. PFS was calculated from the start of FOLFIRINOX to the date of progression or death. Survival functions were estimated using the Kaplan-Meier method in SPSS (version 21). Adverse events were graded using National Cancer Institute (NCI) Common Toxicity Criteria (CTC 4.0). Radiological responses were assessed using RECIST 1.1.[13] Histopathological response was graded by the tumor regression grading of the College of American Pathologists.[14]

The 1-year OS rate in a historical cohort of patients within our institution with LAPC treated with the combination of Uracil/Tegafur plus leucovorin and celecoxib in combination with conventional radiotherapy was 40%.[15] We hypothesized that with the current treatment sequence a 1-year survival rate of 60% could be achievable.

Calculations were made with a two-sided 5% significance test, a power of 80%, and a 20% dropout rate. Using Hern's design for non-randomized phase II trials, a minimum of 51 patients was needed for this study, to be able to include 42 patients for the final analysis.[16]

Results

Seventy-two patients were eligible and gave informed consent . Eighteen (25%) patients were found to have metastatic disease at staging laparoscopy, three patients had metastatic disease after restaging imaging before treatment. 51 patients could start the assigned treatments. One patient withdrew consent before treatment (Figure 1). In the final Intention to Treat analysis, 50 patients (50% males, median age 63 years) were included. The tumor was located in the pancreatic head in 29 (58%) patients, pancreatic body in 19 (38%) patients, and pancreatic tail in 2 (4%) patients. Median tumor size was 40 mm [IQR 30-46]. The median pretreatment serum levels of CA19-9 and CEA were 171 kU/l [IQR 56 - 876] and 4.2 ug/l [IQR 3.0 – 10.0], respectively. The median time between staging laparoscopy and start of treatment was 18 days [IQR 12 - 22]. All baseline characteristics are shown in table 1.

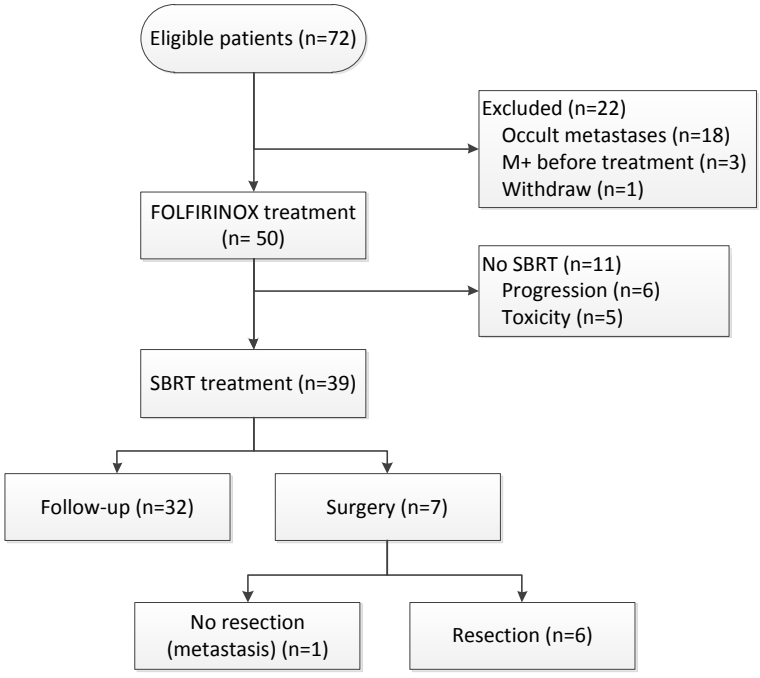


Figure 1. Flowchart of the included patients.

Table 1. Baseline characteristics.

Baseline characteristics	N=50 (%) or [IQR]
Age, median	63 [53-68]
Gender, male	25 (50)
BMI	23.8 [21.6 – 27.6]
Tumor origin	
Head	29 (58)
Body	19 (38)
Tail	2 (4)
Pretreatment median CA 19.9 (µg/L)	171 [56-876]
Jaundice	21 (42)
Pretreatment median CEA (kU/L)	4.2 [3.0-10.0]
Diabetes	12 (24)
Abdominal pain	
Yes	39 (78)
Missing	1 (2)
Weight loss	
Yes	39 (78)
Missing	6 (12)
Maximum tumor size (mm), median	40 [12-22]
Vascular involvement	
Venous >270 degrees	7 (14)
Arterial >90 degrees	10 (20)
Both	33 (66)

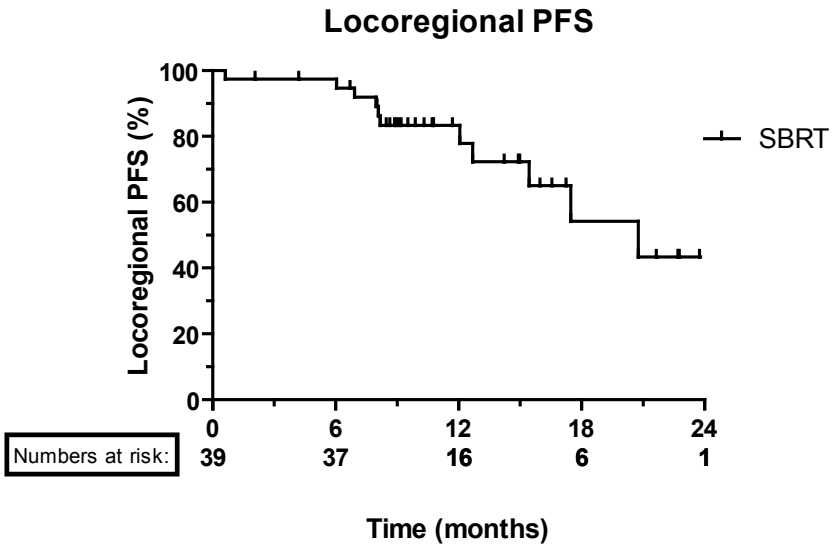
FOLFIRINOX was given to all 50 patients with a median of 8 cycles [IQR 4-8], with 43 (86%) patients completing 4 or more cycles. The reasons for not completing the assigned chemotherapy were toxicity (n=14), disease progression (n=6), and patient's preference (n=1). Dose reductions were applied in 46% of patients. Thirty grade 3 or 4 adverse events during the FOLFIRINOX mainly consisted of diarrhea (n=10), infection (n=8), vomiting (n=4), hepatic toxicity (n=2), neuropathy (n=1), gastro-intestinal perforation (=1), mucositis (n=1), and fatigue (n=1). No deaths were attributed to FOLFIRINOX. Sequential to FOLFIRINOX, 39 (78%) patients received SBRT. All patients received the assigned dose of 40 Gray. One (3%) patient had a grade 3 vomiting as adverse event, one (3%) patient a grade 4 gastro-intestinal bleeding after SBRT and two (5%) patients had a grade 5 gastro-intestinal bleeding after SBRT. Both events were observed within three months after completing SBRT. In one patient a duodenal-pancreatic fistula with an aneurysm of the AMS was diagnosed, while one patient refused any further diagnostics. All adverse events of FOLFIRINOX and SBRT are summarized in table 2.

