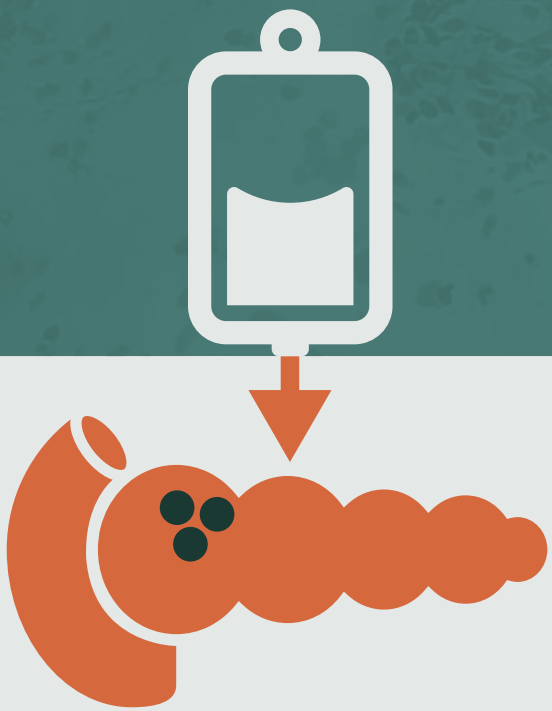
NEOADJUVANT TREATMENT OF PANCREATIC CANCER

Diagnostic workup, chemotherapy, and radiotherapy



KIKI (Q.P.) JANSSEN

NEOADJUVANT TREATMENT OF PANCREATIC CANCER

DIAGNOSTIC WORKUP, CHEMOTHERAPY, AND RADIOTHERAPY

KIKI JANSSEN

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CHAPTER 1

Introduction and outline of this thesis

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is currently the seventh leading cause of cancer-related deaths worldwide.[1] Due to its aggressive tumor biology, only 10% of patients survive more than 5 years from diagnosis.[2] An important reason for this dismal prognosis is that PDAC is often diagnosed at an advanced stage, with 40% of patients presenting with metastatic disease. For these patients, palliative treatment with systemic chemotherapy is offered with the aim to prolong survival and to improve quality of life. Other palliative treatment options include targeted treatment in patients with known genomic alterations or immunotherapy. The majority of patients with metastatic disease, however, will only receive best supportive care.[3,4] Approximately 40% of patients presents with locally advanced (i.e., unresectable) disease at diagnosis due to extensive vascular involvement of the tumor. Conventional treatment for this stage includes systemic chemotherapy, potentially followed by local therapies such as radiotherapy, irreversible electroporation (IRE) or radiofrequency ablation therapy (RFA).[5] In about 25% of these patients, treatment response will allow for subsequent surgical resection.[6,7] The remaining 20% of all patients have borderline resectable or resectable PDAC at diagnosis. For these patients, surgical resection combined with systemic chemotherapy is the standard of care.

The focus of this thesis is on patients diagnosed with borderline resectable and resectable PDAC.

Borderline resectable and resectable pancreatic cancer

Uniform criteria to define the different PDAC stages are lacking. The National Comprehensive Cancer Network (NCCN) criteria are widely used in many countries, whilst the criteria proposed by the Dutch Pancreatic Cancer Group (DPCG) are used in the Netherlands. The DPCG criteria are considered more conservative compared to the NCCN criteria. In general, patients with only minor or no vascular involvement of the tumor are considered upfront resectable, whilst patients with extensive vascular involvement precluding a complete resection are considered locally advanced unresectable. Tumors with vascular contact in between the extremes of resectable and locally advanced PDAC are considered borderline resectable. For many decades, the primary treatment for patients with both borderline resectable and resectable PDAC has been upfront surgery. Although a resection provides the best chance for long-term survival, cure remains scarce, as is shown by a 10-year survival rate of 4% after resection.[8] Initial trials comparing adjuvant treatment to observation alone have shown that the addition of adjuvant systemic treatment can improve 5-year survival from about 10% to 20%.[9-11] Thereafter, several large randomized controlled trials (RCTs) have focused on optimizing the adjuvant treatment regimen.[12,13] Currently, multi-drug regimens including modified FOLFIRINOX (5-fluorouracil with leucovorin, irinotecan, and oxaliplatin) and gemcitabine with capecitabine are the recommended adjuvant chemotherapy regimens for patients with a good performance status.[14] However, the strategy of upfront surgery followed

by adjuvant chemotherapy has several drawbacks. First, unexpected locally advanced or occult metastatic disease is found in approximately 20% of patients, precluding a resection.[15] Second, pancreatic tumor resection requires major abdominal surgery which is associated with considerable morbidity and mortality. As a consequence, nationwide studies show that up to 40% of patients do not recover sufficiently and timely enough to receive adjuvant chemotherapy after resection.[16-18] Without adjuvant treatment, about 50% of patients will experience disease recurrence or death within 6 months after resection.[11]

Neoadjuvant treatment

Neoadjuvant treatment has already been implemented in other solid malignancies such as rectal, breast, and gastroesophageal cancer.[19-22] The rationale behind a neoadjuvant approach is manifold. First, studies on recurrence show that PDAC should be considered a systemic disease, even in patients with apparent early stage disease on CT-scan.[23,24] With a neoadjuvant approach, patients immediately receive systemic treatment directly addressing possible micro-metastatic disease. Second, almost all patients can benefit from systemic treatment without the risk that postoperative complications or clinical deterioration preclude adjuvant chemotherapy. Third, the neoadjuvant treatment period provides a test of time, improving patient selection for surgery and preventing patients with rapidly progressive disease to undergo futile surgery. Fourth, neoadjuvant treatment may increase the likelihood of a microscopically radical (R0) resection by reducing the tumor volume and tumor-vessel contact.[25] Last, neoadjuvant treatment may reduce the risk of severe complications of pancreatic surgery.[26-28] Altogether, these factors may improve survival. However, this approach requires high-level evidence to investigate the efficacy of neoadjuvant treatment for borderline resectable and resectable PDAC. The risks associated with neoadjuvant therapy should also be acknowledged, including biliary drainage required prior to chemotherapy, requirement of preoperative tissue acquisition to confirm malignancy, tumor progression during treatment, severe immunosuppression, and deconditioning due to chemotherapy-related toxicity.

OUTLINE OF THIS THESIS

A neoadjuvant approach requires tissue acquisition prior to treatment. Therefore, part I of this thesis concerns endoscopic procedures for tissue acquisition of focal pancreatic lesions. Part II is the core of this thesis with a focus on neoadjuvant treatment for PDAC. Finally, part III investigates the role of subsequent radiotherapy and adjuvant systemic treatment.

PART I: DIAGNOSTIC WORKUP OF FOCAL PANCREATIC LESIONS

PDAC is the most feared pancreatic lesion. Fortunately, not all focal pancreatic lesions have a dismal prognosis. The types of focal pancreatic lesions are numerous and differ in treatment and prognosis. In general, surgery is not needed for patients with asymptomatic benign lesions and pre-malignant lesions with low risk of malignant transformation. On the other hand, high risk pre-malignant and malignant lesions may require timely surgery. The differentiation between low-risk and high-risk lesions can be challenging, with the risk of both surgical overtreatment and undertreatment. **Chapter 2** and **Chapter 3** specifically focus on the diagnostic procedures in patients with focal lesions in the pancreatic body and tail, which is often underexposed in literature. In **Chapter 2**, the additional diagnostic value of EUS besides conventional cross-sectional imaging is evaluated. In **Chapter 3,** the diagnostic accuracy of the different imaging modalities used in the preoperative work-up of focal pancreatic body and tail lesions is investigated.

Tissue can be obtained by endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), or endoscopic periampullary biopsies in case of tumor growth into the ampulla or duodenum. The effectiveness of these techniques depends on the performance of both the gastroenterologist performing the procedure and the pathologist examining the tissue sample. In **Chapter 4,** the sensitivity for malignancy of these tissue acquisition techniques prior to start of neoadjuvant treatment is evaluated, using data from two nationwide RCTs: the PREOPANC and PREOPANC-2 trial.[29,30]

PART II: NEOADJUVANT TREATMENT OF PANCREATIC CANCER

In **part II** of this thesis, several projects investigate the current treatment strategies for patients with localized PDAC, with a focus on patients with borderline resectable and resectable disease. In **Chapter 5,** the rationale and current evidence for neoadjuvant treatment is described. Furthermore, challenges in the interpretation of different trial designs are outlined and the most important ongoing trials are summarized. In **Chapter 6,** all evidence from published RCTs comparing neoadjuvant treatment to upfront surgery is combined with the aim to assess whether neoadjuvant treatment increases overall survival compared to upfront surgery.

The focus on systemic treatment as initial treatment for PDAC is continued in **Chapters 7 - 11,** with a specific interest in FOLFIRINOX chemotherapy. FOLFIRINOX was proven to be supe-

rior to gemcitabine in both the metastatic and adjuvant setting.[13,31] Based on extrapolation of these results, centers worldwide have started using FOLFIRINOX as initial treatment for all stages of PDAC. **Chapter 7** assesses the clinical outcomes following neoadjuvant FOLFIRINOX for borderline resectable PDAC by combining patient-level data from numerous studies.

Although FOLFIRINOX seems a promising treatment for all stages of PDAC, there is much practice variation in the number of cycles, whether to start subsequent radiotherapy, which patients should be offered a resection, and whether to give adjuvant treatment following neoadjuvant treatment. The **Trans-Atlantic Pancreatic Surgery (TAPS) consortium,** an international collaboration of five high-volume PDAC referral centers from the United States of America[3] and the Netherlands[2], was initiated to create the world's largest database including all consecutive patients with localized PDAC (i.e. locally advanced, borderline resectable, resectable) who received FOLFIRINOX as initial treatment. **Chapters 8** and **11** represent the initial studies of the TAPS consortium. **Chapter 8** provides a general overview of subsequent treatment and outcomes following FOLFIRINOX. In addition, baseline prognostic factors for survival were assessed, with the aim to improve the expectations prior to start of treatment.

PART III: RADIOTHERAPY AND ADJUVANT TREATMENT OF PANCREATIC CANCER

The role of neoadjuvant radiotherapy after neoadjuvant chemotherapy remains debated. **Chapter 9** first describes the study protocol for the PREOPANC-2 trial, which completed accrual in January 2021. This trial investigated whether total neoadjuvant FOLFIRINOX (8 cycles) without adjuvant treatment is superior to neoadjuvant gemcitabine-based chemoradiotherapy (3 cycles) and adjuvant gemcitabine (4 cycles) for patients with borderline resectable or resectable PDAC.

To further elucidate the role of subsequent radiotherapy after FOLFIRINOX, **Chapter 10** and **Chapter 11** compare the outcomes of patients who received neoadjuvant FOLFIRINOX alone or followed by radiotherapy. In **Chapter 10,** this is assessed by combining evidence for borderline resectable or resectable PDAC from published studies. In **Chapter 11,** data from the TAPS consortium is used to investigate the effect of radiotherapy using propensity-score matched analysis and to compare different radiotherapy regimens.

Adjuvant modified FOLFIRINOX is currently the standard of care in the Netherlands for patients with resectable PDAC, but requires a good performance status. Gemcitabine with capecitabine is recommended for patients who may not tolerate FOLFIRINOX. The ESPAC-4 trial published in 2019 showed that adjuvant gemcitabine with capecitabine is superior to adjuvant gemcitabine monotherapy. In **Chapter 12**, we compared outcomes after adjuvant gemcitabine with capecitabine versus adjuvant gemcitabine monotherapy in a nationwide cohort of patients who underwent resection for PDAC.

SUMMARY OF RESEARCH QUESTIONS ADDRESSED IN THIS THESIS

Chapter	Research question
2	What is the additional diagnostic value of EUS in patients with pancreatic body and tail lesions?
3	What is the diagnostic accuracy of CT, MRI, and EUS-FNA/B in the preoperative workup of pancreatic body and tail lesions?
4	What is the performance of endoscopy-guided tissue acquisition for resectable and borderline resectable pancreatic cancer within the PREOPANC and PREOPANC-2 trials
5	What is the current evidence for neoadjuvant treatment in patients with resectable and borderline resectable pancreatic cancer?
6	Does neoadjuvant treatment increase overall survival compared to upfront surgery in patients with resectable and borderline resectable pancreatic cancer?
7	What is the expected overall survival and resection rate after neoadjuvant FOLFIRINOX as first-line treatment for patients with borderline resectable pancreatic cancer?
8	What are the subsequent treatments and outcomes following FOLFIRINOX as initial treatment for localized pancreatic cancer?
9	Does total neoadjuvant FOLFIRINOX improve overall survival compared with neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine in patients with resectable and borderline resectable pancreatic cancer (PREOPANC-2 trial)?
10	What is the evidence in literature of the added value of radiotherapy following neoadjuvant FOLFIRINOX for resectable and borderline resectable pancreatic cancer?
11	What is the added value of radiotherapy following neoadjuvant FOLFIRINOX for resectable and borderline resectable pancreatic cancer?
12	What are the real-world outcomes following adjuvant gemcitabine with capecitabine or gemcitabine monotherapy in a nationwide cohort of patients who underwent resection for pancreatic cancer?

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PART I

DIAGNOSTIC WORKUP OF FOCAL PANCREATIC LESIONS

CHAPTER 2

Endoscopic ultrasonography as additional preoperative workup is valuable in half of the patients with a pancreatic body or tail lesion

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ABSTRACT

Background

The management of pancreatic body and tail lesions is underexposed. It remains unclear whether endoscopic ultrasonography (EUS) increases the accuracy of the preoperative workup. This study assessed the diagnostic value and safety of EUS in addition to cross-sectional imaging in a surgical cohort of patients with pancreatic body or tail lesions.

Methods

A multicenter retrospective cohort study was performed of patients who underwent distal pancreatectomy from 2010 - 2017. The composite primary outcome was the additional value of EUS, defined as: (a) EUS confirmed an uncertain diagnosis on cross-sectional imaging, (b) EUS was correct in case of discrepancy with cross-sectional imaging, or (c) EUS provided tissue diagnosis for neoadjuvant treatment. Furthermore, serious adverse events and needle tract seeding were assessed.

Results

In total, 181 patients were included, of whom 123 (68%) underwent EUS besides cross-sectional imaging. Postoperative pathology was heterogeneous: 91 was malignant, 49 pre-malignant, 41 benign. Most lesions were solid (n=117). EUS had additional value in 59/123 (48%) patients; 27/50 (54%) of cystic and 32/73 (44%) of solid lesions. No serious adverse event or needle tract seeding following EUS occurred.

Conclusion

EUS had additional value besides cross-sectional imaging in half of the patients and showed low associated risks.

INTRODUCTION

The management of lesions in the pancreatic body or tail is underexposed in literature. Although distal pancreatectomy is less extensive than surgery for pancreatic head or neck tumors, it is still associated with an estimated major complication rate of 20% and mortality of 3%.[1, 2] Moreover, longterm morbidity includes endocrine and exocrine pancreatic insufficiency with associated increased cardiovascular risk.[3] The majority of pancreatic lesions are benign or low-risk lesions for which a conservative approach can be justified. Unfortunately, differentiating benign from high-risk premalignant or malignant lesions, which do require surgical intervention, can be challenging. As a consequence, surgical overtreatment for low-risk pathology is a considerable problem in patients with pancreatic body or tail lesions, even if international guidelines are applied.[4-7]

To prevent unnecessary major abdominal surgery, a thorough diagnostic workup is essential. This often includes cross-sectional imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), and/or magnetic resonance cholangiopancreatography (MRCP). Although endoscopic ultrasonography (EUS) is an invasive modality, it is used increasingly due to several advantages over cross-sectional imaging only. EUS has the ability to create high-quality images because of its close proximity to the lesion. Hence, EUS provides particularly good examination of cyst morphology and can differentiate mural nodule-like mucus lumps from true mural nodules when intravenous contrast is used simultaneously.[8, 9] Furthermore, it allows for EUS-guided tissue acquisition (TA) to provide a pathological diagnosis, which is helpful in case of unclear imaging and even necessary to start neoadjuvant treatment in case of malignancy. Last, cyst fluid sampling can help distinguish different cyst etiologies.[10, 11] On the other hand, additional evaluation by EUS is not always required and may even be harmful. Potential disadvantages of EUS include the possibility of sampling errors or non-diagnostic sampling, adverse events (e.g. acute pancreatitis, infection, bleeding) in 1 to 4% of patients, and possible treatment delay.[12, 13] In addition, needle tract seeding following transgastric EUS-guided TA for pancreatic body or tail tumors has been described in several case reports.[14-18] The actual risk of needle tract seeding remains unclear, with a number of retrospective studies reporting varying results and conclusions.[19-21] Although it is generally considered a rare phenomenon, it remains an area of concern especially for pancreatic body or tail tumors since the puncture route from transgastric TA is situated outside of the surgical resection bed. In contrast, the transduodenal puncture route for pancreatic head or neck tumors is often resected.

Clinicians need to consider the pros and cons of any additional examination. Studies describing the value of EUS following cross-sectional imaging specifically in patients with a pancreatic body or tail lesion are lacking. Therefore, it remains unclear how often EUS provides the correct diagnosis in case of an uncertain or incorrect diagnosis based on cross-sectional imaging, or provides a definite tissue diagnosis necessary for neoadjuvant treatment. In these

scenarios, EUS can be considered of additional diagnostic value, thereby guiding the appropriate treatment plan and potentially even preventing unjustified major surgery. We aimed to determine the diagnostic value of EUS in addition to cross-sectional imaging in patients who underwent a distal pancreatectomy for a focal lesion in the pancreatic body or tail.

METHODS

Study Design and Patients

We performed a multicenter retrospective cohort study of consecutive patients who underwent a distal pancreatectomy for a pancreatic body or tail lesion between April 2010 and August 2017 at the Erasmus MC University Medical Center and Amsterdam UMC, location AMC. All patients underwent a resection based on the guidelines that were commonly used at time of study protocol.[22-24] The local institutional review board of the Erasmus MC University Medical Center approved the study and waived the requirement to obtain informed consent.

Data collection and definitions

Baseline characteristics and data on clinical presentation, diagnostic workup, postoperative diagnosis, and clinical follow-up were collected retrospectively. Lesions were classified as solid or cystic based on cross-sectional imaging reports. For lesions with both solid and cystic features, the dominant component was determined after independent review of the imaging reports and images by the researchers. The first mentioned diagnosis in the cross-sectional imaging report was used as the most likely radiologic diagnosis. For patients who underwent both a CT- and MRI-scan, the last available report prior to resection was used. For the most likely endoscopic diagnosis, both the endoscopic report, TA, and cystic fluid analysis were taken into account, relying on the treating physicians' report of the most likely diagnosis.[25] Disagreements on both lesion type and the most likely radiologic and endoscopic diagnoses were resolved through discussion and consensus in a new multidisciplinary meeting including two gastroenterologists (JvH and LvD with 18 and 4 years of experience in HPB-related diseases) and a hepato-pancreato-biliary surgeon (BGK with 10 years of experience). The resection was considered justified if postoperative pathological examination showed the presence of malignancy, high-grade dysplasia, pNET, MCN, SPN, or if the resection was performed for improvement of symptoms in case of a benign lesion. Lesions with low- or moderate-grade dysplasia and benign lesions that were not resected for symptom relief were considered unjustified or premature resections, since these lesions are regarded to have very low risk (<5%) of malignant progression and would have therefore been manageable with observation.[22, 26, 27] Needle tract seeding was defined as any highly suspect or pathologically proven gastric wall recurrence without connection to the pancreatic remnant in patients who underwent preoperative EUS-guided TA for a malignant tumor (i.e. PDAC, metastasis from other primary tumors). Adverse events grade following the EUS procedure were defined and graded according to the Clavien-Dindo classification.[1]

Outcomes and statistical analysis

The primary outcome was the percentage of patients with additional diagnostic value of EUS, defined as a composite of three scenarios: (a) EUS confirmed an uncertain diagnosis on cross-sectional imaging, (b) EUS provided the correct diagnosis in case of discrepancy between cross-sectional imaging and EUS, or (c) EUS-guided TA provided a correct tissue diagnosis necessary for neoadjuvant treatment. In contrast, EUS was considered of no additional diagnostic value if: (d) EUS did not provide any complementary diagnostic information, or (e) if EUS provided an incorrect diagnosis. The primary outcome was calculated based on patients who underwent preoperative EUS. Furthermore, a sensitivity analysis was performed including all patients irrespective of preoperative EUS.

Secondary outcomes were the percentage of patients with a justified resection based on final pathological examination (i.e. for all patients, irrespective of diagnostic workup) and the additional value of EUS for each preoperative radiological diagnosis (i.e. for patients who underwent EUS). Furthermore, we assessed how often EUS imaging and EUS-guided TA correctly changed the treatment plan (i.e. a justified resection or neoadjuvant treatment). Last, we assessed the potential disadvantages of EUS, including the rate of needle tract seeding and serious adverse events grade 3 or higher following EUS.

Categorical variables were presented as frequencies and proportions. Continuous variables were presented as medians with interquartile range (IQR). Statistical analysis was performed with SPSS Version 25.0 statistic software package.