Table 2. Grade 3 or higher adverse events for FOLFIRINOX and SBRT.

	FOLFIRINOX		SBRT		
Description	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 5**
Diarrhea	9	1	-	-	-
Infection	5	3	-	-	-
Vomiting	1	3	1	-	-
Liver toxicity	2	-	-	-	-
Neuropathy	1	-	-	-	-
GI bleeding	-	1	-	1	2
Mucositis	1	-	-	-	-
Fatigue	-	1	-	-	-
Other	2	-	-	-	-
Total	**21**	**9**	**1**	**1**	**2**

After FOLFIRINOX and SBRT treatment, four (10%) patients showed local progression, 19 (49%) distant progression, and four (10%) patients both distant and local progression. Seven (14%) patients underwent an explorative laparotomy of whom six patients underwent a potentially curative resection. One patient did not undergo a resection due to a solitary 3 mm occult liver metastasis found during the operation. Histopathological examination showed a complete histological response in two (33%) patients, moderate response in three (50%) patients, and no histological response in one (17%) patient.. In all patients resection margins were negative (e.g., closest margin > 1mm).

All patients had a minimum follow-up of 1 year, with a median follow-up of 29 months (95% CI 23-36). The 1-year OS rate in the intention to treat population was 64% (95% CI 50-76). The 1-year PFS rate was 34% (95% CI 22-48). OS and PFS rates are shown in figure 2. The median OS and PFS were 15 (95% CI 11-18)and 9 months (95% CI: 8-10), respectively. The 1-year OS rates for patients who had finished their assigned SBRT was 79% (95% CI 65-89), while the 1-year OS rate for patients who had also undergone curative resection was 83% (95% CI 44-97). The median OS for patients who had finished SBRT was 17 months (95% CI 14-21) and was 7 months (95% CI 6-8) in patients who had not received SBRT ($p<0.001$). The median OS for the six patients that underwent resection was 23 months (95% CI 13-34). The median OS after starting SBRT was 10 months (95% CI 7-12). Median locoregional PFS in all patients was 17 months (95% CI 11-24), 20 months (95% CI 14-28) for the SBRT group and 3 months (95% CI 2-4) for the non-SBRT group ($p<0.001$). The median distant PFS in all patients was 11 months (95% CI 10-12), for the SBRT group 11 months (95% CI 9-13), and 3 months (95% CI 2-4) in the non SBRT group ($p<0.001$). The locoregional and metastasis PFS are shown in figure 3.



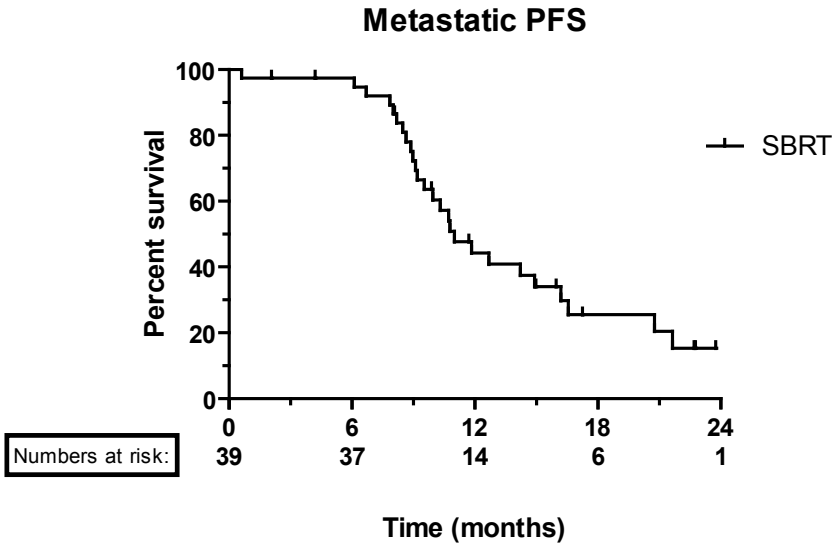


Figure 2. Kaplan-Meier of overall survival (OS), and progression free survival (PFS) of all patients (N=50).