RESULTS

Patient characteristics

We included 181 patients who underwent distal pancreatectomy between April 2010 and August 2017. The characteristics of the 181 included patients are described in Table 1, section A. Of all patients, 117 (65%) had a solid lesion and 64 (35%) had a cystic lesion.

Diagnostic workup

The characteristics of the diagnostic workup are described in Table 1, section B. Preoperatively, CT was performed in 160 patients (88%), MRI/MRCP in 72 patients (40%), and both CT and MRI/MRCP in 53 patients (29%). In addition to cross-sectional imaging, EUS was performed in 123 patients (68%), more frequently in patients with a cystic lesion (solid: 73 (62%); cystic: 50 (78%)). Tissue acquisition was performed in 78 patients (43%). EUS-guided TA was performed in a comparable proportion of solid and cystic lesions (solid: 45%; cystic: 39%).

Table 1. Patient characteristics

	Entire cohort (n = 181)	Solid (n = 117)	Cystic (n = 64)
A. Clinical characteristics			
Age at surgery in years, median (IQR)	62 (51 – 69)	61 (49 – 68)	64 (52 – 71)
Female, n (%)	102 (56%)	57 (49%)	45 (70%)
First presentation, n (%)			
Symptomatic	96 (53%)	64 (55%)	32 (50%)
Incidental	65 (36%)	40 (34%)	25 (39%)
FU for pancreatic cyst	7 (4%)	2 (2%)	5 (8%)
FU for mutation / familiar PDAC	8 (4%)	6 (5%)	2 (3%)
FU for lesion outside of pancreas [a]	5 (3%)	5 (4%)	0
B. Diagnostic workup			
Imaging modalities, n (%)			
CT	160 (88%)	112 (96%)	48 (75%)
MRI	72 (40%)	39 (33%)	33 (52%)
CT / MRI + EUS	123 (68%)	73 (62%)	50 (78%)
CT / MRI + EUS + TA	78 (43%)	53 (45%)	25 (39%)
Attempts of TA, 1 vs. 2, n	71 vs. 7	49 vs. 4	22 vs. 3
C. Postoperative pathology			
Malignant lesions	91 (50%)	79 (68%)	12 (19%)
PDAC	43 (24%)	34 (29%)	9 (14%)
pNET	44 (24%)	41 (35%)	3 (5%)
Metastasis other primary	4 (2%)	4 (3%)	0
Premalignant lesions	49 (27%)	8 (7%)	41 (64%)
IPMN – HGD	4 (2%)	0	4 (6%)
IPMN – LGD or MGD	15 (8%)	1 (1%)	14 (22%)
MCN	23 (13%)	0	23 (36%)
SPN	7 (4%)	7 (6%)	0
Benign lesions	41 (23%)	30 (26%)	11 (17%)
Pancreatitis	25 (14%)	23 (20%)	2 (3%)
Pseudocyst	1 (1%)	0	1 (2%)
SCN	6 (3%)	0	6 (9%)
Other benign lesion or no tumor [b]	9 (5%)	7 (6%)	2 (3%)
Justified resection, n (%)	148 (82%)	105 (90%)	43 (67%)

[a] Presentation during follow-up for other lesions: neuroendocrine tumor, retroperitoneal fibrosis, renal cell carcinoma, granular tumor esophagus, hemangiopericytoma.

[b] Two patients had no detectable lesion and one patient had a pathological complete response after induction treatment for pancreatic cancer.

Abbreviations: CT = Computed Tomography. EUS = Endoscopic ultrasound. Fam. = family. FNA = fine needle aspiration. FNB = fine needle biopsy. FU = follow-up. HGD = high-grade dysplasia. IPMN = Intraductal papillary mucinous neoplasm. IQR = interquartile range. LGD = low-grade dysplasia. MCN = mucinous cystic neoplasm. MGD = moderate-grade dysplasia. MPD = main pancreatic duct. MRI = Magnetic Resonance Imaging. N = number of patients. NA = not applicable. PDAC = pancreatic ductal adenocarcinoma. pNET = pancreatic neuroendocrine tumor. SPN = solitary pseudopapillary neoplasm. SCN = serous cystic neoplasia. TA = tissue acquisition.

Postoperative pathology and justified resection

The postoperative pathology is shown in Table 1, section C. Ninety-one patients (50%) had a malignant diagnosis, including PDAC (*n=43)* and pNET (*n=44)*. Forty-nine patients (27%) had a premalignant diagnosis*.* Forty-one patients (23%) had benign diagnoses, mostly pancreatitis (*n*=25). Based on final pathology examination, resection was justified in 148 patients (82%). By lesion type, 105 patients with solid lesions underwent a justified resection, compared with 67% with cystic lesions. Within the subgroup of 58 patients (32%) who underwent resection without preoperative EUS, the diagnosis based on cross-sectional was correct in 50 patients (86%). Moreover, the resection was justified for the vast majority of this subgroup, yet five patients (9%) underwent an unjustified resection (Suppl. Table 1).

Additional diagnostic value of EUS

Table 2 shows the percentage of patients with additional diagnostic value of EUS by lesion type, with further specifications on how EUS provided this additional value in Suppl. Table 2. Overall, EUS was considered of additional diagnostic value in 59 patients (48%) who underwent EUS. By lesion type, EUS was of additional value for 32 patients (44%) with a solid lesion and 27 patients (54%) with a cystic lesion. For both lesion types, the additional value of EUS was mostly based on providing the correct diagnosis in case of discrepancy with cross-sectional imaging (b). In total, 53 patients had discrepancies between the cross-sectional imaging and endoscopic diagnosis, of whom EUS provided the correct diagnosis in 30 (57%). More specifically, providing the correct diagnosis resulted in a change of treatment plan in 20 patients (27%) with a solid lesion and 14 patients (28%) with a cystic lesion. This change of treatment plan was mostly based on EUS imaging for patients with a cystic lesion versus EUS-guided TA in patients with a solid lesion. Without taking into account the inherent obvious value of EUS-guided TA necessary for neoadjuvant treatment, EUS was of additional value in 25 patients (34%) with a solid lesion and 27 patients (54%) with a cystic lesion. In patients with no additional value of EUS (*n=64)*, EUS was correct but provided no additional information in 54 patients (d: 44%), whilst the diagnosis based on EUS was incorrect in 10 patients (e: 8%) (Suppl. Table 3). In a sensitivity analysis based on all patients (i.e. including patients who did not undergo EUS), EUS was of additional value in 32 patients (27%) with a solid lesion and 27 patients (42%) with a cystic lesion (Suppl. Table 4).

Additional diagnostic value of EUS by cross-sectional radiological diagnosis

Table 3 shows the percentage of patients with additional value of EUS by cross-sectional radiological diagnosis. For solid lesions, EUS was of additional value in 25 patients (47%) with radiological suspicion of a malignant or premalignant lesion and in seven patients (35%) with suspicion of a benign lesion. For cystic lesions, this was the case in 20 patients (49%) with suspicion of a malignant or premalignant lesion and in seven patients (78%) with suspicion of a benign lesion.

Table 2. Additional diagnostic value of EUS with or without tissue acquisition

	Entire cohort (n = 123)	Solid (n = 73)	Cystic (n = 50)
Additional value	59 (48%)	32 (44%)	27 (54%)
a. EUS confirmed an uncertain diagnosis	20 (16%)	10 (13.7%)	10 (20%)
b. Discrepancy with CT/ MRI, EUS correct	30 (24%)	13 (18%)	17 (34%)
c. EUS provided tissue diagnosis for neoadjuvant treatment	9 (7%)	9 (12%)	0
Change of treatment plan based on EUS imaging [a]	19 (15%)	6 (8%)	13 (26%)
Change of treatment plan based on EUS-guided TA [a]	15 (12%)	14 (19%)	1 (2%)
No change of treatment plan [a]	5 (4%)	2 (3%)	3 (6%)
No additional value	64 (52%)	41 (56%)	23 (46%)
d. No complementary information	54 (44%)	35 (48%)	19 (38%)
e. EUS incorrect	10 (8%)	6 (8%)	4 (8%)

[a] Further subdivision of total group of patients with additional value of EUS based on discrepancy with CT/ MRI (b) and tissue diagnosis for neoadjuvant treatment (c).
Abbreviations: CT = Computed Tomography. EUS = Endoscopic ultrasonography. MRI = Magnetic Resonance Imaging. TA = tissue acquisition.

Table 3. Additional diagnostic value of EUS by cross-sectional radiological diagnosis in patients who underwent EUS

Diagnosis based on cross-sectional imaging	Solid (n, %)	Cystic (n, %)
Malignant	22/47, 47%	2/3, 67%
PDAC	10/23, 44%	2/3, 67%
pNET	9/21, 43%	-
Metastases other	2/2, 100%	-
GIST	1/1, 100%	-
Premalignant	3/6, 50%	18/38, 47%
IPMN	-	10/23, 44%
MCN	1/2, 50% [a]	8/15, 54%
SPN	2/4, 50%	-
Benign	7/20, 35%	7/9, 78%
Pancreatitis	5/14, 36%	1/1, 100% [b]
Pseudocyst	-	5/5, 100%
SCN	-	1/3, 33%
No tumor	2/6, 33%	-
Total	**32/73, 44%**	**27/50, 54%**

[a] Two patients had solid lesions with cystic components, therefore considered as solid lesions. [b] One patient had differential diagnosis of IPMN based on EUS yet pancreatitis with enlarged main pancreatic duct based on cross-sectional imaging; therefore considered as cystic lesion. Abbreviations: EUS = endoscopic ultrasonography. GIST = gastrointestinal stromal tumor. IPMN = Intraductal papillary mucinous neoplasm. MCN = mucinous cystic neoplasm. PDAC = pancreatic ductal adenocarcinoma. pNET = pancreatic neuroendocrine tumor. SCN = serous cystic neoplasia. SPN = solitary pseudopapillary neoplasm.

Disadvantages of EUS

Out of the 22 patients who underwent EUS-guided TA with a malignant final diagnosis, three patients were lost to follow-up and the remaining 19 did not show evidence for needle tract seeding. No serious adverse event following EUS was reported.

DISCUSSION

This multicenter retrospective cohort study aimed to assess the diagnostic value of EUS in addition to cross-sectional imaging in a heterogeneous surgical cohort of patients with pancreatic body or tail lesions. EUS was of additional diagnostic value in half of all patients who underwent an EUS for varying pancreatic etiologies.

In this cohort, the value of EUS seemed somewhat more pronounced in patients with cystic lesions. Corresponding with literature, patients with solid and cystic lesions benefitted from additional EUS in a different manner. For patients with cystic lesions, EUS imaging mostly provided additional diagnostic value, whereas the supplementary value in solid lesions was mostly based on EUS-guided TA.[28-30] Of note, only nine patients (5%) in the current cohort received neoadjuvant treatment for PDAC. With the upcoming use of a neoadjuvant approach and the subsequent need for TA, plus the introduction of newer diagnostic techniques such as EUS-guided 'through-the-needle' (Moray) biopsies, the additional value of EUS is expected to even further increase.[31-33]

Our study underlines the value of EUS at a broad spectrum of diagnoses. Due to the relatively small number of patients per pancreatic etiology, it is difficult to specifically define when to pursue with additional EUS following cross-sectional imaging. In addition, our study was not designed to assess which of all patients presenting with a pancreatic body/tail mass should undergo an additional EUS (i.e., "denominator data"). However, some general conclusions can be drawn from our data. First, in patients with discrepancies between diagnoses based on EUS and cross-sectional imaging, EUS more often provided the correct diagnosis. Second, EUS seems very safe with no serious adverse events and no evidence for needle tract seeding. Third, even further minimizing the adverse effect of EUS, 10 patients with incorrect endoscopic diagnosis underwent a resection that was nonetheless justified based on final pathology or patients' wish to undergo surgery despite the discussed risk of surgical overtreatment. Together, these arguments further substantiate the recommendation for additional EUS in a broad selection of patients. On the other hand, EUS may be considered unnecessary in patients with a clearly resectable pancreatic mass on cross-sectional imaging, since the benefit of neoadjuvant treatment for early stage PDAC has not been established yet and guidelines recommend upfront surgery followed by adjuvant chemotherapy in these patients.[34, 35] In the setting of possible neoadjuvant treatment, EUS-guided TA remains essential. Large studies including all consecutive patients who underwent an EUS following

CT and/or MRI may further specify the added value of EUS for all patients presenting with a pancreatic body/tail mass, although confirmation bias presents an inevitable challenge in this setting.

Despite thorough diagnostic workup and clinical guidelines, distal pancreatectomy was justified for only 67% of patients with a cystic lesion and in 90% of patients with a solid lesion in our study. In other words, one out of three patients with a cystic lesion has undergone unjustified or premature major abdominal surgery with associated risk of complications and long-term adverse effects. Other studies assessing surgical overtreatment in focal pancreatic lesions often do not report this outcome specifically for pancreatic body and tail lesions. Within studies reporting this outcome, the proportion of body and tail lesions is 40% or less, thereby limiting direct comparison of our results with other studies. While taking this difference into account, these studies do confirm our finding of surgical overtreatment in a substantial percentage of patients with cystic lesions.[4-7] A prospective cohort study by Lekkerkerker et al. reported a justified resection in 52 out of 115 patients (45%) with cystic pancreatic lesions.[4] Of note, this study only classified resection of MCN to be justified in case of HGD or cancer whilst all resections for MCN were considered justified in our study based on the commonly used guidelines at time of study protocol.[22-24] Similarly, a multicenter retrospective study of 251 patients who underwent resection for IPMN showed surgical overtreatment for low-grade dysplasia in 51% of patients.[5] For branch-duct IPMN specifically, a large single-institutional series of 240 patients demonstrated a justified resection percentage of only 22% when the criteria used in our study are applied.[6] Although relatively less common, 12 out of 117 patients (10%) with a solid lesion in our study underwent an unjustified resection. This percentage is comparable to a retrospective study including 75 patients with a pancreatic body or tail lesion suspect for a solid neoplasm who underwent distal pancreatectomy, of whom 11% had a benign lesion.[7] Overall, our study emphasizes the complexity of the clinical management of pancreatic body or tail lesions, especially cystic lesions, balancing between the risk of surgical overtreatment and the clear error of missing a malignancy. Prospective studies may elaborate on the risk of progression or malignant transformation during watchful waiting strategies for specific pancreatic lesions, such as asymptomatic pancreatic cystic lesions (PACYFIC study, www.pacyfic.net) and small non-functional pNETs (Trial NL9584).[36]

To our knowledge, this is the first study that focused specifically on the value of EUS in pancreatic body or tail lesions. Other strengths of our study are the ability to verify the final diagnosis in all patients and the inclusion of a diversity of pancreatic lesions of both cystic and solid etiology. However, the findings of our study should be interpreted in light of some limitations. First, after prospective patient selection, most of the data were collected retrospectively. As a consequence, some outcomes were dependent on the quality of the radiological and endoscopic reports, possibly introducing information bias. Second, selection bias was introduced by including only patients who underwent a resection. However,

without this selection, final pathological diagnoses would be missing with subsequent introduction of verification bias. We performed a sensitivity analysis including the 58 patients (32%) who did not undergo EUS following cross-sectional imaging to provide insight in potential additional selection bias for our primary outcome. In this analysis, the value of EUS was obviously lower compared to our primary analysis since only the denominator increased. Still, the additional value remained substantial, especially for cystic lesions. Third, the decision for a resection in this patient cohort was based on applicable guidelines at time of study protocol (i.e. 2010 – 2017).[22-24] Hence, clinical decision-making may have differed from current practice, wherein neoadjuvant treatment for PDAC is increasing and active surveillance for non-functional asymptomatic pNET <2 cm is considered standard practice.[34, 37]

In conclusion, our study showed that EUS had additional diagnostic value besides cross-sectional imaging in half of the patients who underwent a distal pancreatectomy for a pancreatic body or tail lesion with low associated risks. Therefore, we believe EUS should always be considered in case of an uncertain radiological diagnosis or the need for tissue diagnosis.

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SUPPLEMENTARY FILES

Supplementary Table 1. Differences between diagnosis based on cross-sectional imaging and postoperative diagnosis in patients who underwent resection without preoperative EUS

Diagnosis based on cross-sectional imaging	Postoperative diagnosis (n, %)
PDAC (n = 11)	PDAC (10, 91%) pNET (1, 9%)
pNET (n = 20)	pNET (17, 85%) PDAC (1, 5%) SPN (1, 5%) No tumor (1, 5%) [c]
Metastasis other primary (n = 1)	Metastasis other primary (1, 100%)
IPMN (n = 5)	IPMN – invasive (1, 20%) IPMN – HGD (1, 20%) IPMN – LGD or MGD (1, 20%) [c] SCN (1, 20%) [c] No tumor (1, 20%) [c]
MCN (n = 7)	MCN (7, 100%)
SCN (n = 2) [a]	SCN (2, 100%)
SPN (n = 2)	SPN (2, 100%)
Pancreatitis (n = 9)	Pancreatitis (8, 89%) IPMN – LGD or MGD (1, 11%) [c]
Pseudocyst (n = 1) [b]	MCN (1, 100%)
Total correct	**50/58, 86%**
Total unjustified resections [c]	**5/58, 9%**

[a] Two patients underwent resection for radiologic suspicion of large symptomatic SCN, therefore decided for resection despite benign etiology.

[b] One patient underwent resection for radiologic suspicion of large pseudocyst with differential diagnosis of MCN, with peroperative decision for marsupialization or resection based on frozen section of cystic wall.

[c] Five patients underwent an unjustified resection, with final pathology examination including no tumor (*n=2),* SCN (*n=1)*, and IPMN with LGD or MGD (*n=2).*

Abbreviations: EUS = endoscopic ultrasonography. HGD = high-grade dysplasia. IPMN = Intraductal papillary mucinous neoplasm. LGD = low-grade dysplasia. MCN = mucinous cystic neoplasm. MGD = moderate-grade dysplasia. PDAC = pancreatic ductal adenocarcinoma. pNET = pancreatic neuroendocrine tumor. SCN = serous cystic neoplasia. SPN = solitary pseudopapillary neoplasm.

Supplementary Table 2. Specification on the added value of EUS, to support Table 2

Confirmation uncertain diagnosis (n=20):
PDAC on EUS imaging (n=5) and/or with TA (n=4)
pNET on EUS imaging (n=1) and/or with TA (n=1)
IPMN on EUS imaging (n=2)
MCN on EUS imaging (n=6) and/or with TA (n=4)
Pancreatitis on EUS imaging, exclusion of other disease entity (n=1)
Metastasis from other primary with TA (n=2)

Discrepancy with CT/MRI (n=30):
Differentiation of PDAC vs pNET with TA (n=1)
Differentiation of PDAC versus MCN/SCN with TA (n=1)
Differentiation of PDAC versus pancreatitis on EUS imaging (n=1) and/or with TA (n=1)
Differentiation of PDAC versus mucus on EUS imaging (n=1)
Differentiation of PDAC versus IPMN on EUS imaging (n=5) and/or with TA (n=1)
Differentiation of pNET versus PDAC with TA (n=1)
Differentiation of pNET versus SPN on EUS imaging (n=1) and/or with TA (n=1)
Differentiation of pNET versus no tumor on EUS imaging (n=1) and/or with TA (n=1)
Differentiation of SPN versus pNET with TA (n=1)
Differentiation of SPN versus GIST with TA (n=1)
Differentiation of IPMN versus SCN on EUS imaging (n=1)
Differentiation of IPMN versus benign obstruction on EUS imaging (n=1)
Differentiation of IPMN versus pancreatitis on EUS imaging (n=1)
Differentiation of MCN versus IPMN on EUS imaging (n=1)
Differentiation of MCN versus pseudocyst on EUS imaging (n=4) and/or CF analysis (n=1)
Differentiation of pseudocyst versus MCN on EUS imaging (n=4)
Exclusion of second lesion on EUS imaging, preventing total pancreatectomy (n=1)

Tissue diagnosis for neoadjuvant treatment (n=9)
Confirmation of PDAC with TA (n=6)
Confirmation of pNET with TA (n=3)

Change of plan based on EUS imaging (n=19):
Differentiation of PDAC versus mucus on EUS imaging (n=1)
Differentiation of PDAC versus MCN/SCN on EUS imaging (n=1)
Differentiation of PDAC versus pancreatitis on EUS imaging (n=2)
Differentiation of PDAC versus IPMN on EUS imaging (n=4)
Differentiation of pNET versus no tumor on EUS imaging (n=1) and/or TA (n=1)
Differentiation of SB-IPMN versus PDAC as second lesion on EUS imaging (n=1)
Differentiation of IPMN versus SCN on EUS imaging (n=1)
Differentiation of IPMN versus benign obstruction on EUS imaging (n=1)
Differentiation of IPMN versus pancreatitis on EUS imaging (n=1)
Differentiation of MCN versus IPMN on EUS imaging (n=1)
Differentiation of MCN versus pseudocyst on EUS imaging (n=4)
Exclusion of second lesion on EUS imaging, preventing total pancreatectomy (n=1)

Change of plan based on EUS-guided TA / cyst fluid analysis (n=15)
Differentiation of PDAC versus MCN/SCN with TA (n=1)
Differentiation of pNET versus no tumor on EUS imaging (n=1) and/or TA (n=1)
Differentiation of pNET versus PDAC with TA (n=1)
Differentiation of SPN versus GIST with TA (n=1)
Differentiation of MCN versus pseudocyst with cyst fluid analysis (n=2) and/or TA (n=2)
Neoadjuvant treatment for PDAC based on TA (n=6)
Neoadjuvant treatment for pNET based on TA (n=3)

Supplementary Table 3. Incorrect diagnosis by EUS with or without tissue acquisition

Clinical course	Diagnosis based on EUS with or without tissue acquisition	Diagnosis based on cross-sectional imaging	Final pathological diagnosis
EUS during genetic pancreatic cancer screening for BRCA-mutation. Patients' wish to undergo surgery despite ongoing uncertainty with risk of overtreatment.	PDAC	No tumor	Myxoid soft-tissue tumor
EUS during familial pancreatic cancer screening. Patients' wish to undergo surgery despite ongoing uncertainty with risk of overtreatment.	PDAC	No tumor	Pancreatitis
EUS following findings of a new lesion on cross-sectional imaging, potentially malignant	PDAC	Pancreatitis	Pancreatitis
EUS following findings of a new lesion on cross-sectional imaging, potentially malignant. Patients' wish to undergo surgery despite ongoing uncertainty with risk of overtreatment.	PDAC	Pancreatitis	Pancreatitis
EUS following findings of a new lesion on cross-sectional imaging, potentially malignant	PDAC	PDAC	Pancreatitis
EUS after findings of new lesion on cross-sectional imaging, potentially malignant	No tumor	PDAC	PDAC
EUS in follow-up for IPMN (NB MRI 6 months prior to EUS and resection showed no high-risk stigmata)	IPMN with high-risk stigmata (nodule) and worrisome features (size, wall thickening)	IPMN with worrisome features	IPMN with LGD
EUS following findings of a large cystic lesion on cross-sectional imaging, symptomatic	Pseudocyst	MCN	MCN
EUS following findings of a large cystic lesion on cross-sectional imaging, symptomatic	Pseudocyst	MCN	MCN
EUS following an uncertain diagnosis on CT.	MCN	SCN	SCN

Abbreviations: CT = Computed Tomography. EUS = Endoscopic ultrasonography. IPMN = Intraductal papillary mucinous neoplasm. LGD = low-grade dysplasia. MCN = mucinous cystic neoplasm. MGD = moderate-grade dysplasia. MRI = Magnetic Resonance Imaging. PDAC = pancreatic ductal adenocarcinoma. pNET = pancreatic neuroendocrine tumor. SCN = serous cystic neoplasia.