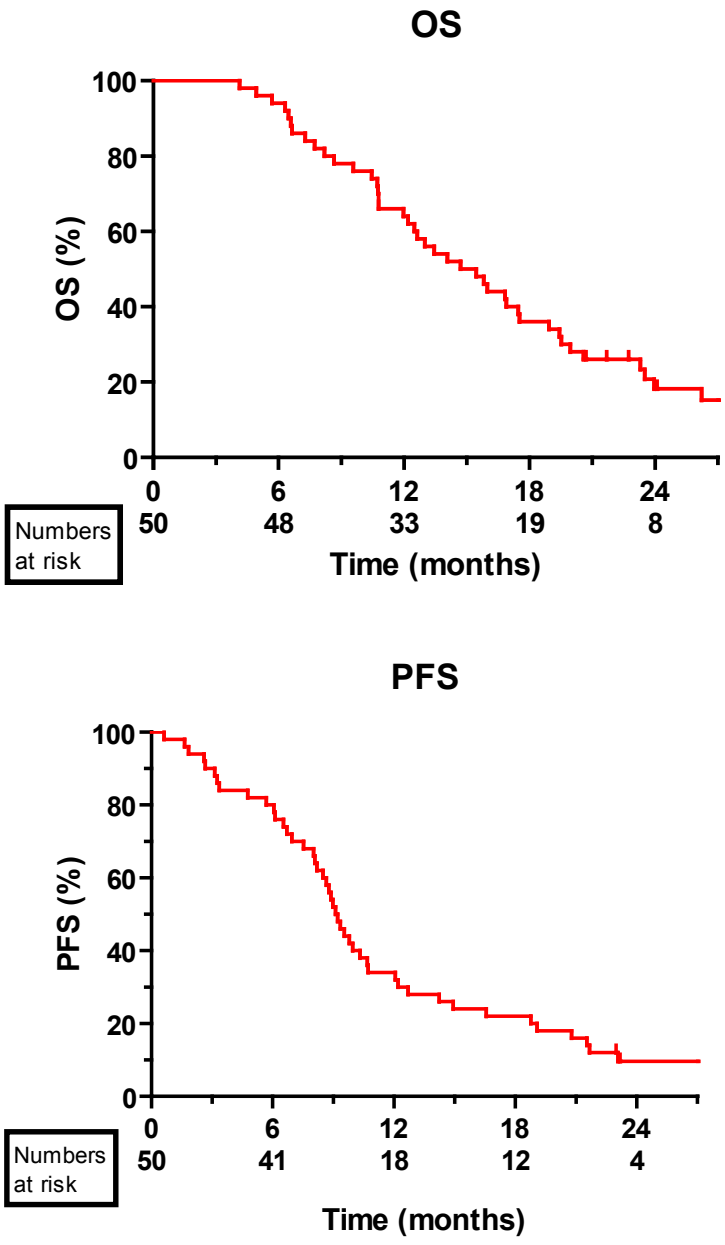


Figure 3. Kaplan-Meier of locoregional progression free survival (PFS), and metastatic PFS in patients after stereotactic body radiotherapy (SBRT) treatment (N=39).

Discussion

In this multicenter open-label phase II trial, patients with LAPC were sequentially treated with FOLFIRINOX and SBRT consisting 5 fractions of 8 Gray. To our knowledge, this is the first trial that has prospectively investigated feasibility and antitumor activity of this combined approach in patients with LAPC. The 1-year OS rate of 64% is significantly higher than the 1-year OS rate of 40% achieved in our own historic cohort. Most patients (78%) completed the assigned treatment of FOLFIRINOX and SBRT. No deaths were attributed to the FOLFIRINOX treatment, while two deaths (5%) were possibly attributable to SBRT. The resection rate was 12%, and in all patients the resection turned out to be radical.

In the last decade, FOLFIRINOX has emerged as a possible new standard therapy for LAPC.[6] Although no RCTs have been published to confirm this finding, many case series have demonstrated promising survival rates of FOLFIRINOX in patients with LAPC.[8] A recent patient-level meta-analyses of 315 patients showed even a 1-year OS rate of 80%. This somewhat unexpected finding most likewise will be the result of patient selection due to the retrospective design of most of the included studies, as only one prospective study comprising 11 patients with LAPC was included in this analysis.[17] In the patient-level meta-analysis about 60% of the patients received subsequent (chemo)radiotherapy after FOLFIRINOX. However, studies that applied RT more frequently did not report better OS.[8]

Radiotherapy can be considered as a rational local treatment approach in patients with LAPC in whom no metastatic disease is seen after systemic therapy.[6] There is consensus that staging laparoscopy should be included in the diagnostic work-up in patients in whom an initial diagnosis of LAPC is considered.[18] Our study confirms that staging laparoscopy frequently (25% in this study) discovers metastatic disease that was not seen on initial radiologic analyses. It is obvious that localized treatment options in patients with metastatic disease are futile.

In our study 6 (12%) patients underwent resection, all resulting in radical (R0) resections. This rate is lower than the 28% R0 resection rate in a recent meta-analysis.[19] In our study, surgical exploration after FOLFIRINOX and SBRT was only considered if imaging showed "disencasement" with arterial tumor contact not exceeding 90 degrees and venous tumor contact not exceeding 270 degrees. After induction therapy some centers consider surgical exploration more liberally, even in all patients provided that distant metastatic disease is absent.[6, 20] It remains uncertain which patients will benefit from surgical exploration.[8] The most recent ASCO guideline suggests that patients should undergo a resection only after radiological response to induction therapy.[6] There is a need for prospective trials to investigate the role of surgical exploration and resection in patients with LAPC after induction therapy.

Grade 3 or 4 adverse event rate during FOLFIRINOX our study was 30 events in 50 patients, which is comparable with the previously reported series.[19] Four (10%) grade 3 or higher adverse events after SBRT were observed, with two patients suffering from a fatal GI bleeding within 3 months after completing SBRT. These mortality rates are comparable to reported results from the literature.[21]

Several ablative therapies such as radiofrequency ablation (RFA) and irreversible electroporation (IRE) are currently being assessed in clinical studies in patients with LAPC. [11] The median OS in patients with LAPC treated in one single center with RFA varies from 19 to 26 months..[11] In this series no specified treatment protocol was used as patients could have been treated with RFA after chemotherapy or could have received RFA as first-line treatment.[22] Therefore, a comparison between our study and the published studies on RFA is difficult. Morbidity after RFA is reported between 0 and 28% , while 30-day mortality ranges from 0 to 3%.[22-24]

Several studies on IRE treatment in LAPC patients are published, with largest cohort that of Martin et al. consisting of 200 patients.[25] The study reports on patients receiving IRE after chemo(radiotherapy) treatment. Patients underwent after initial systemic treatment, IRE treatment or IRE combined with resection for margin accentuation with a median OS of 23 months and 28 months, respectively. Other studies reported median OS between 15 and 27 months after IRE treatment in LAPC.[11] Morbidity after IRE was reported between 10 and 57%, while mortality was found between 1 to 3%.[11]

The main limitation of the current study is that was designed as a single-arm non-randomized phase II study making any comparison virtually impossible. Another relevant issue is that the current definitions of LAPC vary significantly,. The definition for LAPC in this trial is based on the Dutch Pancreatic Cancer Group definition, which is more conservative than the AHPBA/SSO/SSAT definition of LAPC. Finally, all patients in this study received FOLFIRINOX according to the schedule that was described in the PRODIGE 4 trial.[17] However, several studies have meanwhile reported that a so-called modified FOLFIRINOX schedule which uses a 25% reduction of 5-FU gives comparable survival outcomes, but with a decreased toxicity profile.[26]

In conclusion, FOLFIRINOX followed by SBRT existing of 5 fractions of 8 Gray was safe and feasible. The observed antitumor activity, resulting in a 1-year OS rate of 64%, a 1-year PFS rate of 34%. Furthermore, ultimately 6 (12%) patients were able to undergo potentially curative R0 resection. In our view, this warrants further analysis in randomized trials. . Nonetheless, distant progression remains the biggest concern in LAPC patients treated with FOLFIRINOX and SBRT. Therefore, new and other studies are needed to further explore the potential role of this protocolled regimen combined with other systemic therapies. Immunotherapy is emerging as a synergetic treatment to radiotherapy.[27, 28] Sequential treatment of chemotherapy and SBRT followed by immunotherapy, could potentially improve outcomes in this group of patients.

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Part III

Summary, general discussion, and appendices

Chapter 7
Summary

Pancreatic cancer is divided in four stages: resectable, borderline resectable, locally advanced, or metastatic disease.[1] Locally advanced pancreatic cancer (LAPC) comprises one-third of the patients diagnosed with pancreatic cancer.[2] Staging of LAPC is based on computed tomography (CT) of chest, abdomen and pelvis.[3] Some centers perform a staging laparoscopy in the diagnostic work-up of LAPC. However, there is no consensus on the role of staging laparoscopy in the diagnostic work-up of LAPC.[1, 4]

In the past, LAPC patients were usually studied together with metastatic pancreatic cancer and are often referred as advanced pancreatic cancer patients.[5] Currently, there are some advances in the treatment of pancreatic cancer, with new chemotherapeutic combinations, and new local ablative therapies.[6-8] This has led to a new interest in LAPC, as combination therapy with systemic and local therapies is hypothesized to improve survival of these patients.[9] As a result, LAPC has emerged as a distinct patient population, mainly due to the evolution in local therapies.

In the last decade, FOLFIRINOX has emerged as a new combination chemotherapy. Several cohort studies show promising survival data for LAPC patients.[10] If progression is halted by systemic chemotherapy, radiotherapy is indicated for LAPC.[3] Nowadays, stereotactic body radiotherapy (SBRT) is considered as alternative to conventional radiotherapy for local ablative treatment in LAPC.[11]

In this thesis, we aimed to optimize the staging of LAPC, and examined the potential survival benefit of FOLFIRINOX in combination with radiotherapy.

Part I: Staging of LAPC

The National Comprehensive Center Network (NCCN) recommend routine chest CT-scans in pancreatic cancer. However, many centers do not perform these scans routinely for (borderline) resectable pancreatic cancer, as it has no influence on survival.[12] There are no studies addressing the clinical value of follow-up chest CT-scans in patients with LAPC. In **chapter 2**, we describe the findings of chest CT-scans in 119 LAPC patients. On first staging chest CT-scans, 13% of the patients showed pulmonary nodules too small to characterize. In follow-up chest CT-scans, available in 111 patients, only 4% of the patients showed malignant-appearing pulmonary nodules. All these malignant pulmonary nodules were seen as nodules too small to characterize on first staging chest CT-scan. Notably, no difference in treatment management or survival was found between patients with and without nodules too small to characterize on first staging chest CT-scan.

In the past, staging laparoscopy has been reported to upstage one-third of LAPC patients to metastatic disease.[13, 14] In **chapter** 3, we evaluated the current yield of staging laparoscopy for occult metastasis in LAPC. Ninety-one patients underwent a staging laparoscopy after diagnosed with biopsy-proven LAPC. The yield of staging

laparoscopy for metastasis was 19% (95% CI: 12 - 28). Only serum tumor marker CEA appeared to be a significant preoperative predictor for occult metastasis found with staging laparoscopy (OR 1.056, 95% CI: 1.007 - 1.107, p=0.02). There was no significant 1-year survival rate difference between patients with and without occult metastasis (29% vs. 53%, p=0.11).