Supplementary Table 4. Additional diagnostic value of EUS with or without tissue acquisition based on total cohort

	Entire cohort (n = 181)	**Solid** (n = 117)	**Cystic** (n = 64)
Additional value	59 (33%)	32 (27%)	27 (42%)
a. EUS confirmed an uncertain diagnosis	20 (11%)	10 (9%)	10 (16%)
b. Discrepancy with CT/ MRI, EUS correct	30 (17%)	13 (11%)	17 (27%)
c. EUS provided tissue diagnosis for neoadjuvant treatment	9 (5%)	9 (8%)	0
Change of treatment plan based on EUS imaging [a]	19 (11%)	6 (5.1%)	13 (20%)
Change of treatment plan based on EUS-guided TA [a]	15 (8%)	14 (12%)	1 (2%)
No change of treatment plan [a]	5 (3%)	2 (2%)	3 (5%)
No additional value	122 (67%)	85 (73%)	37 (58%)
d. No complementary information	54 (30%)	35 (30%)	19 (30%)
e. EUS incorrect	10 (6%)	6 (5%)	4 (6%)
No EUS performed	58 (32%)	44 (38%)	14 (22%)

[a] Additional subdivision of total group of patients with additional value of EUS based on discrepancy with CT/MRI (b) and tissue diagnosis for neoadjuvant treatment (c).

Abbreviations: CT = Computed Tomography. EUS = Endoscopic ultrasonography. MRI = Magnetic Resonance Imaging. TA = tissue acquisition.

CHAPTER 3

Sensitivity of CT, MRI, and EUS-FNA/B in the preoperative workup of histologically proven left-sided pancreatic lesions

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ABSTRACT

Background

Left-sided pancreatic lesions are often treated surgically. Accurate diagnostic work-up is therefore essential to prevent futile major abdominal surgery. Large series focusing specifically on the preoperative work-up of left-sided pancreatic lesions are lacking. This surgical cohort analysis describes the sensitivity of CT, MRI, and EUS-FNA/B in the diagnostic work-up of left-sided pancreatic lesions.

Methods

We performed a post-hoc analysis of patients who underwent surgery for a left-sided pancreatic lesion between April 2010 and August 2017 and participated in the randomized CPR trial. Primary outcome was the sensitivity of CT, MRI, and EUS-FNA/B. Sensitivity was determined as the most likely diagnosis of each modality compared with the postoperative histopathological diagnosis. Additionally, the change in sensitivity of EUS versus EUS-FNA/B (i.e., cyst fluid analysis, and/or tissue acquisition) was measured.

Results

Overall, 181 patients were included (benign: 23%, premalignant: 27%, malignant: 50%). Most patients had solid lesions (65%). Preoperative imaging included CT (86%), MRI (41%), EUS (68%). Overall, CT and EUS-FNA/B reached a sensitivity of both 71%, compared with 66% for MRI. When EUS was combined with FNA/B, sensitivity rose from 64% to 71%. For solid lesions, CT reached the highest sensitivity (75%) when compared with MRI (70%) and EUS-FNA/B (69%). For cystic lesions, EUS-FNA/B reached the highest sensitivity (75%) when compared with CT and MRI (both 62%).

Conclusion

CT is the most sensitive diagnostic modality for solid and EUS-FNA/B for cystic left-sided pancreatic lesions. EUS-FNA/B was associated with an increased sensitivity when compared with EUS alone.

INTRODUCTION

Solid and cystic pancreatic lesions comprise a heterogeneous group of entities, ranging from benign disease to malignant neoplasms. To prevent unnecessary major abdominal surgery and to minimize the risk of misdiagnosing (pre)malignant lesions, optimizing the preoperative diagnostic workup of pancreatic lesions is essential.

Interestingly, the sensitivity of CT, MRI, and EUS to diagnose pancreatic lesions in general and left-sided pancreatic lesions specifically has not been thoroughly studied. The authors of a recent Cochrane review on the sensitivity and specificity of diagnostic imaging for pancreatic lesions (i.e., any location) state that no firm conclusions can be drawn due to a limited amount of published studies, large heterogeneity in the estimates, and questionable methodological quality.[1]

Since optimal characterization by imaging partly depends on the lesion type and may require different imaging modalities, most patients undergo multiple imaging modalities to correctly characterize pancreatic lesions. The choice of cross-sectional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) also depends on factors such as availability, costs, risks, contraindications, and the experience and preference of the treating physician.[2]

In case of an uncertain diagnosis, endoscopic ultrasound (EUS), with possible fine-needle aspiration or fine-needle biopsy (FNA/FNB), can be performed to further differentiate the lesion. Especially pancreatic cystic neoplasms (PCN) pose a diagnostic challenge. Even if best clinical practice is applied, only 72% of PCN are diagnosed according to the correct subtype.[3] PCN range from serous cystadenomas (SCN), which are benign and typically do not require intervention, to (pre)malignant entities such as mucinous cystadenomas (MCN) and intraductal papillary mucinous neoplasms (IPMN), which require follow-up or even surgical resection. Whilst distal pancreatectomy is less invasive than pancreatoduodenectomy, it still has a postoperative mortality of 1-2%. Also, 20% of the patients develop postoperative complications like delayed gastric emptying and pancreatic fistula.[4,5] Furthermore, distal pancreatectomy regularly involves spleen resection and induces lifelong exocrine insufficiency in up to 70% of patients and insulin-dependent diabetes mellitus in 29%.[6,7]

In order to improve clinical decision making and prevent futile major abdominal surgery, we performed a post-hoc analysis of a surgical cohort to give a descriptive overview of the sensitivity of CT, MRI, and EUS-FNA/B in the preoperative work-up of left-sided focal pancreatic lesions when compared to the postoperative histopathological diagnosis as the gold standard.

PATIENTS AND METHODS

Study Design and Patients

We performed a bi-center post-hoc analysis of patients who underwent a distal pancreatectomy for a pancreatic body and/or tail lesion between April 2010 and August 2017 at the Amsterdam UMC (location AMC) and the Erasmus MC University Medical Center. All patients participated in the randomized controlled multicenter CPR trial.[8] We will report the sensitivity of CT, MRI, and EUS-FNA/B specifically since our cohort merely consisted of surgically treated patients and therefore lacks a control group of patients not having the disease. As a consequence, it is not feasible to report the specificity and overall diagnostic accuracy. The current study was performed according to the STARD guidelines.[9] The local institutional review board of the Erasmus MC approved the study and waived the requirement to obtain informed consent. The indication for resection was based on the guidelines that were commonly used between 2010 and 2017.[10-12] The indication for surgery was discussed at the multidisciplinary meeting including a team of pancreatobiliary-dedicated gastroenterologists, surgeons, radiologists, pathologists, and oncologists.

Data collection and definitions

We classified lesions as either solid or cystic based on the postoperative pathology reports and all available radiology reports. When lesions consisted of both solid and cystic components, two authors (LvD and JvH) independently reviewed the reports to determine the most prominent type. Disagreement was solved through discussion. CT and MRI scans were interpreted by expert radiologists from our two centers. If radiologic imaging was obtained at a referring institution, the scans were re-read by our radiologists. EUS was performed by a core group of experienced endoscopists in our centers. All imaging was reviewed at the multidisciplinary meeting.

The definition of sensitivity per postoperative diagnosis is presented in **Supplementary Table S1**. In short, preoperative imaging diagnosis was classified as correct if it was in accordance with the postoperative histopathological diagnosis. Cyst fluid (CF) analysis was classified as correct if carcinoembryonic antigen (CEA) levels ≥ 192 µmol/L were found in mucinous lesions or if a CEA level ≤ 5 µmol/L was found in non-mucinous lesions.[13,14] If the resection specimen revealed pseudocysts, CF analysis was classified as correct if both the CEA level was ≤ 5 µmol/L and the amylase level was > 250 µmol/L [14]. Tissue acquisition (TA) was performed at the discretion of the endoscopist and consisted of either FNA and/or FNB. TA was classified as correct if the most likely diagnosis based on the diagnostic cytology and/or histology report was in accordance with the postoperative histopathological diagnosis.

To provide insight in the quality of radiologic imaging, we assessed the imaging characteristics per imaging modality (i.e., the administration of intravenous contrast and the presence

of multiple phases for CT, and the presence of intravenous contrast, diffusion-weighted images (DWI), and magnetic resonance cholangiopancreatography (MRCP) sequences for MRI). EUS-FNA/B diagnosis consisted of the most likely diagnoses based on EUS and possible FNA and/or FNB. To establish the preoperative diagnosis by CT, MRI, and EUS-FNA/B, we used the only one or, in case of a differential diagnosis, the first mentioned and therefore most likely diagnosis in the corresponding imaging report. In case of unclear or undetermined differential diagnosis, the report of the multidisciplinary meeting following the image modality was reviewed. For ongoing ambiguity, the reports and images were independently reviewed by the researchers and consensus was reached on the final diagnosis in a new multidisciplinary meeting.

The primary outcome was the sensitivity which was calculated for CT, MRI, and EUS-FNA/B, based on postoperative histopathological diagnosis. As secondary aim, we analyzed the change in sensitivity of EUS versus EUS-FNA/B.

Medical records were retrospectively assessed to determine the primary and secondary outcomes. Inconclusive cases were independently reviewed by LvD and JvH. Disagreements were resolved through discussion.

Statistical Analysis

Baseline characteristics were presented as frequencies and proportions for categorical variables, and median with interquartile range (IQR) for continuous variables. Sensitivity of imaging modalities was presented as percentages of the total cohort and separately by lesion type (i.e., solid or cystic). Data were analyzed with the use of IBM SPSS Statistics version 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

RESULTS

Patient characteristics and postoperative pathology

Overall, 181 patients who underwent a distal pancreatectomy were included, see **Table 1** for patient and lesion characteristics. Most patients had a solid lesion (65%) and 53% presented with symptoms (e.g., weight loss, abdominal pain, pancreatitis), whereas the lesion was found incidentally in 36% of the patients. For the remainder of the patients, the resection indication developed during follow-up for a pancreatic cyst, familiar pancreatic ductal adenocarcinoma (PDAC), or a lesion outside of the pancreas. Postoperative histopathological diagnosis revealed malignancy in 51%, premalignant lesions in 27% and benign lesions in 22% of the patients. Pancreatic neuroendocrine tumor (pNET) and PDAC were the most prevalent diagnoses, each diagnosed in 24% of the patients.

Table 1. Patient and lesion characteristics

	Entire cohort (n = 181)	Solid lesion (n = 118)	Cystic lesion (n = 63)
A. Clinical characteristics			
Age at surgery in years, median (IQR)	62 (51 – 69)	61 (49 – 68)	64 (52 – 70)
Female, n (%)	102 (56)	58 (49)	44 (70)
First presentation, n (%)			
Symptomatic[1]	96 (53)	65 (55)	31 (49)
Incidental	65 (36)	40 (34)	25 (40)
FU for pancreatic cyst	7 (4)	2 (2)	5 (8)
FU for mutation / familiar PDAC	8 (4)	6 (5)	2 (3)
FU for lesion outside of pancreas[2]	5 (3)	5 (4)	-
B. Postoperative histopathology			
Malignant lesions	**92 (51)**		
PDAC[3]	44 (24)	35 (30)	9 (14)
pNET	44 (24)	41 (35)	3 (5)
Metastasis other primary	4 (2)	4 (3)	-
Premalignant lesions	**49 (27)**		
IPMN	20 (11)	-	20 (31)
MCN	22 (12)	-	22 (34)
SPN	7 (4)	7 (6)	-
Benign lesions	**40 (22)**		
Pancreatitis	25 (14)	25 (21)	-
SCN	6 (3)	-	6 (9)
Pseudocyst	1 (1)	-	1 (2)
Other lesion or no tumor[4]	8 (4)	6 (5)	2 (3)
C. Diagnostic workup			
Imaging modalities, n (%)			
CT	156 (86)	108 (91)	47 (75)
MRI	74 (41)	40 (34)	37 (59)
EUS	122 (67)	74 (63)	48 (76)
EUS + TA	78 (64)	54 (73)	24 (50)
EUS + CF	22 (18)	1 (1)	21 (44)

[1] Pancreatic symptoms were defined as pancreatitis, abdominal pain, and/or weight loss.
[2] Presentation during follow-up for other lesions: neuroendocrine tumor, retroperitoneal fibrosis, renal cell carcinoma, granular tumor esophagus, hemangiopericytoma.
[3] Including PDAC derived from IPMN or MCN
[4] Two patients had no detectable lesion, two patients had small inflammatory changes, one patient had a granular tumor, one patient had ectopic spleen tissue, one patient had a retention cyst and one patient had pancreatic intraepithelial neoplasia (PanIN).
Abbreviations: CF = cyst fluid. CT = computed Tomography. EUS = endoscopic ultrasound. FU = follow-up. IPMN = intraductal papillary mucinous neoplasm. IQR = interquartile range. MCN = mucinous cystic neoplasm. MRI = magnetic resonance imaging. N = number of patients. PDAC = pancreatic ductal adenocarcinoma. pNET = pancreatic neuroendocrine tumor. SPN = solid pseudopapillary neoplasm. SCN = serous cystic neoplasm. TA = tissue acquisition.

Diagnostic imaging characteristics

The imaging modalities during preoperative workup are presented in **Table 1.** CT was performed in 156 patients (86%), whereas 74 patients (41%) underwent MRI. Of these, 51 patients (28%) underwent both CT and MRI. **Supplementary Table S2** shows the imaging characteristics per radiological imaging modality. Most patients underwent a CT scan with intravenous contrast and multiple phases (150 patients (97%) and 102 patients (66%), respectively). MRI included intravenous contrast in 62 patients (80%), whereas DWI and MRCP sequences were manufactured in 69% and 62% of the patients, respectively. EUS was performed in 122 patients (67%) in total, of whom 78 patients (64%) underwent additional TA and in 22 patients (18%) CF analysis was performed. The characteristics of EUS-FNA/B procedures are provided in **Supplementary Table S3.**

Sensitivity of imaging modalities

Table 2 shows the results per postoperative diagnosis, separately for solid and cystic lesions. Overall, CT and EUS-FNA/B reached a sensitivity for left-sided pancreatic lesions of both 71%, compared with 66% by MRI.

For solid lesions, CT showed the highest sensitivity (75%) compared with MRI and EUS-FNA/B, which reached a sensitivity of 70% and 69%, respectively (**Table 2A**). For PDAC specifically, EUS-FNA/B reached the highest sensitivity (91%), whilst pancreatitis was diagnosed most sensitively by MRI (90%). The diagnosis of pNET was made most sensitively by CT (82%) and least sensitive by MRI (64%). The diagnosis of solid pseudopapillary neoplasm (SPN) was difficult for all modalities, with sensitivity ranging from 43% to 50%. The diagnosis of solid lesions that were classified as 'other lesions' was even more challenging, with a maximum sensitivity of 33%.

For cystic lesions, EUS-FNA/B reached the highest sensitivity (75%), whilst MRI and CT reached a sensitivity of both 62%. Cystic PDAC was diagnosed most sensitively by EUS-FNA/B (86%), although CT reached a sensitivity of 83% as well. IPMN was diagnosed most sensitively by EUS-FNA/B (89%) and MRI (80%). MCN was diagnosed correctly by CT, MRI, and EUS-FNA/B in 72%, 70%, and 79% of the patients, respectively. SCN was diagnosed correctly by EUS-FNA/B in 33% of the patients, compared to 60% by CT (**Table 2B**). None of the three cystic pNET lesions were correctly diagnosed on cross-sectional imaging.

Sensitivity of EUS with additional analysis

In total, 122 patients underwent EUS, which was combined with TA in 78 patients (64%) and CF analysis in 22 patients (18%). **Supplementary table S4** shows the results per postoperative diagnosis, separately for solid and cystic lesions.

Table 2. Sensitivity of cross-sectional imaging per postoperative diagnosis

Postoperative diagnosis	CT n (%)	MRI n (%)	EUS-FNA/B n (%)
A. Solid lesions (n = 118)			
PDAC (n = 35)	27/34 (79)	7/10 (70)	20/22(91)
pNET (n = 41)	28/34 (82)	9/14 (64)	17/23 (74)
Metastasis other (n = 4)	3/4 (75)	1/1 (100)	2/3 (67)
SPN (n = 7)	3/7 (43)	1/2 (50)	2/4 (50)
Pancreatitis (n = 25)	19/25 (76)	9/10 (90)	10/17 (59)
Other lesions (n = 6)[1]	1/4 (25)	1/3 (33)	0/5 (0)
Total correct solid	**81/108 (75)**	**28/40 (70)**	**51/74 (69)**
B. Cystic lesions (n = 63)			
Cystic PDAC (n = 9)	5/6 (83)	4/6 (67)	6/7 (86)
pNET (n = 3)	0/3 (0)	0/2 (0.0)	0/3 (0)
IPMN (n = 20)	8/13 (61)	12/15 (80)	17/19 (89)
MCN (n = 22)	13/18 (72)	7/10 (70)	11/14 (79)
SCN (n = 6)	3/5 (60)	1/3 (33)	1/3 (33)
Pseudocyst (n = 1)	0/1 (0)	-	1/1 (100)
Other lesions (n = 2)[2]	0/1 (0)	0/1 (0)	0/1 (0)
Total correct cystic	**29/47 (62)**	**23/37 (62)**	**36/48 (75)**
Overall correct	**110/155 (71)**	**51/77 (66)**	**87/122 (71)**

[1] One patient had no detectable lesion, two patients had small inflammatory changes, one patient had a granular tumor, one patient had ectopic spleen tissue and one patient had pancreatic intraepithelial neoplasia (PanIN).
[2] One patient had no detectable lesion and one patient had a retention cyst.
Abbreviations: CT = computed tomography. EUS = endoscopic ultrasound. IPMN = intraductal papillary mucinous neoplasm. MCN = mucinous cystic neoplasm. MRI = magnetic resonance imaging. N = number of patients. PDAC = pancreatic ductal adenocarcinoma. pNET = pancreatic neuroendocrine tumor. SPN = solid pseudopapillary neoplasm. SCN = serous cystic neoplasm.

Overall, EUS provided a correct diagnosis in 64% of the patients. Additional CF analysis reached a sensitivity of 66%, whereas additional TA increased the sensitivity to 70%. EUS including both CF and TA led to a sensitivity of 71%, compared to 64% for EUS alone.

For solid lesions, TA increased the sensitivity when compared with EUS (69% versus 60%, respectively, **Supplementary table S4A**). This was especially profound in PDAC and pNET, with sensitivity rising from 82% to 91% and 61% to 74%, respectively.