Part II: Treatment of LAPC

In 2011, FOLFIRINOX was introduced as the standard first-line chemotherapy for patients with metastasized pancreatic cancer.[15] Since then, many cohort studies have been published, evaluating the efficacy of FOLFIRINOX in the LAPC setting. In **chapter 4**, we conducted a systemic review and a patient-level meta-analysis, reviewing the findings of these cohort studies. A total of 11 studies, comprising 315 patients with LAPC, were included in the patient-level meta-analysis. The pooled patient-level median overall survival (OS) was 24 months (95% CI: 22 – 27), while the pooled patient-level median progression free survival (PFS) was 15 months (95% CI: 14 – 16). The pooled proportion of patients who received radiotherapy treatment was 64% (95% CI: 43 – 82), while the pooled proportion of patients who had resection was 26% (95% CI: 20 – 32). A radical resection was achieved in 79% of the patients (95% CI: 60 – 92). There was no significant association between receiving subsequent radiotherapy and OS (p=0.12). Additionally, there was no significant association between resection rate and OS (p=0.39).

Between 2012 and 2014, all patients with LAPC seen at Erasmus MC, were offered FOLFIRINOX with subsequent conventional radiotherapy. **Chapter 5** presents the results of the patients that were eligible for this protocol. In total, 22 patients started the FOLFIRINOX treatment. Subsequent radiotherapy was given in 77% of the patients. A radical resection was achieved in 14% of the patients. Median OS was 15 months (95% CI: 10 - 20) for the entire cohort, while median PFS was 11 months (95% CI: 8 – 14).

Subsequent to this cohort, we present in a multicenter phase II trial was conducted to investigate the feasibility and efficacy of sequential FOLFIRINOX and SBRT in LAPC patients. Patients received 8 cycles of FOLFIRINOX. If no tumor progression after the FOLFIRINOX treatment was observed, SBRT (5 fractions/8Gray) was given. Resection was considered if downstaging of the tumor was seen on imaging. In **chapter 6** we discuss the findings of this trial. From 2015 till 2017, a total of 50 patients were included in the final analysis and started the FOLFIRINOX treatment. SBRT was given in 78% of the patients, with eventually in 12% of patients a radical resection was achieved. In 4% of the patients, a complete pathological response was seen. In total, 30 grade 3 or 4 events were seen during the FOLFIRINOX treatment. While after SBRT, a grade 3 or 4 adverse events was seen in 5% of the patients, and a grade 5 adverse

event was seen in 5% of the patients. For the whole cohort, the median OS and PFS were 15 (95% CI: 11 - 18) and 9 months (95% CI: 8 - 10), respectively. The median OS for patients who had completed SBRT was 17 months (95% CI: 14 - 21) versus 7 months (95% CI: 6 - 8) in patients who had not received SBRT ($p<0.001$). Median locoregional PFS in all patients was 17 months (95% CI 11-24), 20 months (95%: CI 14 - 28) for the SBRT group and 3 months (95% CI: 2 - 4) for the non-SBRT group ($p<0.001$). The median distant PFS in all patients was 11 months (95% CI: 10 - 12), for the SBRT group 11 months (95% CI: 9 - 13), and 3 months (95% CI: 2 - 4) in the non SBRT group ($p<0.001$).

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Samenvatting

Alvleesklierkanker wordt onderverdeeld in vier stadia: resectabel, borderline resectabel, lokaal irresectabel of gemetastaseerde ziekte.[1] Lokaal irresectable alvleesklierkanker (LAPC) omvat één derde van de patiënten.[2] Stagering van LAPC is gebaseerd op computertomografie (CT) van de thorax, de abdomen en het bekken.[3] Sommige centra includeren ook een diagnostische laparoscopie voor de stagering van LAPC. Echter, momenteel bestaat er geen consensus over de rol van diagnostische laparoscopie in de diagnostiek van LAPC.[1, 4]

In het verleden werd er geen onderscheid gemaakt tussen LAPC-patiënten en patiënten met gemetastaseerde ziekte. Beide groepen werden aangeduid als patiënten met gevorderde alvleesklierkanker.[5] In de afgelopen jaren zijn er veel vorderingen gemaakt in de behandeling van alvleesklierkanker. Nieuwe chemotherapeutische combinaties worden onderzocht en nieuwe lokale ablatieve therapieën zijn ontwikkeld.[6-8] Deze ontwikkeling heeft geleid tot een nieuwe interesse in LAPC, aangezien verondersteld wordt, dat een combinatietherapie bestaande uit systemische en lokale therapie, de overleving van LAPC-patiënten zou moeten verbeteren.[9] Als gevolg van de ontwikkelingen binnen de lokale therapieën, worden LAPC patiënten sinds kort als een aparte groep beschouwd.

In het laatste decennium is FOLFIRINOX naar voren gekomen als een nieuwe potentiële combinatiechemotherapie. De resultaten met betrekking tot de overleving in LAPC-patiënten zijn veelbelovend. [10] Indien systemische chemotherapie tumorprogressie remt, is aanvullend radiotherapie aanbevolen in LAPC patiënten. [3] Momenteel is er veel aandacht voor stereotactische radiotherapie (SBRT) als een alternatief voor de conventionele radiotherapie in de LAPC-setting. [11]

In dit proefschrift focussen wij ons op het optimaliseren van de stadiëring van LAPC-patiënten en onderzoeken wij het potentiële overlevingsvoordeel van FOLFIRINOX in combinatie met radiotherapie.

Deel I: stadiëring van LAPC

Het National Comprehensive Center Network (NCCN) adviseert routinematige thorax-CT-scans bij patiënten met alvleesklierkanker. Echter, veel centra voeren deze scans niet routinematig uit voor (borderline) resectabele alvleesklierkanker, omdat het geen invloed heeft op de overleving.[12] Tot op heden zijn er geen studies die de klinische meerwaarde van follow-up thorax CT-scans in patiënten met LAPC beschrijft.

In **hoofdstuk 2** beschrijven wij de bevindingen van thorax CT-scans bij 119 LAPC-patiënten. Op de eerste CT-scan liet 13% van de patiënten een pulmonale nodus zien die te klein was om te karakteriseren. Van 111 patiënten was de follow-up CT-scan

beschikbaar, waarvan slechts 4% een maligne pulmonale nodus liet zien. Al deze maligne pulmonale noduli waren te klein op de eerste CT-scan om te karakteriseren. Er werd geen verschil in behandeling of overleving gevonden tussen patiënten met en zonder pulmonale noduli die te klein waren om te karakteriseren op de eerste CT-scan.