In patients with cystic lesions, both additional CF and TA analysis led to a slight increase in sensitivity when compared to EUS (75%, 73%, and 71%, respectively). This increase is predominantly caused by the sensitivity for MCN lesions, which increased from 64% to 71% with TA and to 79% when additional CF analysis was performed.

DISCUSSION

This bi-center study on the sensitivity of CT, MRI, and EUS-FNA/B in the preoperative workup of left-sided pancreatic lesions found that CT reached the highest sensitivity in patients with solid lesions (75%), whereas EUS-FNA/B reached the highest sensitivity in patients with cystic lesions (75%). Overall, CT and EUS-FNA/B showed a higher sensitivity than MRI for diagnosing left-sided pancreatic lesions (71% and 71% vs. 66%, respectively).

To our knowledge, no study has been published on the sensitivity of CT, MRI nor EUS in left-sided pancreatic lesions specifically, thereby precluding direct comparison with our results. Since diagnostically challenging lesions, including MCN and SPN, mainly occur in the pancreatic body or tail and therefore influence the sensitivity for left-sided lesions, it is difficult to compare our results with available literature on pancreatic lesions in general.[15-18] Furthermore, despite the fact that several studies report on the sensitivity of CT, MRI, and EUS in pancreatic lesions (i.e., any location), a recent systematic review concluded that no firm conclusions can be drawn because of the limited number of published studies and heterogeneity in the estimates.[1]

For solid lesions, when looking at CT in particular, this heterogeneity is also illustrated by the range in sensitivity for diagnosing solid malignant pancreatic lesions specifically, varying from 68 to 92%.[19,20] The results of the current study are comparable, since CT reached a sensitivity of 74%. When focusing on MRI, previous studies report a high sensitivity to discriminate focal pancreatitis from PDAC.[21] The findings in the current study were similar, with MRI showing a high sensitivity of around 90% in diagnosing pancreatitis specifically. In this cohort, EUS reached the highest sensitivity for PDAC, especially when combined with FNA/B. This finding is in agreement with the estimates reported by Best et al. in 133 patients, where EUS yielded a sensitivity of 0.95 and a specificity of 0.53 to discriminate malignant lesions. When EUS-guided FNA/B was added, specificity rose to 1.00.[1] Thus, EUS-FNA/B should be considered in patients with a suspicion of malignancy on radiological imaging, especially considering the increased use of neoadjuvant therapy for PDAC.[22] EUS-FNA/B was also of clear value in patients with SPN, which is commonly difficult to diagnose due to its low prevalence and heterogeneous appearance. This finding is in line with the results of Jani et al., who reported a sensitivity of 75% for EUS-TA in diagnosing SPN.[23] Therefore, TA should be strongly considered in lesions with both solid and cystic components which are difficult to classify with EUS.

The diagnostic work-up for pancreatic cysts may differ from solid lesions. Cystic lesions are often found incidentally on radiological imaging performed for other reasons.[24-28] MRI is frequently used as additional modality to further classify the lesion. Therefore, one might expect a higher sensitivity of MRI for cystic lesions. However, similar to the results in previously published studies, MRI and CT showed a similar sensitivity for cystic lesions in our

study.[29,30] This finding may be partly caused by the use of a short-protocol MRI in daily clinical practice. In the current study, MRCP sequences and DWI were obtained in around two-thirds of the patients. This may have led to an underestimation of the sensitivity of MRI, although the added value of more extensive MRI protocols for both PCN and malignancy is still under debate.[31,32] Furthermore, contemporary techniques and gained knowledge may have improved the sensitivity since the end of the study period. When focusing on the results for EUS-FNA/B in cystic lesions, a recent meta-analysis showed that cytology for diagnosing cystic lesions had a high specificity, while sensitivity remained modest.[33] In our study, the addition of FNA/B to EUS increased the sensitivity. This was especially profound in MCN, showing an almost 15% increase. This might be explained by the relatively high sensitivity (52-78%) of CEA in pancreatic cyst fluid to distinguish mucinous from non-mucinous cysts.[13] In addition, the value of CF analysis likely increased since the study period because of the increasing use of relatively new biomarkers, e.g., KRAS and GNAS, which have the ability to diagnose mucinous cysts with a sensitivity of 94% and 75% for IPMN and MCN, respectively.[34] Focusing on other postoperative histopathological diagnoses, the sensitivity following additional FNA/B either improved or remained equal when compared with EUS. In other words, no harm was done by these additional analyses. Therefore, additional FNA/B should always be considered in patients with cystic lesions of the pancreatic body or tail in case of uncertainty on EUS, especially since EUS is considered a very safe procedure, with a complication rate of 0.98%.[35]

The results of this study should be interpreted in light of some limitations. First, the relatively small sample size did not allow us to draw specific conclusions for each diagnosis. Second, we did not account for the sequence in which the imaging modalities were performed. In daily practice, a CT scan is often used as initial imaging modality due to relatively low costs and broad availability. Therefore, in general, patients who underwent MRI or EUS will represent cases with an uncertain diagnosis on CT or with the need for EUS-FNA/B. This may have resulted in selection bias with a relatively lower sensitivity of MRI and EUS since these were only performed in more difficult cases, whereas the sensitivity of CT was also based on cases with a clear diagnosis. On the contrary, this selection bias may also have resulted in a relatively higher sensitivity of MRI and EUS, since MRI and EUS more likely profited from prior knowledge from previous imaging which the CT scan may have lacked. Of course, this can also be applied to the situation where CT was performed following EUS or MRI and may be different for each patient. Additionally, 36% of the patients underwent EUS without FNA/B. The decision to refrain from FNA/B was made at the discretion of the endoscopist and might therefore have been influenced by the interpretation of EUS imaging in addition to prior knowledge based on previous radiological imaging. Altogether, one should be aware of the possible influence of these biases when interpreting our results. Furthermore, the radiologic imaging was performed in daily clinical practice at both referral and referring centers. As a consequence, scans were performed according to local protocols. Sensitivity may have been higher if all radiological imaging was performed according

to the same protocol. However, the current study does reflect common clinical practice. The imaging details showed that most imaging was performed with intravenous contrast. However, MRI with MRCP sequences and DWI were only manufactured in around two-thirds of the patients, possibly leading to a lower sensitivity of MRI in our cohort. In addition, 22% of EUS procedures were performed in referring centers, thereby increasing the risk of inter-observer variability. Furthermore, both revision of tissue samples acquired at referring centers as well as rapid on-site cytological evaluation in our centers were not standardly performed and might have led to a lower sensitivity in our cohort. Lastly, our surgical cohort did not allow us to analyze the specificity and overall diagnostic accuracy for CT, MRI, and EUS due to the absence of a control group.

To the best of our knowledge, this is the first study to describe the sensitivity of CT, MRI, and EUS-FNA/B in the preoperative work-up for left-sided pancreatic lesions. Our cohort consisted of consecutive patients who underwent a resection for a variety of indications, thereby reflecting daily clinical practice. In addition, the surgical cohort enabled verification of the sensitivity by postoperative histopathological diagnosis.

In conclusion, this study provides insight in the sensitivity of CT, MRI, and EUS-FNA/B in left-sided pancreatic lesions and revealed that CT is the most sensitive modality in diagnosing solid lesions, whereas EUS-FNA/B is the most sensitive modality in diagnosing cystic lesions. EUS-FNA/B was associated with an increased sensitivity when compared to EUS alone.

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SUPPLEMENTARY FILES

Supplementary Table S1. Definitions for sensitivity per postoperative diagnosis

Postoperative diagnosis	Correct if most likely diagnosis on radiologic imaging:
PDAC	PDAC IPMN – high risk stigmata MCN – invasive
pNET	pNET
IPMN – HGD	IPMN – high risk stigmata or worrisome features
IPMN – LGD or IGD	IPMN – high risk stigmata or worrisome features
MCN	MCN – noninvasive MCN – invasive
SCN	SCN
SPN	SPN
Pancreatitis	Pancreatitis Pseudocyst
Pseudocyst	Pseudocyst Pancreatitis
Metastasis other primary	Metastasis other primary
Benign other	Benign lesions or no tumor
Postoperative diagnosis	**Correct if cyst fluid analysis showed:**
PDAC	-
pNET	-
IPMN – HGD	Mucinous (CEA ≥ 192 µmol/L)
IPMN – LGD or IGD	Mucinous (CEA ≥ 192 µmol/L)
MCN	Mucinous (CEA ≥ 192 µmol/L)
SCN	Non-mucinous (CEA ≤ 5 µmol/L)
SPN	-
Pseudocyst	Non-mucinous (CEA ≤ 5 µmol/L) Amylase > 250 µmol/L
Metastasis other primary	-
Benign other	-

Abbreviations: CEA = carcinoembryonic antigen. LGD = low-grade dysplasia. HGD = high-grade dysplasia. IGD = intermediate-grade dysplasia. IPMN = intraductal papillary mucinous neoplasm. MCN = mucinous cystic neoplasm. PDAC = pancreatic ductal adenocarcinoma. pNET = pancreatic neuroendocrine tumor. SCN = serous cystic neoplasm. SPN = solid pseudopapillary neoplasm. µmol/L = micromole per liter.

Supplementary Table S2. Characteristics of radiologic imaging modalities

	Entire cohort (n = 181)	Solid (n = 118)	Cystic (n = 63)
A. CT			
IV contrast, n (%)	150/155 (97)	105/108 (97)	45/47 (96)
Multiple phases, n (%)	102/155 (66)	76/108 (70)	26/47 (55)
B. MRI			
IV contrast, n (%)	62/77 (80)	32/40 (80)	30/37 (81)
Diffusion weighted images, n (%)	53/77 (69)	30/40 (75)	23/37 (62)
MRCP sequences, n (%)	48/77 (62)	24/40 (60)	24/37 (65)

Abbreviations: CT = computed tomography. IV = intravenous. MRCP = magnetic resonance cholangiopancreatography. MRI = magnetic resonance imaging. N= number.

Supplementary Table S3. Characteristics of EUS guided FNA/B

	Entire cohort (n = 78)	Solid (n = 54)	Cystic (n = 24)
EUS performed in referring center, n (%)	17/78 (22)	13/54 (24)	4/24 (17)
Tissue specimen reviewed[1], n (%)	9/17 (53)	9/13 (69)	0/4 (0)
Type of needle, n (%)			
FNA	58/78 (74)	37/54 (69)	21/24 (88)
FNB	11/78 (14)	11 (20)	-
Both	9/78 (11)	6 (11)	3 (12)
Largest needle size, n (%)			
19 Gauges	14 (18)	5 (9)	9 (38)
20 Gauges	3 (4)	3 (6)	-
22 Gauges	21 (27)	14 (26)	7 (29)
25 Gauges	15 (19)	15 (28)	-
Not described	25 (32)	15 (31)	8 (33)
Needle passes, median (IQR)	2 (2 – 3)	2 (2 – 3)	1.5 (1 – 2)

[1] Tissue samples acquired in a referring center were reviewed by a dedicated hepato-biliary pathologist in one of our tertiary care centers. Abbreviations: EUS = endoscopic ultrasound. FNA = fine-needle aspiration. FNB = fine-needle biopsy. IQR = interquartile range. N = number.

Supplementary Table S4. Sensitivity of endoscopic ultrasound with or without tissue acquisition and/or cyst fluid analysis in patients who underwent EUS

Postoperative diagnosis	EUS n (%)	EUS and CF n (%)	EUS and TA n (%)	EUS including CF and/or TA[1] n (%)
A. Solid lesions (n = 74)				
PDAC (n = 22)	18/22 (82)	18/22 (82)	20/22 (91)	20/22(91)
pNET (n = 23)	14/23 (61)	14/23 (61)	17/23 (74)	17/23 (74)
Metastasis other (n = 3)	1/3 (33)	1/3 (33)	2/3 (67)	2/3 (67)
SPN (n = 4)	0/4 (0)	0/4 (0)	2/4 (50)	2/4 (50)
Pancreatitis (n = 17)	11/17 (65)	11/17 (65)	10/17 (59)	10/17 (59)
Other lesions (n = 5)[2]	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)
Total correct solid	**44/74 (60)**	**44/74 (60)**	**51/74 (69)**	**51/74 (69)**
B. Cystic lesions (n = 48)				
Cystic PDAC (n = 7)	6/7 (86)	6/7 (86)	6/7 (86)	6/7 (86)
pNET (n = 3)	0/3 (0)	0/3 (0)	0/3 (0)	0/3 (0)
IPMN (n = 19)	17/19 (89)	17/19 (89)	17/19 (89)	17/19 (89)
MCN (n = 14)	9/14 (64)	11/14 (79)	10/14 (71)	11/14 (79)
SCN (n = 3)	1/3 (33)	1/3 (33)	1/3 (33)	1/3 (33)
Pseudocyst (n = 1)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
Other lesions (n = 1)[3]	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)
Total correct cystic	**34/48 (71)**	**36/48 (75)**	**35/48 (73)**	**36/48 (75)**
Overall correct	**78/122 (64)**	**80/122 (66)**	**86/122 (70)**	**87/122 (71)**

[1] Carcinoembryonic antigen (CEA) levels and amylase levels were analyzed. CEA values ≥ 192 µmol/L were defined as correct for mucinous cysts, whereas CEA levels ≤ 5 µmol/L were correct for non-mucinous cysts. Cyst fluid analysis was correct for pancreatitis or pseudocyst if cyst fluid analysis showed a CEA level of ≤ 5 µmol/L and an amylase level of > 250 µmol/L.

[2] One patient had no detectable lesion, two patients had small inflammatory changes, one patient had a granular tumor, one patient had ectopic spleen tissue and one patient had pancreatic intraepithelial neoplasia (PanIN).

[3] One patient had no detectable lesion and one patient had a retention cyst.

Abbreviations: CF = Cyst fluid. EUS = Endoscopic ultrasound. IPMN = Intraductal papillary mucinous neoplasm. MCN = mucinous cystic neoplasm. MRI = Magnetic Resonance Imaging. N = number of patients. PDAC = pancreatic ductal adenocarcinoma. pNET = pancreatic neuroendocrine tumor. SPN = solitary pseudopapillary neoplasm. SCN = serous cystic neoplasm. TA = tissue acquisition.

PART II

NEOADJUVANT TREATMENT OF PANCREATIC CANCER

CHAPTER 5

Neoadjuvant treatment in patients with resectable and borderline resectable pancreatic cancer

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ABSTRACT

Approximately 20% of pancreatic ductal adenocarcinoma (PDAC) patients have (borderline) resectable pancreatic cancer ((B)RPC) at diagnosis. Upfront resection with adjuvant chemotherapy has long been the standard of care for these patients. However, although surgical quality has improved, still about 50% of patients never receive adjuvant treatment. Therefore, recent developments have focused on a neoadjuvant approach. Directly comparing results from neoadjuvant and adjuvant regimens is challenging due to differences in patient populations that influence outcomes. Neoadjuvant trials include all patients who have (B)RPC on imaging, while adjuvant-only trials include patients who underwent a complete resection and recovered to a good performance status without any evidence of residual disease.

Guidelines recommend neoadjuvant treatment for BRPC patients mainly to improve negative resection margin (R0) rates. For *resectable* PDAC, upfront resection is still considered the standard of care. However, theoretical advantages of neoadjuvant treatment, including the increased R0 resection rate, early delivery of systemic therapy to all patients, directly addressing occult metastatic disease, and improved patient selection for resection, may also apply to these patients.

A systematic review by intention-to-treat showed a superior median overall survival (OS) for any neoadjuvant approach (19 months) compared to upfront surgery (15 months) in (B)RPC patients. A neoadjuvant approach was recently supported by three randomized controlled trials (RCTs). For resectable PDAC, neoadjuvant treatment was superior in a Japanese RCT of neoadjuvant gemcitabine with S-1 versus upfront surgery, with adjuvant S-1 in both arms (median OS: 37 vs. 27 months, $p = 0.015$). A Korean trial of neoadjuvant gemcitabine-based chemoradiotherapy versus upfront resection in BRPC patients was terminated early due to superiority of the neoadjuvant group (median OS: 21 vs. 12 months, $p = 0.028$; R0 resection: 52 vs. 26%, $p = 0.004$). The PREOPANC-1 trial for (B)RPC patients also showed favorable outcome for neoadjuvant gemcitabine-based chemoradiotherapy versus upfront surgery (median OS: 17 vs. 14 months, $p = 0.07$; R0 resection: 63 vs. 31%, $p < 0.001$). FOLFIRINOX is likely a better neoadjuvant regimen, because of superiority compared to gemcitabine in both the metastatic and adjuvant setting. Currently, five RCTs evaluating neoadjuvant modified or fulldose FOLFIRINOX are accruing patients.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) accounts for 3% of all new cancer diagnoses, and incidence rates continue to slowly increase. In contrast to the decreasing cancer-related death rates for many other solid organ malignancies, PDAC survival has not shown much improvement over the last decades.[1] As a consequence, PDAC is expected to be the second leading cause of cancer-related death in the United States by 2030.[2] An important explanation for the high mortality rate compared to other solid tumors, is that the majority of patients are diagnosed with metastatic disease (40%) or locally advanced disease (40%). For metastatic PDAC, palliative treatment using multi-agent chemotherapy such as a combination of 5-FU, oxaliplatin, and irinotecan (FOLFIRINOX) or gemcitabine with *nab*-paclitaxel is the standard of care based on randomized controlled trials (RCTs).[3, 4] These therapies have been shown to increase life expectancy with two to four months. For locally advanced pancreatic cancer (LAPC), no RCT has been completed, but based on a patient-level meta-analysis and the survival benefit in metastatic PDAC, FOLFIRINOX and gemcitabine with *nab*-paclitaxel are the standard initial treatments.[5] Following induction chemotherapy, some patients will also receive chemoradiation and about 20% of LAPC patients undergoes surgical resection. The remaining 20% of PDAC patients have (borderline) resectable pancreatic cancer ((B)RPC) at diagnosis.

Resection remains the only curative-intent treatment. However, even curative-intent surgery typically does not overcome the aggressive biology, resulting in recurrent disease within 2 years after resection in the vast majority of patients.[6] Studies focusing on recurrence patterns have demonstrated that the initial recurrence in 76% of patients was systemic. [7, 8] Therefore, also (B)RPC could be approached as a systemic disease, irrespective of apparent nonmetastatic disease on imaging.[9]

The objective of this paper is twofold. First, we aim to give a general overview of the current treatment strategies for (B)RPC patients, to discuss the rationale for neoadjuvant and adjuvant therapy, and to consider the challenges when comparing these treatment approaches. Second, we aim to summarize the currently available evidence for neoadjuvant treatment with a special focus on neoadjuvant FOLFIRINOX, including published and ongoing phase II-III trials for neoadjuvant treatment.

METHODS

To identify relevant studies for neoadjuvant treatment, a comprehensive search of Clinicaltrials, Embase, and MEDLINE was performed. Search terms included “neoadjuvant,” “FOLFIRINOX,” “folinic acid,” “fluorouracil,” “irinotecan,” “oxaliplatin,” “pancreas cancer,” “drug combination,” and relevant variants thereof. Only articles written in English were assessed.

Articles were selected based on relevance for our objectives, considering methodological quality, study type, number of included patients, and additional value to current knowledge. A selection was made for prospective studies with restriction to phase II and III trials and publication dates from 2006 to 2019. Furthermore, references of included articles were assessed for additional relevant literature.

Disease staging

Nonmetastatic pancreatic cancer is subdivided into *resectable* PDAC, BRPC, and LAPC. Historically however, BRPC was not recognized as a unique disease stage. In 2001, a first definition of marginally resectable tumors was proposed.[10] The term 'borderline resectable' was thereafter introduced by the 2006 National Comprehensive Cancer Network (NCCN) guidelines for tumors at risk for margin-positive resection when treated with upfront surgery, and adopted by other guidelines. The critical aspects that need to be evaluated are the contact of the tumor with the superior mesenteric vein or portal vein complex (SMV-PVC) as venous structures, and the superior mesenteric artery (SMA), common hepatic artery (CHA), and celiac artery (CA) as major surrounding arteries. Over time, several criteria have been proposed to define resectability status, summarized in Table 1.

Commonly used criteria include the NCCN guidelines,[11, 12] MD Anderson Cancer Center (MDACC) guidelines,[13, 14] the AHPBA/SSAT/SSO expert consensus guidelines,[15] and the International Study Group of Pancreatic Surgery (ISGPS) criteria.[16] The 2013 NCCN guidelines adopted the ISGPS criteria, and minor modifications were made in the following NCCN guidelines. The AHPBA/SSAT/SSO guidelines require less vascular abutment to classify patients as BRPC compared to the NCCN and MDACC guidelines. For example, tumors with any SMV-PVC abutment are BRPC in the AHPBA/SSAT/SSO guidelines. In contrast, the other two guidelines require venous occlusion (MDACC) or vein contour irregularity (NCCN), regardless of the extent of abutment of the tumor with the SMV-PVC.

Several factors associated with these criteria have complicated comparison of study outcomes. First, no uniformly accepted set of criteria exists. Second, the NCCN guidelines have been modified several times. Third, most guidelines include ambiguous terms to define the resectability stages, including 'abutment, impingement, involvement, and encasement'. The classifications are based on apparent contact on imaging of tumor and blood vessel. The actual presence of tumor cells surrounding the vessels (or invading the vessel wall) is rarely known before pathological examination of the resected specimen. However, patients with extensive apparent contact on imaging often undergo a surgically incomplete (R1) resection, suggesting imaging is indeed a good predictor of the presence of tumor cells surrounding and/or invading the vessel wall. Lack of international agreement on the definition of an R0 resection (i.e. >1mm vs. >0mm) and standardized protocols for pathological examination (i.e. axial slicing vs. bivalving) may explain variation in published R0 resection rates.[17, 18] At a consensus meeting in 2016, it has been proposed to add biological and functional risk

Table 1. Comparison of imaging-based criteria distinguishing resectable, borderline resectable, and locally advanced pancreatic cancer

	MD Anderson (2008) [13, 14]*	AHPBA/SSAT/SSO (2009) [15]	ISGPS (2014)**[16]	NCCN (2019)*** [12]
Resectable pancreatic cancer				
SMA	No contact			
CHA				
CA				
SMV - PVC	Patent	No abutment, distortion, thrombus, or encasement	No distortion	No contact or ≤180° without vein contour irregularity
Borderline resectable pancreatic cancer				
SMA	≤180°			
CHA	≤180° or short-segment encasement (>180°) without extension to celiac axis or hepatic artery bifurcation, allowing for safe and complete resection and reconstruction	Encasement of gastroduodenal artery up to CHA with short segment encasement or direct abutment of CHA without extension to celiac axis		Contact without extension to celiac axis or hepatic artery bifurcation, allowing for safe and complete resection and reconstruction.
CA	≤180°	No abutment or encasement		≤180° or (for corpus) >180° without aortic involvement and intact gastroduodenal artery permitting modified Appleby procedure.
SMV – PVC	Segmental occlusion with possibility of reconstruction	Abutment, encasement or short-segment occlusion with possibility of reconstruction	Distortion, narrowing, or occlusion with possibility of reconstruction	>180° or ≤180° with contour irregularity or occlusion with possibility of complete resection and reconstruction, or solid tumor contact with inferior vena cava.
Locally advanced pancreatic cancer				
SMA	>180°			
CHA	≤180° or >180° with extension to celiac axis, splenic or left gastric junction	Encasement of gastroduodenal artery up to CHA with short segment encasement or direct abutment of CHA with extension to celiac axis		Contact with extension to celiac axis or hepatic artery bifurcation
CA	>180°	Abutment or encasement and technically not reconstructable	Abutment, or any contact with aortic involvement	>180° or any contact with aortic involvement
SMV - PVC	Occluded or encased and technically not reconstructable			Unreconstructable duo to tumor involvement or occlusion, or contact with most promixal draining jejunal branch into SMV

SMA = superior mesenteric artery, CHA = common hepatic artery, CA = celiac artery, SMV - PVC = superior mesenteric vein – portal vein complex, AHPBA/SSAT/SSO = Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract, NCCN = National Comprehensive Cancer Network.* Patients with poor functional status and/or severe medical comorbidities (type C), as well as those with technically resectable disease but with imaging studies suspicious for metastatic disease (type B) are also classified as borderline resectable. **The ISGPS criteria were adopted by the 2013 NCCN criteria. ***The NCCN criteria have changed over the years. The most recent criteria (3.2019) are included.

factors to the resectability criteria. Biological factors include elevated Carbohydrate Antigen (CA) 19.9 levels above 500 units/mL, regional lymph node metastases, and suspicion of distant metastases without the possibility for pathological proof. The functional factors include performance status and comorbidity.[19] These biological and functional factors have also been implemented in the NCCN 2018 and American Society of Clinical Oncology (ASCO) 2019 guidelines, further decreasing the number of patients classified as *resectable* PDAC.[20, 21] Similarly, within the MDACC guidelines, three sub-types of BRPC are distinguished; based on local tumor-artery contact (type A), based on tumor marker levels or imaging suggestive of metastatic disease but lacking pathological proof (type B), or based on marginal performance status prior to treatment (type C).[13, 14]

Adjuvant treatment – practice changing trials

Upfront surgery followed by adjuvant chemotherapy has long been the standard of care for patients with potentially *resectable* PDAC. Initial adjuvant treatment strategies included both chemotherapy and radiotherapy. In 2004, the long-term results from the ESPAC-1 (European Study Group for Pancreatic Cancer) trial were published.[22] This multicenter European collaboration used a 2x2 factorial design to compare adjuvant 5-FU-based chemoradiotherapy alone (arm A, n = 73), adjuvant 5-FU based chemoradiotherapy followed by 5-FU (arm B, n = 72), adjuvant 5-FU alone (arm C, n = 75), and observation alone (arm D, n = 69). The trial was not powered for a direct comparison of the four groups, yet survival was longer in patients who received chemotherapy compared to patients who did not (median OS: 20 vs. 16 months, hazard ratio (HR) 0.71, p = 0.009). Furthermore, comparison of patients with or without chemoradiotherapy showed *inferior* median OS for patients who received chemoradiotherapy (median OS: 16 vs. 18 months, HR 1.28, 95% CI: 0.99 – 1.66, p = 0.05). The CONKO-001 (Charité Onkologie 001) trial found that adjuvant gemcitabine was superior to observation alone with a 5-year survival rate of 21% vs 10% (p = 0.01).[6] In 2017, the ESPAC-4 trial included 730 patients comparing gemcitabine (n = 366) to gemcitabine plus capecitabine (n = 364).[23] Median OS was 26 months with gemcitabine alone and 28 months with gemcitabine plus capecitabine (HR 0.82, 95% CI: 0.68 – 0.98, p = 0.032). In 2018, the results of the PRODIGE 24/CCTG PA.6 trial comparing adjuvant gemcitabine to modified FOLFIRINOX (mFOLFIRINOX) exceeded expectations.[24] The median OS was 54 months with mFOLFIRINOX compared to 35 months with gemcitabine (stratified HR 0.64, 95% CI: 0.48 – 0.86, p = 0.003). mFOLFIRINOX is currently the best adjuvant treatment for patients with a good performance score.

Neoadjuvant treatment – rationale

The strategy of chemotherapy following surgery has several drawbacks. First, approximately 20% of patients with (B)RPC on imaging will never undergo a resection because of occult metastatic or locally irresectable disease.[25] More advanced disease is often diagnosed at exploratory laparotomy, which has considerable morbidity and mortality, and the majority of these patients will not receive any palliative chemotherapy. Even after successful resection,

only about 55% of patients are able to receive adjuvant chemotherapy due to postoperative complications, clinical deterioration, or early progressive disease.[26-29] Especially those patients not able to receive adjuvant chemotherapy have very poor prognosis. The CONKO-001 RCT reported that about 50% of patients in the observation arm (i.e. without adjuvant chemotherapy) had recurrent disease or died within 6 months after surgery; the median DFS was only 6.7 months after surgery without adjuvant chemotherapy.[6] In an attempt to overcome some of these drawbacks, there is an ongoing paradigm shift towards a neoadjuvant approach. This is supported by promising results in other malignancies such as breast cancer, rectal cancer, and esophagogastric cancer.[30-32] Theoretical advantages of a neoadjuvant approach are numerous. First, a much larger population can benefit from effective systemic treatment. Second, neoadjuvant systemic therapy directly addresses radiographically occult metastatic disease. Third, delaying surgery during neoadjuvant treatment allows for restaging prior to surgery. This provides improved patient selection by identifying those individuals who have responded to neoadjuvant treatment and may benefit from a resection, whilst preventing futile surgery in patients with rapidly progressive disease. Furthermore, several studies have shown that complication rates, including postoperative pancreatic fistula and postpancreatectomy hemorrhage, are lower following neoadjuvant treatment.[33-36] Lastly, neoadjuvant treatment may reduce tumor volume, with increased likelihood of a margin negative (R0) resection.[25, 37]

Conversely, the neoadjuvant approach has some potential drawbacks. First, patients might have progressive disease during neoadjuvant treatment, precluding curative-intent resection. However, it is unlikely that patients with progressive disease during chemotherapy would have been cured with upfront resection, since cure is exceedingly rare with a 10-year OS of only 4% after surgery.[38] Furthermore, since patients with progression during neoadjuvant treatment do not seem to respond to chemotherapy, it is likely that these patients would not have responded to adjuvant chemotherapy either, increasing their risk of early recurrent or metastatic disease following surgery. Thus, rather than a missed opportunity of cure, it is more likely that these patients have been spared futile surgery. Another potential drawback is the risk of deterioration during neoadjuvant treatment. Chemotherapy may reduce the patients' performance status and quality of life because of toxicities. More specifically, FOLFIRINOX is known for its gastrointestinal complications, increased risk of infections, fatigue, and sensory peripheral neuropathy.[24] Fortunately, it is rare that patients become unfit for surgery due to chemotherapy, and no deaths have been attributed to FOLFIRINOX in two systematic reviews.[5, 39] A final potential drawback is that biliary drainage is required before chemotherapy in patients with obstructive jaundice. Biliary drainage is associated with mainly infectious complications, but this can be avoided with upfront surgery.[40]

Comparing adjuvant with neoadjuvant trials

The PRODIGE 24/CCTG PA.6 trial showed a median survival of almost 5 years for patients with *resectable* PDAC treated with upfront resection and adjuvant mFOLFIRINOX; a survival

estimate far superior than previously reported for other treatments.[24] However, these results apply only to a highly selected subset of patients. Only patients with favorable tumor biology and good performance status after a complete curative-intent resection are eligible for adjuvant trials. Several hurdles need to be taken by patients with *resectable* PDAC on imaging. A small percentage of patients becomes unfit for surgery in the preoperative phase due to stent-related complications causing clinical deterioration. In the operative phase, a resection is not performed in about 20% of patients who are found to have occult metastatic or locally irresectable disease. Next, patients need to recover sufficiently within 12 weeks after surgery to receive adjuvant chemotherapy. In large cohorts, only about 50% of patients received adjuvant gemcitabine after a complete resection.[26-29] For adjuvant mFOLFIRINOX, patients need to have an even better World Health Organization (WHO) performance status of 0 or 1. Lastly, for the PRODIGE 24/CCTG PA.6 trial, patients were ineligible if the CA 19.9 level was above 180 U/mL before start of chemotherapy or in the event of early postoperative disease recurrence on imaging. We estimate that on a nationwide level only about 25% of patients with (B)RPC on imaging could become eligible for adjuvant mFOLFIRINOX. This also explains the low accrual rate of the PRODIGE 24/ CCTG PA.6 trial of only 1-2 patients on average per center per year.

Patients do not need to overcome most of these hurdles for inclusion in a neoadjuvant trial. Most patients presenting in the clinic with (B)RPC on imaging are eligible for neoadjuvant trials after adequate biliary drainage. Thus, direct comparison of outcomes of neoadjuvant and adjuvant trials is biased, because neoadjuvant trials can include almost all patients whilst for adjuvant trials only the 25% of patients with the best tumor biology and performance status can be included.

Neoadjuvant treatment – Systematic Reviews and Meta-analyses

One of the first studies describing neoadjuvant treatment for pancreatic cancer was published in 1980.[41] Over time, different single-agent or multi-agent chemotherapy regimens were used, including 5-FU, gemcitabine, mitomycin C, and platinum compounds. Three large meta-analyses have been published for nonmetastatic PDAC patients describing outcomes after preoperative treatment (irrespective of the regimen used) compared to upfront surgery (Table 2).[25, 37, 42] The first meta-analysis by Gillen *et al.* included 111 studies published from 1980 – 2009. Chemotherapy regimens were mainly gemcitabine or 5-FU based, and 94% of studies used chemoradiotherapy.[42] This meta-analysis showed that 33% of patients initially staged as unresectable pancreatic cancer (BRPC and LAPC) were able to undergo a resection after preoperative treatment. Furthermore, estimated survival following resection and R0 resection rates for patients with initially unresectable PDAC were comparable to patients with *resectable* PDAC (Median OS: 23 vs. 21 months; R0 resection: 82 vs. 79%). A second meta-analysis by Dhir *et al*. provided an update of the literature published since 2009, which marks the endorsement of the AHPBA/SSAT/SSO consensus criteria, as well as the introduction of newer preoperative regimens.[37] In

Table 2. Meta-analyses on neoadjuvant treatment for (borderline) resectable pancreatic cancer

Author, year [reference]	No. studies	No. patients	No. (B) RPC	Treatment	Stage(s)	OS in months (95% CI)	Resection % (95% CI)	R0 resection % (of resected) (95% CI)
Gillen et al., 2010 [42]	111	4394	NR	Any preoperative treatment *	Resectable	23 (12 – 54) ′ 8 (6 – 14) ″	74 (66 – 81)	82 (73 – 90)
					BRPC/LAPC	21 (9 – 62) ′ 10 (6 – 21) ″	33 (26 – 41)	79 (72 – 85)
				Any preoperative treatment **				
Dhir et al. 2017 [37]	96	5520	2193		Resectable	18 (13 – 28)	76 (68 – 84)	88 (80 – 94)
				Any neoadjuvant treatment ***	BRPC	19 (9 – 45)	69 (59 – 78)	84 (67 – 96)
Versteijne et al. 2018 [25]	38	3484	1738		Resectable	18 (10 – 50)	67 (64 – 70)	85 (NR)
				FOLFIRINOX ± (chemo)radiotherapy	BRPC	19 (11 – 32)	65 (62 – 68)	89 (NR)
Janssen et al., 2019 [39]	20	283	283		BRPC	22 (19 – 26) ‴	68 (60 – 75)	84 (77 – 89)

No. = number. (B)RPC = (borderline) resectable pancreatic cancer. BRPC = borderline resectable pancreatic cancer. CI: confidence interval. LAPC = locally advanced pancreatic cancer.
OS = Overall Survival.
* Neoadjuvant chemotherapy in 96% of studies, main agents gemcitabine, 5-FU, mitomycin C, and platinum compounds. Neoadjuvant radiotherapy in 94% of studies with doses ranging 24 – 63 Gy.
** Main chemotherapy agents FOLFIRINOX (810 patients), gemcitabine/taxane/capecitabine (410 patients), other three-drug regimens (60 patients), two-drug regimens (1112 patients), single drug gemcitabine/5-FU/capecitabine (1521 patients). *** All studies used at least chemotherapy as neoadjuvant treatment, including gemcitabine in 26 of 35 studies. Radiotherapy was given in 29 of 35 studies. No study used radiotherapy as sole neoadjuvant treatment. ′Resected. ″Not-resected. ‴Based on patient-level data.

this meta-analysis of 96 studies, the median OS after neoadjuvant treatment for *resectable* PDAC and BRPC was similar (18 vs. 19 months). Furthermore, the R0 resection rate of 85% was much higher than previously reported in the setting of upfront resection. The third meta-analysis by Versteijne *et al.* included only studies that did not exclude patients who didn't undergo resection after neoadjuvant treatment or patients who didn't undergo adjuvant chemotherapy after resection.[25] These criteria allowed for intention-to-treat analysis of the survival outcomes. Reporting by intention-to-treat reflects actual clinical practice and outcomes, because it allows for noncompliance and protocol deviations, increasing the generalizability of the results.[43] This reduces potential bias of the treatment effect, because the study population is not limited to patients that received planned treatment such as surgery or adjuvant chemotherapy. Without the intention-to-treat analysis, a selection of patients with better outcomes due to immortal time bias is likely to occur.[44] This meta-analysis of 38 studies comprising 3843 (B)RPC patients found superior survival following any neoadjuvant treatment compared to upfront resection (weighted median OS: 19 vs. 15 months). Only a negligible number of patients received neoadjuvant FOLFIRINOX. The resection rate was higher with upfront surgery (66 vs. 81%, $p < 0.001$), but the R0 resection rate was better after neoadjuvant treatment (87 vs. 67%, $p < 0.001$).

Following the ACCORD-11/PRODIGE-4 trial for metastatic PDAC by Conroy *et al*. in 2011, FOLFIRINOX emerged as a potential preoperative treatment for nonmetastatic PDAC.[3] No RCT has been performed for neoadjuvant FOLFIRINOX in the setting of (B)RPC. The best available estimate for the outcomes of patients treated with neoadjuvant FOLFIRINOX comes from a patient-level meta-analysis by Janssen *et al.* that included 283 BRPC patients and showed a median OS of 22.2 months.[39] The pooled resection rate was 68%, with an R0 resection rate of 84%.

Neoadjuvant treatment – large retrospective series

In addition to these meta-analyses, two large retrospective studies investigated the neoadjuvant approach.[45, 46] The largest retrospective study used data from the National Cancer Database (NCDB) including patients with clinical stage I and II resected PDAC.[45] A propensity score matched analysis was conducted comparing outcomes for patients who received neoadjuvant treatment before resection ($n = 2005$) to patients who underwent upfront resection ($n = 6015$). The neoadjuvant patients had a longer median OS compared to patients who underwent upfront resection (26 vs. 21 months, adjusted HR 0.72, 95% CI: 0.68 – 0.78, $p < 0.01$). Moreover, compared with a subgroup of patients who received adjuvant therapy after upfront resection, the neoadjuvant group still had better survival (26 vs. 23 months, adjusted HR 0.83, 95% CI: 0.73 – 0.89, $p < 0.01$). Second, a large observational cohort study from Verona Hospital included all consecutive BRPC ($n = 267$) and LAPC ($n = 413$) patients.[46] Of all patients with newly diagnosed BRPC or LAPC, 7% received only supportive care owing to clinical deterioration. FOLFIRINOX (46%) and gemcitabine with *nab*-paclitaxel (22%) were the most commonly used regimens, and additional radiotherapy

was applied in 23% of patients. Resection rate was 24% for BRPC patients, with an R0 resection rate of 58% for all patients combined. No differences were found in R0 resection rates between BRPC and LAPC patients and chemotherapy regimens used.

Published neoadjuvant FOLFIRINOX trials (phase II and III)

Three nonrandomized small (<50 patients) phase II studies on neoadjuvant FOLFIRINOX for (B)RPC have been published to date (Table 3A)[47-49]. In 2016, the first prospective multicenter trial was published (ALLIANCE A021101), including 22 BRPC patients who received preoperative mFOLFIRINOX (4 cycles) followed by capecitabine-based chemoradiotherapy (50.4Gy in 28 fractions).[47] This study demonstrated the feasibility of recruiting patients in a multi-institutional neoadjuvant FOLFIRINOX study. Fifteen patients (68%) completed the neoadjuvant treatment and underwent a resection, with an R0 resection rate of 93%. The median OS was 22 months. In 2018, a similar study was published to determine the tolerability and efficacy of four cycles of mFOLFIRINOX both pre- and post-operative in *resectable* PDAC.[48] Twenty-one patients were included, of whom 81% underwent a resection with an R0 resection rate of 94%. Following resection, 82% of patients completed 4 cycles of adjuvant mFOLFIRINOX. The largest study was a single-arm phase II clinical trial conducted at the Massachusetts General Hospital.[49] In this study, 48 BRPC patients were treated with 8 cycles of neoadjuvant FOLFIRINOX followed by individualized chemoradiotherapy. In patients with resolution of vascular involvement, FOLFIRINOX was followed by short-course capecitabine-based chemoradiotherapy (25Gy in 5 fractions), whilst patients with persistent vascular involvement were treated with long-course chemoradiotherapy (50.4Gy in 28 fractions). Forty-four patients (92%) proceeded to chemoradiotherapy, of whom 27 (56%) received short-course chemoradiotherapy and 17 (35%) received long-course chemoradiotherapy. Surgical resection was performed in 32 (67%) patients, of whom 31 (97%) had an R0 resection. After a median follow-up of 18 months, median OS was 38 months, with a 2-year OS of 56% (NCT0591733).

Although the three studies slightly differ in the treatment regimen and sequence, neoadjuvant (m)FOLFIRINOX treatment with or without chemoradiotherapy is feasible with high R0 resection rates. The survival estimates are promising, but need confirmation in larger RCT's.