In het verleden is gerapporteerd dat diagnostische laparoscopie een derde van de LAPC-patiënten alsnog als metastatische ziekte stadieert.[13, 14] In **hoofdstuk 3** evalueren we de huidige opbrengst van diagnostische laparoscopie voor occulte metastasen in LAPC. In totaal ondergingen 91 patiënten een diagnostische laparoscopie nadat de diagnose van LAPC met een biopsie was bevestigd. De opbrengst van diagnostische laparoscopie voor metastase was 19% (95% CI: 12 - 28). Alleen serumtumormarker CEA bleek een significante preoperatieve voorspeller te zijn voor occulte metastasen (OR 1.056, 95% CI: 1.007 - 1.107, p = 0.02). Er was geen significant verschil in overlevingspercentage van 1 jaar tussen patiënten met en zonder occulte metastasen (29% vs. 53%, p = 0.11).

Deel II: Behandeling van LAPC

In 2011 werd FOLFIRNOX geïntroduceerd als de standaard eerstelijns chemotherapie voor patiënten met gemetastaseerd alvleesklierkanker.[15] Sindsdien zijn er veel studies gepubliceerd, waarbij de effectiviteit van FOLFIRINOX in de LAPC-setting werd geëvalueerd.

In **hoofdstuk 4** hebben wij een systematische review en een meta-analyse op patiëntniveau uitgevoerd en beschrijven wij de bevindingen van deze cohortstudies. In totaal zijn er 11 studies, bestaande uit 315 patiënten met LAPC, geïncludeerd in de individuele patiëntniveau meta-analyse. De mediane overall survival (OS) op patiënt niveau was 24 maanden (95% CI: 22 - 27), waar de mediane progression free survival (PFS) 15 maanden was (95% CI: 14 - 16). Het gepoolde aantal patiënten dat radiotherapie ontving was 64% (95% CI: 43 - 82), terwijl het gepoolde percentage van de patiënten met resectie 26% was (95% CI: 20 - 32). Een radicale resectie was uitgevoerd in 79% van de patiënten (95% CI: 60 - 92). Er was geen significant verband tussen behandeling met radiotherapie en de OS (p = 0.12). Daarnaast was er ook geen significant verband tussen de resectie ratio en OS (p = 0.39).

Tussen 2012 en 2014 kregen alle patiënten met LAPC in Erasmus MC, FOLFIRINOX aangeboden met aanvullend conventionele radiotherapie. **Hoofdstuk 5** beschrijft de resultaten van de patiënten die in aanmerking kwamen voor dit protocol. In totaal waren er 22 patiënten gestart met FOLFIRINOX behandeling. Aanvullende radiotherapie werd gegeven bij 77% van de patiënten. Een radicale resectie werd bereikt in 14% van de patiënten. Voor de totale cohort was de mediane OS en PFS 15 maanden (95% CI: 10 - 20) en 11 maanden (95% CI: 8 - 14) respectievelijk.

Als vervolg op deze studie, hebben wij een multicenter fase II-studie opgezet om de haalbaarheid en effectiviteit van FOLFIRINOX met aanvullende SBRT te onderzoeken in LAPC-patiënten. Patiënten werden behandeld met 8 cycli FOLFIRINOX. Indien er geen tumorprogressie werd waargenomen na de behandeling met FOLFIRINOX, was SBRT (5 fracties/ 8 Gray) geïndiceerd. Chirurgische resectie werd overwogen indien de tumor op beeldvorming als resectabel werd geacht. In **hoofdstuk 6** bespreken we de bevindingen van deze studie. Van 2015 tot 2017 werden in totaal 50 patiënten geïncludeerd en behandeld met FOLFIRINOX. Aanvullend werd SBRT gegeven bij 78% van de patiënten, waarbij uiteindelijk bij 12% van de patiënten een radicale resectie werd bereikt. In 4% van de gevallen werd een complete pathologische response gezien. In totaal werden er 30 graad 3 of 4 adverse events gezien tijdens de behandeling met FOLFIRINOX. In 5% van de gevallen trad graad 3 of 4 adverse events op na SBRT, waarbij in 5% van de patiënten een graad 5 adverse event werd gezien. Voor de totale cohort was de mediane OS en PFS 15 (95% CI: 11 - 18) en 9 maanden (95% CI: 8 - 10), respectievelijk. De mediane OS voor patiënten die SBRT hadden gekregen was 17 (95% CI: 14 - 21) versus 7 maanden (95% CI: 6 - 8) bij patiënten die geen SBRT hadden ontvangen ($p<0.001$). De mediane locoregionale PFS bij alle patiënten was 17 maanden (95% CI 11-24), waarvan 20 maanden (95%: CI 14 - 28) voor de SBRT-groep en 3 maanden (95% CI: 2 - 4) voor de niet-SBRT groep ($p <0.001$). De mediane afstands PFS bij alle patiënten was 11 maanden (95% CI: 10 - 12), voor de SBRT-groep 11 maanden (95% CI: 9 - 13) en 3 maanden (95% CI: 2-4) in de niet-SBRT-groep ($p<.001$).