Published neoadjuvant trials, regimens other than FOLFIRINOX (phase II and III)

A number of phase II-III trials have been conducted using other neoadjuvant regimens, yet several of these RCTs were terminated early due to slow accrual. This emphasizes the difficulties in conducting large neoadjuvant RCTs in pancreatic cancer. Table 3B shows eight published studies on neoadjuvant regimens other than FOLFIRINOX. Three RCTs have been published on neoadjuvant gemcitabine-based chemoradiotherapy versus upfront surgery for patients with (B)RPC.[50-52] The study by Golcher *et al.* was terminated early due to slow accrual after inclusion of 73 (29%) patients.[50] They concluded that neoadjuvant

Table 3. Recently published neoadjuvant trials in (borderline) resectable pancreatic cancer from 2016 - 2019

A. Neoadjuvant FOLFIRINOX

Trial (year)	Sample size	Stage	Criteria	Treatment regimen (cycles)	Comparator (cycles)	Survival (*p*–value)	Resection (*p*–value)	R0 Resection (*p*–value)
Nonrandomized studies								
ALLIANCE A021101 (2016) [47]	22	BRPC	Intergroup	Neoadj. mFOLFIRINOX(4) + capecitabine-based CRT	-	Median OS: 22 mo	68%	93%′
De Marsh et al. (2018) [48]	21	Resectable	NCCN	Periop. mFOLFIRINOX(4+4)	-	Median OS: 36 mo (resected only)	81%	94%″
Murphy et al. (2018) [49]	48	BRPC	NR	Neoadj. FOLFIRINOX(8) + short-course or long-course capecitabine-based CRT	-	Median OS: 38 mo	67%	97%′
B. Neoadjuvant regimens other than FOLFIRINOX								
Randomized trials								
Golcher et al. (2015) [50]	73*	Resectable	<180° arterial or venous contact	Neoadj. gemcitabine+cisplatin based CRT + adj. gemcitabine(6)	Surgery + adj. gemcitabine(6)	Median OS: 17 vs. 14 mo (*p*=0.96)*	58% vs. 70% (*p*=0.31)*	89% vs. 70% (*p*=0.81)*[nr]
PACT-15 (2018) [53]	93	Resectable	No vascular contact	c. Periop. PEXG(3+3)	**a.** Surgery + adj. gemcitabine(6) **b.** Surgery + adj. PEXG(6)	Median OS: 38 (c) vs. 20 (a) vs. 26 (b) mo (NR) 1-YR DFS: 66% (c) vs. 23% (a) vs. 50% (b) (NR)	84% (c) vs. 85% (a) vs. 90% (b) (NR)	63% (c) vs. 27% (a) vs. 37% (b) (NR)[nr]
Jang et al. (2018) [51]	50	BRPC	NCCN	Neoadj. gemcitabine-based CRT + adj. gemcitabine(4)	Surgery + adj. gemcitabine-based CRT+ gemcitabine(4)	Median OS: 21 vs. 12 mo (*p*=0.028) 2-YR OS: 41% vs. 26%	63% vs. 78% (NR)	52% vs. 26% (*p*=0.004)‴

Table 3. Recently published neoadjuvant trials in (borderline) resectable pancreatic cancer from 2016 - 2019 (continued)

Trial (year)	Sample size	Stage	Criteria	Treatment regimen (cycles)	Comparator (cycles)	Survival (*p*–value)	Resection (*p*–value)	R0 Resection (*p*–value)
PREOPANC-1 (2018) [52]	246	(B)RPC	DPCG	Neoadj. gemcitabine-based CRT(3) + adj. gemcitabine(4)	Surgery + adj. gemcitabine(6)	Median OS: 17 vs. 14 mo** (p=0.07) Median DFS: 10 vs. 8 mo** (p=0.02)	60% vs. 72%** (p=0.065)	63% vs. 31%** (p<0.001)‴
Preop-02/JSAP-05 (2019) [57]	364	Resectable	NR	Neoadj. S-1 + gemcitabine(2) + adj. S-1(6mo)	Surgery + adj. S-1(6mo)	Median OS: 37 vs. 27 mo (p=0.015)	NR***	NR*** [nr]
Nonrandomized studies								
Tsai et al. (2018) [54]	130	(B)RPC	<180° SMA or CA, short segment abutment HA, venous reconstructable	Neoadj. 5-FU- or gemcitabine-based chemo(radio)therapy (8w), depending on molecular profiling	-	Median OS: 38 mo 80% 5-FU-based 20% gemcitabine-based	82%	81%″
ACOSOG Z5041 (2018) [55]	114	Resectable	No arterial contact, <180° venous contact, no occlusion	Periop. gemcitabine + erlotinib (2+2)	-	Median OS: 21 mo 2-YR OS: 40%	73%	81% [nr]
JASPAC-05 (2019) [56]	52	BRPC	<180° SMA, CHA, or CA. Bilateral impingement of SMV/PV.	Neoadj. S1-based CRT	-	Median OS: 26 mo 2-YR OS: 51%	NR**	52% [nr]

FOLFIRINOX = folinic acid + irinotecan + oxaliplatin + leucovorin. BRPC = borderline resectable pancreatic cancer. LAPC = locally advanced pancreatic cancer. NCCN = National Comprehensive Cancer Network. DPCG = Dutch Pancreatic Cancer Group. NR = not reported. DFS = disease free survival. OS = overall survival. Neoadj. = neoadjuvant. Adj. = adjuvant. Periop. = perioperative. CRT = chemoradiotherapy. mo = months. d = days. PEXG = cisplatin, epirubicin, gemcitabine, and capecitabine. YR = year. YRS = year survival. SMA = superior mesenteric artery. CHA = common hepatic artery. CA = celiac artery. SMV = superior mesenteric vein. PV = portal vein. *Results after early termination of the trial due to slow accrual. **Results at interim analysis, after 85% of events needed. ***Not reported in abstract, paper not yet published. ′R1 if microscopic tumor at any margin. ″R1 if microscopic tumor at SMA margin, common bile/hepatic duct or pancreatic transaction margins. ‴R1 if microscopic tumor <1 mm of any surface or margin. [nr] definition of resection margin not reported.

chemoradiation is safe with respect to toxicity, postioperative morbidity, and mortality, but no difference in OS could be demonstrated (median OS: 17 vs. 14 months, $p = 0.96$). In the Korean randomized phase II-III trial, BRPC patients were randomly assigned to receive gemcitabine-based chemoradiotherapy (45Gy in 25 fractions and 9Gy in 5 fractions) (arm A) or upfront surgery followed by chemoradiotherapy following the same protocol as the neoadjuvant group (arm B).[51] Both groups received 4 cycles of gemcitabine as maintenance chemotherapy after completion of initial treatment. After inclusion of 50 patients, interim-analysis showed superior median OS (21 vs. 12 months, HR = 1.97, 95% CI: 1.07 – 3.62, $p = 0.028$), better 2-year survival rate (41 vs. 26%), and a superior R0 resection rate (52 vs. 26%, $p = 0.004$) in the neoadjuvant group compared to upfront surgery. Consequently, the study was discontinued due to superiority and lack of equipoise (NCT01458717). At ASCO 2018, the Dutch phase III PREOPANC-1 trial presented preliminary results, after inclusion of 246 (B)RPC patients who were randomly allocated to neoadjuvant gemcitabine-based chemoradiotherapy followed by a resection and adjuvant 4 cycles of gemcitabine (arm A), or upfront surgery followed by 6 cycles of gemcitabine (arm B).[52] After 85% of events needed, the interim analysis showed superior R0 resection rate (63 vs. 31%, $p < 0.001$) and superior DFS (10 vs. 8 months, $p = 0.02$) in the neoadjuvant group, but a difference in OS could not be demonstrated (17 vs. 14 months, HR = 0.74, $p = 0.07$). To allow for comparison with adjuvant trials, a subgroup analysis was performed of patients who received at least one cycle of adjuvant chemotherapy, showing a median OS of 42 months in the neoadjuvant group and 19 months in the upfront surgery group ($p = 0.006$). Final results are awaited soon. The PACT-15 trial was an Italian multicenter phase II trial, in which 93 *resectable* PDAC patients were randomly assigned (1:1:1) to receive adjuvant gemcitabine (arm A), adjuvant PEXG (cisplatin, epirubicin, gemcitabine, and capecitabine) (arm B), or 3 cycles of PEXG pre- and postoperative (arm C).[53] Median OS was 20 months in arm A, 26 months in arm B, and 38 months in arm C (*p*-value not reported). Three nonrandomized studies on regimens other than FOLFIRINOX have been published.[54-56] The phase II trial from Tsai *et al.* used molecular profiling of pretreatment EUS-FNA guided tumor biopsies using 6 biomarkers to guide neoadjuvant therapy in 130 (B)RPC patients.[54] Eighty percent of patients received 5-FU based treatment whilst 20% received gemcitabine-based treatment. The median OS was 38 months, with a 5-year survival of 34%, a resection rate of 82%, and an R0 resection rate of 81%. The ACOSOG Z5401 single-arm phase II trial was a study of neoadjuvant gemcitabine plus erlotinib for *resectable* PDAC.[55] This study demonstrated a favorable 2-year OS for 114 evaluable patients of 40% (95% CI: 31 – 49%), with a median OS of 21 months. At the 2019 ASCO congress, final results of two Japanese trial were presented. The JASPAC-05 study was a multicenter, single-arm, phase II of neoadjuvant S-1 based chemoradiotherapy.[56] Fifty-two BRPC patients were included, and 50 (96%) patients completed the neoadjuvant treatment. The 2-year OS was 51%, with a median OS of 26 months, and an R0 resection rate of 52%. The phase II-III Preop-02/JSAP-05 trial was a large collaboration study of 57 centers in which 364 patients with *resectable* PDAC were randomized to either neoadjuvant gemcitabine and S-1 chemotherapy (2 cycles) or upfront

surgery, both followed by 6 months of adjuvant S-1.[57] This study also showed superior survival following neoadjuvant treatment, with a median OS of 37 vs. 27 months (HR = 0.72, 95% CI: 0.55 – 0.94, p = 0.015). No differences were found regarding the resection rate, R0 resection rate, and postoperative morbidity. Although S-1 is only used as standard-of-care in East Asia, the study does provide additional proof of the superiority of neoadjuvant therapy over upfront resection for patients with *resectable* PDAC.

In summary, although based on only three RCTs, a neoadjuvant approach seems to be consistently superior to upfront resection for R0 resection rates, at least equal or superior for DFS, and at least equal or superior for OS in both BRPC and *resectable* PDAC patients. The results of the R0 resection rates were notable, with a twofold increase in two out of the three evaluable RCTs. However, it remains unclear whether superior R0 resection rate is an appropriate intermediate outcome for OS in the neoadjuvant setting. The results of ongoing larger RCTs may further clarify the survival benefit of neoadjuvant treatment as opposed to upfront resection for (B)RPC patients.

Standard of care – current guidelines

The NCCN guideline, ASCO Clinical Practice Guideline, and European Society for Medical Oncology (ESMO) Clinical Practice Guideline are commonly used guidelines for pancreatic cancer treatment.[12, 21, 58, 59] Due to the lack of large RCTs for neoadjuvant treatment of PDAC, most recommendations in these guidelines are based on systematic reviews of cohort studies, providing Oxford Levels of Evidence category 2A.[60]

The 2019 NCCN guidelines [12] recommend upfront surgery followed by adjuvant treatment for *resectable* PDAC, but advise to consider neoadjuvant treatment in patients with high-risk features, preferably in the setting of a clinical trial. High-risk features include imaging findings suspicious of advanced or metastatic disease, significantly elevated Carcinogen Antigen (CA) 19-9, large primary tumors or regional lymph nodes, excessive weight loss, and notable pain. The adjuvant treatment of first choice is mFOLFIRINOX. For BRPC patients, neoadjuvant treatment is recommended, with therapeutic options including FOLFIRINOX or gemcitabine/*nab*-paclitaxel, both with or without subsequent chemoradiotherapy. The 2019 ASCO Clinical Practice Guideline [21] recommends primary surgical resection for patients without any radiographic evidence of metastatic disease, with no interface between the primary tumor and surrounding mesenteric vasculature, CA 19.9 level suggestive of potentially curable disease, and a performance status and comorbidity profile appropriate for major abdominal surgery. However, neoadjuvant therapy can also be offered as an alternative strategy for patients with *resectable* PDAC. For patients who do not meet all of these criteria, the ASCO guideline recommends neoadjuvant therapy. No specific neoadjuvant treatment regimen is recommended. Options for consideration include FOLFIRINOX or gemcitabine/*nab*-paclitaxel ± subsequent chemoradiotherapy. In the adjuvant setting, mFOLFIRINOX is recommended as treatment of first choice. In case of concern for toxicity

and tolerance, doublet therapy with gemcitabine and capecitabine, or monotherapy with either gemcitabine or fluorouracil (5-FU) can be offered. Following neoadjuvant therapy, patients may be candidates for additional chemotherapy following surgery, depending on their performance status and initial response to the neoadjuvant treatment. The ASCO guideline recommends a total of 6 months of chemotherapy, considering both neoadjuvant and adjuvant treatment. Adjuvant chemoradiotherapy may be offered to patients who underwent primary resection with microscopically positive margins (R1) and/or node-positive disease after completion of systemic adjuvant chemotherapy. The 2019 ESMO guideline [58, 59] recommends adjuvant mFOLFIRINOX as first therapeutic option in selected and fit individuals with resectable tumors. For patients with age > 70 years, WHO performance status 2, or patients who have any contraindication for FOLFIRINOX, doublet therapy with gemcitabine-capecitabine can be offered as alternative. Gemcitabine monotherapy should be used only in frail patients. For BRPC patients, neoadjuvant treatment with gemcitabine or FOLFIRINOX followed by chemoradiotherapy and surgery is recommended.

Ongoing neoadjuvant FOLFIRINOX trials (phase II and III)

The optimal chemotherapy regimen in the neoadjuvant setting, the number of cycles pre- and postoperatively, the additional benefit of (chemo)radiotherapy, and the timing of surgery after neoadjuvant treatment still need to be further investigated. Several ongoing phase II and III trials are investigating these aspects of neoadjuvant treatment regimens in patients with (B)RPC. Table 4A presents selected ongoing trials including neoadjuvant FOLFIRINOX, and Table 4B shows ongoing trials for neoadjuvant regimens other than FOLFIRINOX.

Of the nine RCTs, two originate from France: the PANDAS-PRODIGE44 trial for BRPC patients, and the PANACHE01-PRODIGE48 trial for *resectable* PDAC. In the PANDAS-PRODIGE44 trial, 90 BRPC patients will receive neoadjuvant mFOLFIRINOX with (arm A) or without capecitabine-based chemoradiotherapy (arm B), both followed by surgery and adjuvant gemcitabine or modified LV5FU (NCT02676349). This study uses R0 resection rate as primary endpoint. The PANACHE01-PRODIGE48 is a three-arm trial with 2:2:1 allocation to 4 cycles of neoadjuvant mFOLFIRINOX (arm A) or FOLFOX (arm B), both followed by 8 cycles of adjuvant chemotherapy, or upfront surgery followed by 12 cycles of adjuvant chemotherapy (arm C) (NCT02959879).[61] The choice of adjuvant chemotherapy regimen will be left to the medical teams, according to guidelines during the recruitment period. The trial will include 160 *resectable* PDAC patients, and the primary endpoint is 1-year OS. The SWOG S1505 trial is a randomized phase II study for patients with *resectable* PDAC designed to determine the most promising perioperative regimen for a larger phase III trial (NCT02562716). This study has completed accrual and randomized 147 patients to either 3 cycles of perioperative mFOLFIRINOX (arm A) or perioperative gemcitabine with *nab*-paclitaxel (arm B). The primary outcome is 2-year OS, and results are anticipated in 2020. The ALLIANCE A021501 was initially designed to evaluate the additional value of hypofractionated radiation therapy to systemic therapy as neoadjuvant treatment for BRPC

Table 4. Ongoing neoadjuvant trials for (borderline) resectable pancreatic cancer
A. Neoadjuvant FOLFIRINOX

Trial	Sample size	Stage	Criteria	Treatment regimen (cycles)	Comparator (cycles)	Primary outcome	Start	Status**
Randomized trials								
ESPAC-5F ISRCTN89500674	85	BRPC	NR	**a.** Neoadj. FOLFIRINOX(4) **b.** Neoadj. gemcitabine(1)+ capecitabine(2)	**c.** Neoadj. capecitabine-based CRT **d.** Surgery + adj. gemcitabine(6) or 5-FU(6)	Recruitment, R0 resection rate	04-2014	Results pending
NEPAFOX NCT02172976	40	(B)RPC	Venous reconstructable, no contact SMA or CA	Periop. FOLFIRINOX (4-6 + 4-6)	Surgery + adj. gemcitabine(6)	OS	11-2014	Results pending
SWOG S1505 NCT02562716	112	Resectable	<180° venous, no arterial	Periop. mFOLFIRINOX (3 + 3)	Periop. gemcitabine/ *nab*-paclitaxel (3 + 3)	OS at 2-yr	10-2015	Results pending
NorPACT-1 NCT02919787	90	Resectable	NCCN	Neoadj. FOLFIRINOX(4) + adj. gemcitabine-capecitabine(4)	Surgery + adj. gemcitabine-capecitabine(6)	OS at 1-yr (resected only)	09-2016	Recruiting
PANDAS-PRODIGE 44 NCT02676349	90	BRPC	NCCN	Neoadj. mFOLFIRINOX + capecitabine-based CRT + adj. gemcitabine or mLV5FU	Neoadj. mFOLFIRINOX + adj. gemcitabine or mLV5FU	R0 resection rate	10-2016	Recruiting
ALLIANCE A021501 NCT02839343	134	BRPC	Intergroup	Neoadj. FOLFIRINOX(8) + adj. mFOLFOX6(4)	Neoadj. mFOLFIRINOX(7) + SBRT + adj. FOLFOX(4)	OS at 1.5-yr	12-2016	Suspended (interim analysis)
PANACHE01-PRODIGE48 NCT02959879	160	Resectable	NCCN	**a.** Neoadj. mFOLFIRINOX(4) + adj chemotherapy(8) **b.** Neoadj. FOLFOX(4) + adj. chemotherapy(8)	**c.** Surgery + adj. chemotherapy(12)	OS at 1-yr	03-2017	Recruiting
PREOPANC-2 NTR7292	368	(B)RPC	DPCG	Neoadj. FOLFIRINOX(8)	Neoadj. gemcitabine-based CRT(3) + adj. gemcitabine(4)	OS	06-2018	Recruiting

Table 4. Ongoing neoadjuvant trials for (borderline) resectable pancreatic cancer. (continued)

Trial	Sample size	Stage	Criteria	Treatment regimen (cycles)	Comparator (cycles)	Primary outcome	Start	Status**
ALLIANCE A021806	344	Resectable	<180° venous, patent confluence, no arterial	Periop. mFOLFIRINOX (8 + 4)	Surgery + adj. mFOLFIRINOX (12)	OS	2020	Start recruiting 2020
Nonrandomized studies								
Lacy et al., Yale NCT02047474	46	Resectable	No venous occlusion/ encasement, no arterial	Periop. mFOLFIRINOX (6 + 6)	-	PFS at 1-yr	09-2013	Recruiting
IUCRO-0473 NCT02178709	48	Resectable	NR	Neoadj. FOLFIRINOX(4)	-	Pathological complete response*	04-2014	Recruiting
B. Neoadjuvant regimens other than FOLFIRINOX								
Randomized trials								
UVA-PC-PD101 NCT02305186	56	(B)RPC	NR	Neoadj. pembrolizumab + capecitabine-based CRT	Neoadj. capecitabine-based CRT	Toxicity, TILs	03-2015	Recruiting
Laheru et al. Johns Hopkins NCT00727441	87	Resectable	No contact SMA/CA, patent SMV/PV	Periop. GVAX(1+5) + neoadj. cyclophosphamide iv (**a**) or oral (**b**) + adj. CRT	**c.** Periop. GVAX(1+5) + adj. CRT	Safety, feasibility, immune response	03-2015	Final results pending
NEONAX NCT02047513	166	Resectable	No arterial contact	Periop. gemcitabine/*nab*-paclitaxel(2+4)	Surgery + adj. gemcitabine/*nab*-paclitaxel(6)	DFS	04-2015	Recruiting

Table 4. Ongoing neoadjuvant trials for (borderline) resectable pancreatic cancer. (continued)

Trial	Sample size	Stage	Criteria	Treatment regimen (cycles)	Comparator (cycles)	Primary outcome	Start	Status**
Nonrandomized studies								
Park et al. National Cancer Center Korea NCT01333124	64	Resectable	NR	Neoadj. gemcitabine-based CRT	-	R0 resection rate	04-2014	Recruiting
Okada et al. Wakayama NCT02926183	60	BRPC	NCCN	Neoadj. gemcitabine/*nab*-paclitaxel(2)	-	OS	10-2016	Recruiting
PRO30720 NCT03322995	125	(B)RPC	NR	Adaptive modification of neoadj. treatment based on clinical response + CRT***	-	Completion neoadj. regimen incl. resection	06-2018	Recruiting
ESR-16-12315 NCT03572400	71	(B)RPC	Stage I or II AJCC 8th	Neoadj. gemcitabine/ dervalumab-based CRT(6) + adj. gemcitabine/ dervalumab(6) + dervalumab(12mo)	-	DFS	11-2018	Recruiting

(B)RPC = (borderline) resectable pancreatic cancer. BRPC = borderline resectable pancreatic cancer. NCCN = National Comprehensive Cancer Network. AJCC = American Joint Committee on Cancer.

NR = not reported. DFS = disease-free survival. OS = overall survival. Neoadj. = neoadjuvant. Adj. = adjuvant. Periop. = perioperative. CRT = chemoradiotherapy. IORT = intraoperative radiation therapy. SBRT = stereotactic body radiation therapy. FOLFIRINOX = folinic acid + irinotecan + oxaliplatin + leucovorin. mFOLFIRINOX = modified FOLFIRINOX. FOLFOX6 = folinic acid + leucovorin + oxaliplatin. mLV5FU = modified folicin acid + leucovorin. PV = portal vein. SMA = superior mesenteric artery. CA = celiac artery. Incl. = including. mo = months. Vs. = versus. RCT = randomized controlled trial. TIL = tumor-infiltrating lymphocytes.

*Evaluated by MRI or CT. ** Based on clinicaltrials.gov, assessed on 21-08-2019. *** Adaptive modification of neoadjuvant therapy: after 2 months, first-line chemotherapy is continued in responders, changed to second-line therapy in patients with stable disease, or changed to chemoradiation in patients with local disease progression. After 4 months of chemotherapy, patients will be treated with chemoradiotherapy. Patients who underwent a resection after receiving <4 months of neoadjuvant chemotherapy, will be offered adjuvant therapy at the discretion of their physician.

of the pancreatic head, with 18-month OS rate as primary outcome(NCT02839343).[62] The initial design of this study was to randomize 134 patients to receive 8 cycles of mFOLFIRINOX (arm A), or 7 cycles of mFOLFIRINOX followed by either hypofractionated stereotactic body radiation therapy (SBRT, 33Gy in 5 fractions) or hypofractionated image guided radiation therapy (HIGRT, 25Gy in 5 fractions) (arm B). Following surgery, all patients were scheduled for 4 cycles of adjuvant modified FOLFOX6 (mFOLFOX6). However, an interim analysis of the R0 resection rate was conducted after accrual of 30 patients, after which the radiotherapy arm (B) was suspended due to futility. The NorPACT-1 trial is a multicenter trial for patients with *resectable* PDAC of the pancreatic head, in which patients are randomized in a 3:2 ratio to receive 4 cycles of neoadjuvant FOLFIRINOX and adjuvant 4 cycles of gemcitabine-capecitabine (arm A), or upfront surgery followed by 6 cycles of adjuvant gemcitabine-capecitabine (arm B) (NCT02919787).[63] The sample size is 90 patients, and the primary endpoint is 1-year OS for those patients who ultimately undergo a resection. The PREOPANC-2 trial is a multicenter study performed by the Dutch Pancreatic Cancer Group (DPCG) (NTR7292).[64] In this study, 368 (B)RPC patients will be randomized to receive 8 cycles of neoadjuvant FOLFIRINOX (arm A) or 3 cycles of neoadjuvant gemcitabine-based chemoradiotherapy with adjuvant 4 cycles of gemcitabine, with median OS as primary endpoint. Last, the ALLIANCE A021806 trial will compare 8 cycles of neoadjuvant and 4 cycles of adjuvant mFOLFIRINOX to all 12 cycles adjuvant mFOLFIRINOX for *resectable* PDAC. This trial will start recruiting patients by the beginning of 2020 and will include 344 patients using median OS as primary endpoint. The remaining three studies investigate neoadjuvant FOLFIRINOX with a sample size of less than 50 patients, thereby limiting potential impact on future guidelines (NCT02047474, NCT02178709, NCT02172976 (NEPAFOX)).

Ongoing neoadjuvant trials – regimens other than FOLFIRINOX (phase II and III)

At least three ongoing randomized phase II-III trials (NCT02305186, NCT00727441, NCT02047513) and four ongoing single-arm phase II trials are investigating neoadjuvant regimens other than FOLFIRINOX (NCT01333124, NCT02926183, NCT03322995, NCT03572400) (Table 4B). The three-arm trial from Johns Hopkins aims to study the feasibility and toxicity of perioperative GVAX vaccine therapy ± cyclophosphamide (oral or intravenous) in addition to standard adjuvant chemoradiotherapy for *resectable* PDAC (NCT00727441). This study is awaiting final results. In the randomized NEONAX trial, 166 patients with *resectable* PDAC are randomized to receive 6 cycles of gemcitabine with *nab*-paclitaxel perioperative (2 neoadjuvant, 4 adjuvant) (arm A), or all cycles adjuvant (arm B).[65] In the PRO30720 study, the neoadjuvant regimen depends on the response on CT or MRI scan, tumor marker levels, and performance status assessment (NCT03322995). Sample size is 125 (B)RPC patients, who will all start with 2 months of neoadjuvant chemotherapy. Subsequent treatment depends on the response and may include a therapy switch to an alternative chemotherapy regimen or chemoradiotherapy. With this adaptive design, the feasibility of personalized treatment will be evaluated. The other ongoing trials comprise

a variety of interventions, including chemoradiotherapy (NCT02305186, NCT01333124, doublet chemotherapy (NCT02926183) and a combination of chemotherapy and immunotherapy (NCT03572400).

Most ongoing studies of both neoadjuvant FOLFIRINOX and other neoadjuvant regimens are underpowered to detect a clinically relevant difference (e.g., 3 or 6 months) in OS. Some studies are hypothesis-generating in their selection of intermediate outcome, such as R0 resection or treatment completion rates. Other studies do have survival as primary outcome, but have a sample size that is too small to detect a clinically relevant survival difference of 3 or 6 months. Assuming an alpha error of 0.05 and a power of 80%, a sample size exceeding 300 patients is needed to detect a difference in median OS of 6 months. An explanation for inadequate sample size is often a concern for feasibility. The PREOPANC-2 trial appears to be the only RCT that may be adequately powered to assess whether neoadjuvant FOLFIRINOX is superior to other regimens. Furthermore, the ALLIANCE A021806 is the only adequately powered RCT comparing perioperative (8+4 cycles) mFOLFIRINOX with adjuvant mFOLFIRINOX (12 cycles).

CONCLUSION

Selection bias hampers comparing survival outcomes between neoadjuvant and adjuvant trials.Patients in neoadjuvant trials may have occult metastatic disease at surgery or may not fully recover from surgery; patients in adjuvant trials were selected after overcoming these hurdles. Only a direct comparison in an RCT will avoid this inevitable selection bias. Despite the limited number of published RCTs comparing a neoadjuvant approach to upfront surgery, patients with resectabel PDAC and BRPC seem to consistently benefit from a neoadjuvant approach with regards to the R0 resection rate. Furthermore, the DFS and OS were at least equal or superior with a neoadjuvant approach compared to upfront surgery. The currently published RCTs supporting neoadjuvant treatment over upfront resection included mostly single-agent based regimens. The multi-agent regimen FOLFIRINOX has considerable toxicity requiring a good performance status. FOLFIRINOX has already been proven superior to gemcitabine in the metastatic and adjuvant setting. Ongoing RCTs will investigate whether FOLFIRINOX is indeed the superior regimen in the neoadjuvant setting. Likely, neoadjuvant FOLFIRINOX may further improve the outcomes of this vulnerable patient group. In addition, future RCTs should study the optimal number of neoadjuvant cycles, the value of additional neoadjuvant chemoradiotherapy, the optimal patient selection for surgical resection, and the need for subsequent adjuvant chemotherapy. For patients with a good performance status, we advocate patient participation in one of the large ongoing RCTs evaluating the potential benefit of neoadjuvant FOLFIRINOX for (B)RPC patients.

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CHAPTER 6

Neoadjuvant therapy or upfront surgery for resectable and borderline resectable pancreatic cancer: a meta-analysis of randomized controlled trials

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ABSTRACT

Background

Neoadjuvant therapy may improve survival compared with upfront surgery in patients with resectable and borderline resectable pancreatic cancer but high quality evidence is lacking.

Methods

We systematically searched for randomized trials comparing neoadjuvant therapy with upfront surgery for resectable and borderline resectable pancreatic cancer published since database inception until December 2020. The primary outcome was overall survival (OS) by intention-to-treat with subgroup analyses for resectability status. Meta-analyses using a random-effects model were performed. Certainty of evidence was assessed using the GRADE approach.

Results

Seven trials with 938 patients were included. All trials included a neoadjuvant gemcitabine-based chemo(radio)therapy arm. None of the studies used adjuvant FOLFIRINOX. Neoadjuvant therapy improved overall survival (hazard ratio [HR] 0.66, 95% CI 0.52–0.85; P=0.001; I^2 46%) compared with upfront surgery. This represents an increase in median overall survival from 19 to 29 months. In the subgroup of resectable pancreatic cancer (ie, venous contact ≤ 180°, no arterial contact), no statistically significant difference in overall survival was observed (HR 0.77, 95% CI 0.53–1.12; P=0.18; I^2 20%). In the subgroup of borderline resectable pancreatic cancer (ie, venous contact >180°, any arterial contact), neoadjuvant therapy improved overall survival (HR 0.61, 95% CI 0.44–0.85; P=0.004; I^2 59%). The GRADE certainty of evidence was high for the outcome of overall survival.

Conclusion

Neoadjuvant therapy improves overall survival compared with upfront surgery in patients with borderline resectable pancreatic cancer. More evidence is required on whether neoadjuvant therapy improves survival for patients with resectable pancreatic cancer.

INTRODUCTION

Pancreatic cancer is the third leading cause of cancer-related death in the United States and the fourth in Europe.[1, 2] With a 5-year survival of 10% it has the lowest survival of all solid tumours.[1] Non-metastatic pancreatic cancer is classified as resectable, borderline resectable, or locally advanced based on the extent of vascular involvement.[3] For resectable pancreatic cancer, resection followed by adjuvant chemotherapy is the standard of care.[3, 4] For borderline resectable pancreatic cancer, NCCN guidelines recommend neoadjuvant therapy while NICE guidelines only recommend neoadjuvant therapy as part of a clinical trial.[3, 4] The recommendations in both guidelines are not based on randomized controlled trials (RCTs).

Upfront surgery with adjuvant therapy may have benefits over neoadjuvant therapy. First, biliary stenting for obstructive jaundice can be omitted. Moreover, patients do not risk preoperative clinical deterioration during chemotherapy. Finally, neoadjuvant treatment delays surgery and tumours not sensitive to chemotherapy may progress and become unresectable. Neoadjuvant treatment has the advantage to guarantee early delivery of systemic chemotherapy. In addition, neoadjuvant treatment might increase the chance of a microscopically complete (R0) resection.[5] Last, neoadjuvant therapy may prevent futile surgery in patients with rapidly progressive disease.

Comparing OS across studies of neoadjuvant therapy and upfront surgery is difficult.[6] Patients in adjuvant trials are a selected subgroup of patients. These patients underwent successful resection, adequately recovered, and in some RCTs they were restaged with a CT scan and postoperative serum carbohydrate antigen 19-9 (CA 19-9) to exclude patients with early progressive disease. In population-based studies only 50% of patients received adjuvant therapy.[7-9] In contrast, neoadjuvant trials include patients who are found to have unresectable or metastatic disease at surgical exploration, who do not recover sufficiently from surgery, and who have early progressive disease.

Initial meta-analyses and large cohort studies comparing neoadjuvant therapy with upfront surgery suggested improved outcomes with neoadjuvant treatment, but were biased by reporting only on patients that underwent a resection.[10, 11] More recently, meta-analyses of non-randomized studies avoided this bias by only including studies that reported intention-to-treat outcomes. These meta-analyses reported a lower resection rate, a higher R0 resection rate but conflicting results concerning OS.[5, 12, 13] Recently, the results of three RCTs comparing neoadjuvant therapy with upfront surgery were reported.[14-16]

Our objective was to perform a meta-analysis including only RCTs comparing neoadjuvant therapy with upfront surgery in patients with resectable and borderline resectable pancreatic cancer, with subgroup analyses for resectability status and type of neoadjuvant treatment.

METHODS

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement and is registered with PROSPERO (CRD42020212886).[17]

Search strategy and selection criteria

We searched Embase, MEDLINE, Web of Science, Cochrane Central Register of Controlled Trials, and Google Scholar for RCTs comparing neoadjuvant therapy with upfront surgery in patients with resectable and borderline resectable pancreatic cancer from database inception until December 3rd, 2020. The exact search terms are displayed in Supplementary Table 1.

After removal of duplicate records, studies were screened on title and abstract by two authors (JvD and QJ). Studies were eligible for inclusion if (1) they were RCTs; (2) included resectable and/or borderline resectable pancreatic cancer patients; (3) had both an neoadjuvant therapy arm and an upfront surgery arm; (4) reported outcomes by intention-to-treat; (5) and were written in the English language. Trials that scheduled adjuvant therapy after neoadjuvant therapy and resection were eligible. After initial screening of abstracts, remaining articles were retrieved for full-text analysis. Both reviewers read the articles and decided on inclusion. Disagreements were resolved by discussion.

Data collection

Data on author, year of publication, inclusion period, sample size, eligibility criteria, treatment regimens, OS, resection rate, microscopically complete (R0) resection rate, negative lymph node (N0) resection rate, surgical complications, and serious adverse events grade ≥ 3 (SAEs) were extracted from the articles separately by two authors (JvD and QJ) using a standardized data extraction form. Disagreement between data extractors were resolved by discussion in consultation with the last author. If the hazard ratio (HR) and confidence interval (CI) were not reported we used indirect methods to obtain them.[18] Additional information about the included RCTs was obtained from the conference presentation, study protocol publication, and trial registration if available.

Outcomes

The primary outcome was OS expressed as a HR. Secondary outcomes were resection rate, R0 resection rate, N0 resection rate, and major surgical complications (Clavien-Dindo ≥ 3). Secondary outcomes were expressed as a risk ratio (RR). All outcomes except surgical complications were analyzed by intention-to-treat; that is, for surgical complications the denominator was the number of patients who underwent a resection rather than all patients assigned to the treatment arm.

Data analysis

Meta-analyses were performed using a random-effects model. A random-effects rather than a fixed-effects model was used because of the expected heterogeneity as a result of the different treatment regimens and varying criteria for resectability.

Studies were assessed for bias using the Cochrane Collaboration's tool for risk of bias in RCTs.[19] We used the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation) to assess the certainty of the evidence.[20] The GRADEpro Guideline Development Tool (McMaster University, Ontario, Canada) was used to create a summary of findings table.

Review Manager (RevMan, Version 5.4, The Cochrane Collaboration, 2020) was used for meta-analysis.

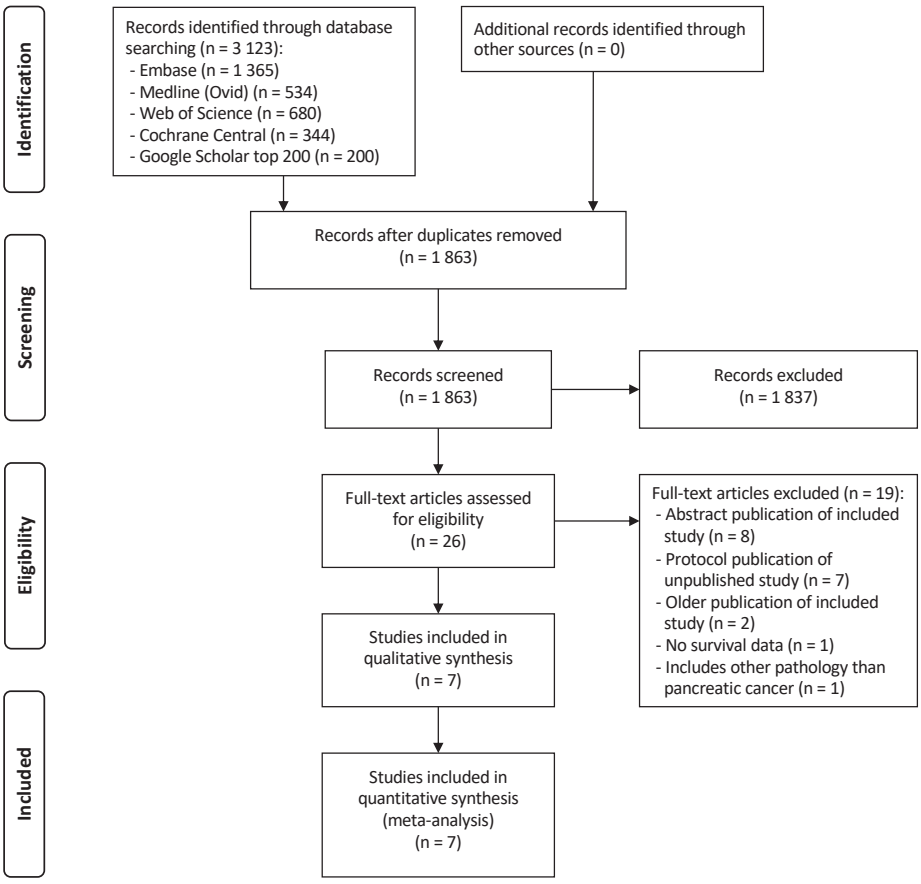

Figure 1. Study selection

Table 1. Study characteristics

	Year of publication	Country	Accrual years	Number of patients	Intervention (cycles)	Comparator (cycles)	Criteria arterial	Criteria venous	Resectability status*
Golcher[21]	2015	Germany, Switzerland	2003-09	66	Neoadj. gemcitabine/cisplatin based CRT (55.8 Gy) + adj. gemcitabine (6)	Adj. gemcitabine (6)	HA/SMA/CA ≤ 180°	SMV/PV ≤ 180°	R/BR
Casadei[22]	2015	Italy	2007-13	38	Neoadj. gemcitabine-based CRT (54 Gy) + adj. gemcitabine (6)	Adj. gemcitabine (6)	No contact with HA/ CA/SMA	SMV/PV ≤ 180°	R
Reni[23]	2018	Italy	2010-15	88	C: Periop. gemcitabine/cisplatin/ epirubicin/capecitabine (3+3)	A: Adj. gemcitabine (6) B: Adj. gemcitabine/ cisplatin/ epirubicin/ capecitabine (6)	Absence of invasion in HA/CA/SMA	Absence of invasion in SMV/ PV	R
Jang[24]	2018	South Korea	2012-14	50	Neoadj. gemcitabine-based CRT (54 Gy) + adj. gemcitabine (4)	Adj. gemcitabine-based CRT (54 Gy) + adj. gemcitabine(4)	2012 NCCN: HA encasement allowed, tumor abutment with SMA ≤ 180°	2012 NCCN: Venous reconstructible (SMV /PV encasement allowed)	BR
Unno[14]	2019	Japan	2013-16	362	Neoadj. gemcitabine/S-1 (2) + adj. S-1 (6 mo)	Adj. S-1 (6 mo)	No arterial abutment of HA/CA/SMA	Venous reconstructible (SMV/PV encasement allowed)	R/BR
Versteijne[15]	2020	The Netherlands	2013-17	246	Neoadj. gemcitabine-based CRT (36 Gy)(3) + adj. gemcitabine (4)	Adj. gemcitabine (6)	R: No arterial contact BR: Arterial contact ≤ 90°	R: Venous ≤ 90° BR: Venous > 90°-270° without occlusion	R/BR
Ghaneh[16]	2020	United Kingdom, Germany	2014-18	88	B: Neoadj. gemcitabine/ capecitabine (2) C: Neoadj. mFOLFIRINOX (4) D: Neoadj. capecitabine-based CRT (50.4 Gy) All arms received adj. gemcitabine or adj. 5-FU/FA (6)	A: Adj. 5-FU/FA or adj. gemcitabine (6)	2013 NCCN: HA encasement allowed, tumor abutment with SMA ≤ 180°	2013 NCCN: Venous reconstructible (SMV /PV encasement allowed)	BR

5-FU/FA, fluorouracil with folinic acid; Adj, adjuvant; BR, borderline resectable; CA, coeliac axis; CRT, chemoradiotherapy; HA, hepatic artery; mFOLFIRINOX, modified fluorouracil with folinic acid, irinotecan, oxaliplatin; NCCN, National Comprehensive Cancer Network; Neoadj, neoadjuvant; PV, portal vein; R, resectable; SMA, superior mesenteric artery; SMV, superior mesenteric vein. *Resectability status according to NCCN definitions.

RESULTS

Study selection

The search yielded 3 123 records. After removal of duplicates, 1 863 records were screened and 26 were retrieved for full-text analysis (Fig. 1). Of these, 19 records were excluded (Supplementary Table 2). Seven RCTs with a total of 938 patients were included in the meta-analysis (Fig. 1).[14-16, 21-24] Two of the seven RCTs were available only as ASCO abstract.[14, 16]

Study characteristics

Study characteristics are displayed in Table 1. Sample size ranged from 38 to 362 patients. Two studies included only patients with resectable disease,[22, 23] two only patients with borderline resectable disease,[16, 24] and three with both resectable and borderline resectable pancreatic cancer patients.[14, 15, 21] The resectability criteria used varied between studies (Table 1).

Of all 938 patients, 471 patients were assigned to upfront surgery and 467 patients to neoadjuvant therapy. Of 467 patients allocated to neoadjuvant therapy, treatment consisted of neoadjuvant chemoradiotherapy (CRT) in 213 patients and neoadjuvant chemotherapy in 254 patients.

All included studies had at least one gemcitabine-based neoadjuvant arm: in the study by Golcher et al. gemcitabine was combined with cisplatin;[21] the PACT-15 study combined gemcitabine with cisplatin, epirubicin, and capecitabine;[23] the Prep-02/JSAP-05 study combined gemcitabine with S-1;[14] and the four-arm ESPAC-5F study included one arm of gemcitabine combined with capecitabine.[16] The ESPAC-5F study also included one arm with neoadjuvant FOLFIRINOX.[16]

In four studies, neoadjuvant therapy consisted of gemcitabine-based CRT.[15, 21, 22, 24] The ESPAC-5F trial included one arm with capecitabine-based CRT.[16] Conventional radiotherapy was used in all studies with neoadjuvant CRT, with a total radiation dose ranging from 36.0 to 55.8 Gy.