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Chapter 8
General Discussion

Part I: Staging of LAPC

The two most commonly used definitions for (borderline) resectable disease and locally advanced disease are defined by the National Comprehensive Cancer (NCCN) and the combined definition of Americas Hepato-Pancreato-Biliary Association (AHPBA), the Society of Surgical Oncology (SSO), and the Society for Surgery of the Alimentary Tract (SSAT).[1, 2] In the Netherlands, the definitions for locally advanced pancreatic cancer (LAPC) is defined by the Dutch Pancreatic Cancer Group (DPCG). Their definition is tumor contact with the arteries superior mesenteric artery (SMA), coeliac artery (CA), or common hepatic artery (CHA) exceeding 90 degrees or contact with the veins superior mesenteric vein (SMV) or portal vein (PV) exceeding 270 degrees.[3] The DPCG definition for LAPC is more conservative than the NCCN and AHPBA/SSO/SSAT definitions. Patients considered as LAPC in the Netherlands could be defined as borderline resectable in the USA. There is a need for a worldwide consensus on the definition for LAPC. This could not only improve the generalizability of future studies on this subject, but also give more insight in the tumor biology of LAPC.

The NCCN guidelines recommend a staging chest, abdomen and pelvic CT-scan in pancreatic cancer.[4] However, many centers do not perform routine chest CT-scans in (borderline) resectable pancreatic cancer patients.[5] This is based on several studies reporting that chest CT-scans have limited implication on treatment management and survival of patients with (borderline) resectable pancreatic cancer.[6-8] In patients with LAPC, chest CT-scan could also be questioned, as our study showed that only in a few patients pulmonary nodules could be considered as malignant in follow-up CT-scans. Moreover, all these nodules were first seen as indefinite pulmonary nodules on first staging CT-scan. These indefinite pulmonary nodules impose a clinical dilemma, with a potential burden for the patient because of invasive diagnostic tests and delay of treatment. For example, transthoracic lung biopsies of small pulmonary nodules can cause a considerable risk of pneumothorax or intrathoracic bleeding.[9] For treatment monitoring purposes, follow-up chest CT-scans can be considered in patients with indefinite pulmonary nodules on first staging CT-scan. However, there is a need for more studies to confirm our findings, as our study is the first that examined the clinical value of chest CT-scans in patients with LAPC.

A consensus report by the AHPBA published in 2009 recommends staging laparoscopy in patients with LAPC.[2] This recommendation is based on two studies, in which the yield of staging laparoscopy in patients with LAPC was about 35%.[10, 11] The AHPBA consensus states that staging laparoscopy could serve for two essential purposes. First, it eliminates the cost, inconvenience, and potential morbidity of radiotherapy. Second, it allows for better understanding of new treatment protocols

since patients with understaged disease are excluded before diluting true outcomes. However, in recent years, the imaging modalities have improved considerably. Despite the advanced in clinical diagnostics with specialized radiologist and multimodality review boards, our data still showed that the yield of staging laparoscopy for occult metastasis is about 20% in patients with LAPC. We advocate that staging laparoscopy should be included in the diagnostic work-up voor LAPC. By finding these occult metastasis, futile local therapies could be avoided. However, the timing of the staging laparoscopy is still debatable. For study purposes, we recommend to perform a staging laparoscopy before any treatment. In this way, patient selection is standardized and data can be generalized. Patients with occult metastasis who have partial response can be seen as false negative for occult metastasis during staging laparoscopy. This might not be an issue in clinical practice, as these patients might benefit from local therapy as well. Unfortunately, only limited data have been published on the role of staging laparoscopy in LAPC setting.[12] Therefore, no definite conclusions can be made on the timing of staging laparoscopy in patients with LAPC.

Part II: Treatment of LAPC

The current treatment in patients with LAPC is systemic chemotherapy.[4] In 2011 an RCT was conducted by Conroy et al. with FOLFIRINOX versus gemcitabine for patients with metastatic and locally advanced pancreatic cancer.[13] Afterwards, many case series have been published with FOLFIRINOX as first-line treatment for LAPC.[14] In this thesis, a patient-level meta-analysis of comprising 315 patients with LAPC treated with first-line FOLFIRINOX showed a median OS of 24 months.[14] Strikingly, this median OS was comparable to patients with BRPC receiving neoadjuvant FOLFIRINOX treatment.[15] However, this median OS found in the patient-level meta-analysis for patients with LAPC should be interpreted with caution. This relatively high survival seen after FOLFIRINOX could be influenced by patients selection and publication bias. In our study, patients with LAPC were treated with induction FOLFIRINOX followed by conventional radiotherapy. Twenty-two patients were included in this cohort, which showed a median OS of 15 months.[16] The lower median OS found in our cohort compared to the meta-analysis could be explained by the prospective nature of our cohort. Although there is no level 1 evidence for the best chemotherapy to use in LAPC, FOLFIRINOX seems to be the most potent chemotherapy.[4, 17] Despite the fact that FOLFIRINOX has a higher toxicity rate than gemcitabine, the quality of life of patients with metastatic pancreatic cancer receiving FOLFIRINOX is significantly better than those receiving gemcitabine.[18] Therefore, for patients with a good performance state we recommend FOLFIIRNOX as first choice of therapy. Alternatives are Nab-paclitaxel-gemcitabine or gemcitabine as first-line treatment.[4] Hopefully, the French trial NEOPANC which randomizes patients with LAPC between FOLFIRINOX

and gemcitabine can give more definite answers on the best chemotherapy in the LAPC setting (ClinicalTrials.gov Identifier: NCT02539537).

Subsequent local (chemo)radiotherapy after induction chemotherapy is recommended in patients with LAPC without any evidence of systemic disease.[4, 19] The main goal of radiotherapy is to delay or prolong local progression. So far, there is no clear evidence which radiotherapy is the best in the LAPC setting.[4] In the last decade, stereotactic body radiotherapy (SBRT) is of interest decade, as it can give higher dosage of radiotherapy with more precision. This could inflict more destruction to the tumor, with less scattering to surrounding organs.[20, 21] We conducted a phase II trial to evaluate the efficacy and feasibility of SBRT after FOLFIRINOX treatment in patients with LAPC. Of the 50 patients that received FOLFIRINOX, eventually 39 patients underwent SBRT. The median OS of the patients receiving SBRT was 17 months. While the median locoregional progression free survival (PFS) was 20 months after SBRT, the median distant PFS was 11 months. Strikingly, systemic control remains the biggest obstacle in the treatment of LAPC, while the local control can be achieved by multimodality treatment. These findings underline the systemic nature of pancreatic cancer. Therefore, new studies should focus on systemic control of LAPC. A possibility is to restart chemotherapy after radiotherapy. However, second-line chemotherapy could have a high burden on a patient as it could be associated with cumulative toxicity.[19] Evermore, Tsang et al. showed that second-line therapy can only be given for a short period of time in advanced pancreatic cancer.[22] Therefore, new innovative systemic therapies are urgently needed in pancreatic cancer. Immunotherapy is emerging as a new possible synergetic treatment to radiotherapy.[23, 24] There are some indications that radiotherapy in pancreatic cancer can induce an abscopal effect.[25] The combination of radiotherapy with anticancer vaccines and checkpoint inhibitors have an in increase in response rates in preclinical trials.[26] The rationale for this treatment regimen is the induction of tumor damage and cell apoptosis by radiotherapy, immunotherapy could boost the immune system to start a chain reaction of immune cells that attacks the primary tumor and non-irradiated tumor metastasis.[26] Anti-PDL1 and IMM-101 are such a immunotherapy agents which induces the innate and adaptive immune system in response to cancer.[27-29] Future studies should focus on systemic treatment regimens after chemotherapy and radiotherapy. Immunotherapy could be a fruitful adjunct therapy for LAPC, by gaining more systemic control after the initial local and systemic control induced by chemotherapy and radiotherapy.

The American Society of Clinical Oncology (ASCO) advices that patients with LAPC could be considered for surgery after significant response to induction therapy was achieved.[19] There is a difficulty in defining dramatic response to induction therapy. Studies have shown that restaging CT-scan after neoadjuvant treatment in LAPC have

a low accuracy to evaluate local tumor size and vitality.[30, 31] Nonetheless, some centers advocate that exploration of LAPC patients without biochemical disease progression or progression on imaging should undergo an exploration.[31, 32] However, there is no data supporting survival benefit or disadvantage of resection after systematic therapy in patients with LAPC. Studies reporting high median OS after resection LAPC setting are usually biased by patient selection.[33] Randomized studies are needed to predict which LAPC patient could benefit from resection after induction therapy.

In the end, even though there are some breakthroughs in the treatment of LAPC, a multidisciplinary approach is essential to achieve the best care. Pancreatic cancer is a systemic disease, and LAPC is no exception in this. Therefore, patients diagnosed with LAPC must be reviewed in a multidisciplinary tumor board, taking into account the preference of the patient.

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Appendices

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About the author

Mustafa Suker was born on the 17th of October 1988 in Baghdad, Iraq. At the age of 8 years, he came together with his parents and sister to the Netherlands. He graduated from Gymnasium in Venray, the Netherlands in 2007. In the same year, he was accepted for medical school by decentralized selection at Erasmus University in Rotterdam. During his study, he developed interest for surgery and science, which resulted in research projects in pancreatic surgery under supervision of prof. dr. C.H.J. van Eijck. After graduating from medical school in 2014, he was offered an PhD program under the same professor and co-promoter dr. B. Grootkoerkamp, which has led to this thesis. In 2018, he started as resident doctor in the department of surgery at Reinier de Graaf Hospital, Delft (supervisor: Dr. M.R. de Vries). Currently, he started with his surgical training to become a surgeon at Erasmus Medical Center Rotterdam and Amphia Hospital, Breda under supervision of dr. B.P.L. Wijnhoven and dr. L. van der Laan.

PhD portfolio

Oral presentations (0.5 point/each)		
The International Symposium on Intensive Care and Emergecy Medicine	2015	0.5
Measurement of microcirculatory alterations: A consensus meeting	2015	0.5
Nederlandse Chirurgendagen	2016	0.5
Wetenschapsdag Erasmus MC	2016	0.5
DPCG Pancreas Dag	2016	0.5
European Society of Surgical Research	2016	1.0
Pancreas Club	2017	0.5
Wetenschapsdag Erasmus MC	2016	0.5
Pancreas Club	2018	0.5
International Hepato-Pancreato-Biliary Association	2018	1.0
Poster presentations (0.3 point/each)		
International Hepato-Pancreato-Biliary Association	2016	0.6
European Pancreas Club	2016	0.3
Pancreas Club	2017	0.9
Conferences (0.3 point/day)		
Nederlandse Chirurgendagen	2014 - 2017	1.0
International Hepato-Pancreato-Biliary Association	2016, 2018	1.0
Pancreas Club	2017 - 2018	0.9
General Courses		
SPSS Statistics	2014	0.5
Good Clinical Practice	2014	0.3
CPO-course (Patient Oriented Research: design, conductance, analysis and clinical implications)	2015	0.3
BROK (Basic course Rules and Organization for Clinical researchers)	2015	1.5
Survival Analysis Statistics	2015	0.5
Research Integrity Course	2015	0.3
OpenClinica Course	2016	0.3
Advanced Trauma Life Support (ATLS)	2017	2.0
Reregistration BROK Course	2018	0.5
ESSO-EYSAC Surgical Anatomy Course on Pancreatic Cancer	2019	1.0

Teaching activities		
First aid exams	2014 - 2018	1.0
RISK Education Interns	2015 - 2018	1.0
Minor Gastroenterology	2015	0.3
Tutor first year medical students	2016	1.0
Orginasator Surgical Journal Club of Clinical Oncology	2016 - 2018	1.0
Supervising Master Student B.R. Beumer (Erasmus MC)	2016 - 2017	1.0
Masterclass Verpleegkundigen & Verzorgenden Nederland Jaarcongres	2017	1.0

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