In all studies, adjuvant therapy was scheduled in the neoadjuvant therapy arm. Adjuvant chemotherapy was gemcitabine-based in five RCTs.[15, 21-23] Other adjuvant regimens were S-1 in Prep-02/JSAP-05[14] and gemcitabine or 5-fluorouracil (5-FU) in ESPAC-5F.[16] None of the studies used adjuvant FOLFIRINOX or adjuvant gemcitabine plus nab-paclitaxel.

Four RCTs were discontinued early. Reasons for early termination were slow accrual in the trials by Golcher et al. and Casadei et al.,[21, 22] because the chemotherapy regimen became outdated in the PACT-15 trial,[23] and superiority of neoadjuvant therapy at interim analysis in the study by Jang et al.[24]

Overall survival

Neoadjuvant therapy improved OS compared with upfront surgery (HR 0.66, 95% CI 0.52–0.85; P=0.001; I^2 46%)(Fig. 2A). In the subgroup of studies that included only patients with resectable pancreatic cancer, no statistically significant difference in OS was demonstrated (HR 0.77, 95% CI 0.53–1.12; P=0.18; I^2 20%)(Fig. 2A). Neoadjuvant therapy was associated with superior OS in the subgroup of patients with borderline resectable pancreatic cancer (HR 0.61, 95% CI 0.44–0.85; P=0.004; I^2 59%)(Fig. 2A). Increased survival was observed with both neoadjuvant chemotherapy (HR 0.54, 95% CI 0.34–0.87; P=0.01; I^2 64%)(Fig. 2B) and neoadjuvant CRT compared with upfront surgery (HR 0.74, 95% CI 0.58–0.95; P=0.02; I^2 7%)(Fig. 2B).

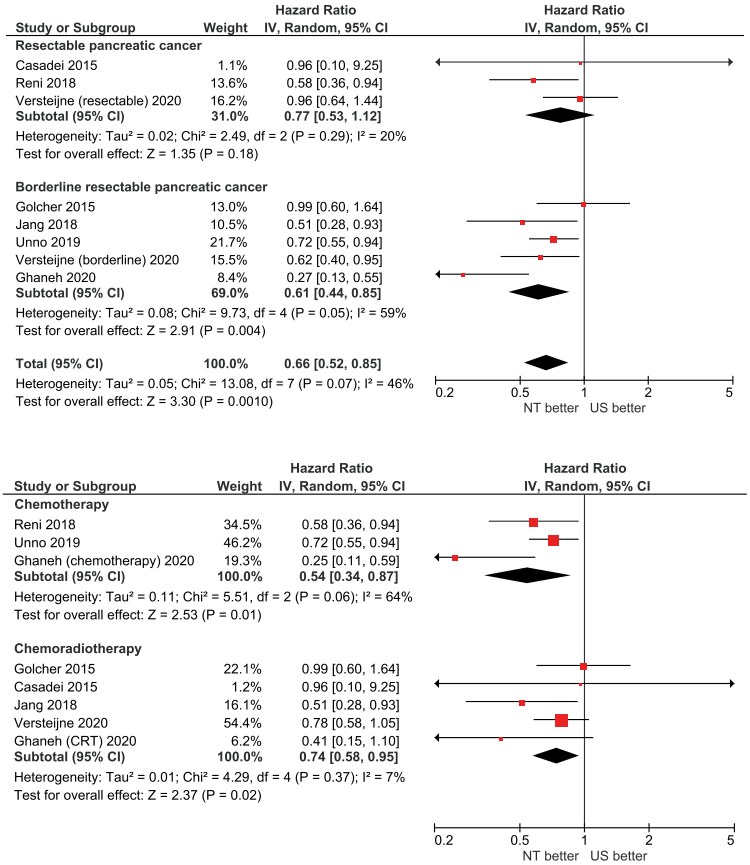

Figure 2. Forest plots for overall survival
A. Overall survival with subgroups for resectability status
B. Overall survival with subgroups for chemotherapy and chemoradiotherapy
Abbreviations: CRT, chemoradiotherapy; NT, neoadjuvant therapy; US, upfront surgery.

Surgical and pathological outcomes

The resection rate was available for all studies and varied between 55% and 86% in the neoadjuvant therapy group and 66% and 88% in the upfront surgery group (Table 2). The resection rate was not statistically significantly different between neoadjuvant therapy and upfront surgery (RR 0.94; 95% CI 0.89–1.01; P=0.08; I^2 0%)(Supplementary Fig. 1A). The R0 resection rate was available for six studies and ranged from 13% to 53% in the neoadjuvant therapy group and from 9% to 48% in the upfront surgery group (Table 2).[15, 16, 21-24] An R0 resection was more common after neoadjuvant therapy (RR 1.47, 95% CI 1.17–1.84; P<0.001; I^2 0%)(Supplementary Fig.1B). The N0 resection rate was available for all studies and ranged from 25% to 44% with neoadjuvant therapy and 6% to 30% with upfront surgery (Table 2). N0 resection rate was higher after neoadjuvant therapy (RR 2.15, 95% CI 1.69–2.72; P<0.001; I^2 0%)(Supplementary Fig. 1C). The rate of major surgical complications was available for three studies and ranged from 11% to 32% with neoadjuvant therapy and 17% to 65% with upfront surgery (Table 2).[21, 23, 24] Major surgical complications did not differ between neoadjuvant therapy and upfront surgery (RR 0.60, 95% CI 0.34–1.05; P=0.08; I^2 0%) (Supplementary Fig. 1D).

The percentage of patients who started adjuvant therapy was available for six studies and ranged from 21% to 72% in the neoadjuvant therapy arm and 30% to 75% in the upfront surgery arm (Table 2).[15, 16, 21-24] The rate of SAEs was available for the neoadjuvant therapy arm for all studies[14-16, 21-24] and for the upfront surgery arm in three studies

Table 2. Outcomes with neoadjuvant therapy or upfront surgery

Reference	Median overall survival (months)		Resection (%)		R0 resection (%)		N0 Resection (%)		Major surgical complications (%)		Started adjuvant therapy (%)		Serious adverse events (%)	
	NT	US	NT	US	NT	US	NT	US	NT	US	NT	US	NT	US
Golcher[21]	17.4	14.4	58%	70%	52%	48%	39%	30%	32%	65%	21%	30%	45%	NR
Casadei[22]	22.4	19.5	61%	75%	39%	25%	28%	10%	NR	NR	22%	75%	39%	NR
Reni[23]	38.2	26.4*	84%	88%	53%	29%	41%	23%	11%	20%	72%	66%	41%	18%
Jang[24]	21.0	12.0	63%	78%	52%	26%	44%	13%	24%	17%	52%	57%	11%	4%
Unno[14]	36.7	26.6	86%	87%	NR	NR	35%	16%	NR	NR	NR	NR	73%	NR
Versteijne[15]	16.0	14.3	61%	72%	43%	16%	40%	16%	NR	NR	46%	51%	52%	41%
Ghaneh[16]	NR	NR	55%	66%	13%	9%	25%	6%	NR	NR	46%	53%	18%	NR
Total			**72%**	**80%**	**40%**	**29%**	**36%**	**17%**	**21%**	**31%**	**45%**	**54%**	**52%**	**31%**

Total proportions were calculated as number of events divided by number of patients. Outcomes are by intention-to-treat except for major surgical complications.

NR, not reported; NT, neoadjuvant therapy; US, upfront surgery.

*In the adjuvant gemcitabine/cisplatin/epirubicin/capecitabine arm, median overall survival was 20.4 months in the adjuvant gemcitabine arm.

(Table 2).[15, 23, 24] The overall proportion of patients with SAEs in the neoadjuvant therapy arm was 52% and 31% in the upfront surgery arm.

Risk of bias and quality of the evidence

The risk of bias was judged as low in four studies and there were some concerns in one domain in three studies (Supplementary Fig. 2). Specifically, the risk of bias was related to the exclusion of patients after randomization, resulting in missing outcome data in more than 5% of randomized patients.[21, 23, 24] The assessment of publication bias was not possible due to the availability of less than 10 studies.

Based on the pooled HR of 0.66, neoadjuvant therapy could potentially improve median survival from 19 months to 29 months (Table 3). The quality of evidence was assessed to be high for OS, moderate for resection rate, R0 resection rate and N0 resection, and low for major surgical complications (Table 3). Quality was lowered for resection rate because of imprecision. The reason for moderate quality for R0 resection rate and N0 resection was

Table 3. GRADE Summary of findings

Outcomes	Anticipated absolute effects (95% CI)*		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)
	Upfront Surgery	Neoadjuvant Therapy			
Median overall survival	19 months†	**29 months** (22 to 37)	**HR 0.66** (0.52 to 0.85)	938 (7 RCTs)	⊕⊕⊕⊕ HIGH
Resection	80 per 100	**75 per 100** (71 to 80)	**RR 0.94** (0.89 to 1.01)	938 (7 RCTs)	⊕⊕⊕◯‡ MODERATE
R0 Resection	29 per 100	**42 per 100** (33 to 52)	**RR 1.47** (1.17 to 1.84)	576 (6 RCTs)	⊕⊕⊕◯§ MODERATE
N0 Resection	17 per 100	**36 per 100** (28 to 46)	**RR 2.15** (1.69 to 272)	938 (7 RCTs)	⊕⊕⊕◯§ MODERATE
Major surgical complications	31 per 100	**19 per 100** (11 to 33)	**RR 0.60** (0.34 to 1.05)	153 (3 RCTs)	⊕⊕◯◯‡,‖ LOW

GRADE category of evidence:[20]
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect;
Moderate certainty: We are moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different);
Low certainty: Our confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of the effect);
Very low certainty: We have very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect).
*The risk in the neoadjuvant therapy group (and its 95% confidence interval) is based on the assumed risk in the upfront surgery group and the relative effect of neoadjuvant therapy (and its 95% CI). Results may slightly differ from Table 2 as a result of random effects analysis.
†Calculated using the method described by Gillen et al.[10]
‡Downgraded for imprecision.
§Downgraded for indirectness.
‖Downgraded for inconsistency.
HR, hazard ratio; RR, risk ratio.

because these are surrogate outcomes and not directly relevant for patients (ie, indirectness in GRADE terminology). Quality for the outcome of major surgical complications was judged as low because of inconsistency and imprecision.

DISCUSSION

In this meta-analysis of RCTs, neoadjuvant therapy improved OS compared with upfront surgery in patients with resectable or borderline resectable pancreatic cancer. In the subgroup of patients with borderline resectable pancreatic cancer, OS was superior with neoadjuvant therapy. For patients with resectable pancreatic cancer, no statistically significant difference was observed.

In all seven RCTs in the present meta-analysis, the neoadjuvant regimen was gemcitabine-based without nab-paclitaxel. Only the ESPAC-5F study had one of the four arms that scheduled 20 patients for neoadjuvant FOLFIRINOX.[16] The French-Canadian PRODIGE 24/CCTG PA.6 trial convincingly demonstrated that FOLFIRINOX is superior to gemcitabine as adjuvant therapy with a median overall survival of 54.4 months with FOLFIRINOX compared with 35.0 months with gemcitabine (HR 0.64; 95% CI 0.48 to 0.86; P=0.003).[25] Many non-randomized studies investigated whether this benefit would extrapolate to the neoadjuvant setting. A patient-level meta-analysis of neoadjuvant FOLFIRINOX in patients with borderline resectable disease found a favorable median OS of 22 months for all patients, including patients not undergoing resection.[26] However, the optimal neoadjuvant regimen remains uncertain. The phase 2 SWOG S1505 trial found no difference in OS between perioperative FOLFIRINOX and perioperative gemcitabine plus nab-paclitaxel in patients with resectable pancreatic cancer.[27] In the Netherlands, the PREOPANC-2 trial compares total neoadjuvant FOLFIRINOX with neoadjuvant gemcitabine-based CRT and adjuvant gemcitabine in 368 patients with resectable and borderline resectable pancreatic cancer.[28]

In all studies, neoadjuvant therapy was followed by adjuvant chemotherapy after resection. In six RCTs, gemcitabine (alone or in combination) was administered as adjuvant chemotherapy in the comparator arm. Only the Prep-02/JSAP-05 trial scheduled patients for adjuvant S-1[14] and ESPAC-5F allowed for 5-FU as an alternative to gemcitabine.[16] None of the RCTs scheduled patients for adjuvant FOLFIRINOX, because they were designed prior to the publication of the PRODIGE 24/CCTG PA.6 trial that demonstrated that FOLFIRINOX is superior to gemcitabine in the adjuvant setting.[25] Adjuvant FOLFIRINOX, however, is scheduled in the upfront surgery arm of all four ongoing or planned RCTs that compare neoadjuvant therapy with upfront surgery for resectable pancreatic cancer (Table 4).[29, 30] The primary concern for adjuvant treatment remains that only 54% of the patients included

Table 4. Ongoing randomized trials of neoadjuvant therapy and upfront surgery in patients with resectable and borderline resectable pancreatic cancer

Trial	Country	Target sample size	Intervention (cycles)	Comparator (cycles)	Criteria arterial	Criteria venous	Resectability status*	Start	Trial status
NorPACT-1 NCT02919787	Norway, Denmark, Finland, Sweden	130	Periop. mFOLFIRINOX (4+8)†	Adj. mFOLFIRINOX (12)†	2015 NCCN: No arterial contact	2015 NCCN: SMV/PV ≤ 180° without vein contour irregularity	R	09-2016	Active, not recruiting‡
PANACHE01-PRODIGE48 NCT02959879	France	160	Periop. mFOLFIRINOX (4+8) or Neoadj. FOLFOX (4) + adj. mFOLFIRINOX (8)	Adj. mFOLFIRINOX (12)	2017 NCCN: No arterial contact	2017 NCCN: SMV/PV ≤ 180° without vein contour irregularity	R	03-2017	Recruiting‡
A021806 NCT04340141	USA	352	Periop. mFOLFIRINOX (8+4)	Adj. mFOLFIRINOX (12)	No arterial contact	SMV/PV < 180° and patent PV/splenic vein confluence	R	07-2020	Recruiting‡
PREOPANC-3 NCT04927780	The Netherlands	378	Periop. mFOLFIRINOX (8+4)	Adj. mFOLFIRINOX (12)	No arterial contact	SMV/PV ≤ 90°	R	08-2021	Recruiting‡

Adj, adjuvant; CA, coeliac axis; CRT, chemoradiotherapy; mFOLFIRINOX, modified fluorouracil with folinic acid, irinotecan, oxaliplatin; FOLFOX, fluorouracil with folinic acid, oxaliplatin; NCCN, National Comprehensive Cancer Network; Neoadj, neoadjuvant; Periop, Perioperative; PV, portal vein; R, resectable; SMV, superior mesenteric vein.

*Resectability status according to the National Comprehensive Cancer Network (NCCN) definitions.

†Personal communication with the principal investigator: Protocol updated in 2018 from adjuvant gemcitabine/capecitabine to adjuvant mFOLFIRINOX.

‡Trial status according to ClinicalTrials.gov.

in the seven RCTs received adjuvant treatment after surgery. This is consistent with results from large nationwide registries.[7-9]

Five out of the seven included RCTs scheduled patients for neoadjuvant chemoradiotherapy rather than chemotherapy only. Subgroup analyses found improved OS for both chemoradiotherapy and chemotherapy only compared with upfront surgery. Evidence from RCTs on the added value of neoadjuvant radiotherapy in addition to neoadjuvant chemotherapy is scarce. In the ALLIANCE A021501 trial, patients with borderline resectable pancreatic cancer were randomized to 8 cycles of neoadjuvant modified FOLFIRINOX or 7 cycles of neoadjuvant modified FOLFIRINOX followed by stereotactic body radiation therapy.[31] According to an abstract presentation at ASCO GI 2021, stereotactic body radiation therapy did not improve OS or R0 resection rate.[32] The ongoing French PANDAS-PRODIGE 44 trial compares neoadjuvant FOLFIRINOX with neoadjuvant FOLFIRINOX followed by capecitabine-based CRT.

Some physicians are concerned that neoadjuvant therapy results in a lower resection rate compared with upfront surgery or may lead to a higher rate of surgical complications. We did not find evidence for this since the resection rate and the rate of surgical complications were not statistically different between neoadjuvant therapy and upfront surgery. In an analysis of the PREOPANC trial, the rate of postoperative pancreatic fistula (grade B or C) was zero after neoadjuvant chemoradiation.[33]

RCTs assessing neoadjuvant therapy for pancreatic cancer are challenging to perform.[34, 35] This is illustrated by the fact that four out of seven included RCTs did not reach their accrual targets.[21-24] Out of the three RCTs that did complete accrual, one was a small feasibility study.[16] Four additional RCTs comparing neoadjuvant therapy with upfront surgery were not included in this meta-analysis, because they did not reach their accrual targets and remain unpublished (Supplementary Table 3).

The strengths of this meta-analysis are the large number of patients, the use of an intention-to-treat analysis, and the quality of the included studies with a low risk of bias. The main limitations of the present meta-analysis are the heterogeneity of the neoadjuvant regimens and the use of gemcitabine-based adjuvant regimens, while the current standard of care is adjuvant FOLFIRINOX. Secondly, external validity and pooled analyses are hampered by the different definitions for resectability across trials. Thirdly, resectability was solely defined on imaging in all studies, while CA 19-9 and performance status are increasingly recognized for their large impact on OS and treatment effect.[36, 37] Finally, two of the seven included trials were presented at the ASCO Annual Meeting and are currently only available as abstract.[14, 16]

Conclusions

This meta-analysis of seven RCTs confirms the superiority of neoadjuvant therapy in patients with borderline resectable pancreatic cancer. Uncertainty remains whether neoadjuvant therapy improves survival for patients with resectable pancreatic cancer. Future studies should investigate whether the neoadjuvant approach is also superior in patients with resectable pancreatic cancer, whether FOLFIRINOX is superior to gemcitabine-based treatments in a neoadjuvant approach, and whether adding (chemo)radiotherapy after neoadjuvant chemotherapy improves survival.

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33. van Dongen JC, Suker M, Versteijne E, Bonsing BA, Mieog JSD, de Vos-Geelen J, et al. Surgical Complications in a Multicenter Randomized Trial Comparing Preoperative Chemoradiotherapy and Immediate Surgery in Patients With Resectable and Borderline Resectable Pancreatic Cancer (PREOPANC Trial). Ann Surg. 2020.

34. Evans DB. The Complexity of Neoadjuvant Therapy for Operable Pancreatic Cancer: Lessons Learned From SWOG S1505. Ann Surg. 2020;272:487-.

35. O'Reilly EM, Ferrone C. Neoadjuvant or Adjuvant Therapy for Resectable or Borderline Resectable Pancreatic Cancer: Which Is Preferred? J Clin Oncol. 2020;38:1757-9.

36. Anger F, Doring A, van Dam J, Lock JF, Klein I, Bittrich M, et al. Impact of Borderline Resectability in Pancreatic Head Cancer on Patient Survival: Biology Matters According to the New International Consensus Criteria. Ann Surg Oncol. 2020/09/14 ed2020.

37. Isaji S, Mizuno S, Windsor JA, Bassi C, Fernandez-Del Castillo C, Hackert T, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology. 2018;18:2-11.

SUPPLEMENTARY FILES

Supplementary Table 1. Search Strategy and results

Database	Search query	Number of records	After deduplication
Embase	('neoadjuvant therapy'/exp OR (neoadjuvant*):ab,ti,kw) AND ('pancreas tumor'/de OR 'pancreas cancer'/de OR 'pancreas carcinoma'/de OR 'pancreas adenocarcinoma'/de OR (((pancrea*) NEAR/6 (cancer* OR carcinoma* OR adenocarcinoma* OR neoplas* OR tumor* OR tumor*))):ab,ti,kw) AND ('Controlled clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups):ab,ti,kw) NOT ([animals]/lim NOT [humans]/lim) AND [English]/lim	1 365	1 294
MEDLINE (Ovid)	(Neoadjuvant Therapy/ OR (neoadjuvant*).ab,ti,kf.) AND (Pancreatic Neoplasms/ OR Carcinoma, Pancreatic Ductal/ OR (((pancrea*) ADJ6 (cancer* OR carcinoma* OR adenocarcinoma* OR neoplas* OR tumor* OR tumor*))).ab,ti,kf.) AND (exp Controlled clinical trial/ OR "Double-Blind Method"/ OR "Single-Blind Method"/ OR "Random Allocation"/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups).ab,ti,kf.) NOT (exp Animals/ NOT Humans/) AND English.lg.	534	65
Web of Science	(TI=(neoadjuvant*) OR AB=(neoadjuvant*)) AND (TI=((pancrea*) NEAR/5 (cancer* OR carcinoma* OR adenocarcinoma* OR neoplas* OR tumor* OR tumor*)) OR AB=((pancrea*) NEAR/5 (cancer* OR carcinoma* OR adenocarcinoma* OR neoplas* OR tumor* OR tumor*))) AND (TI=(random* OR factorial* OR crossover* OR (cross NEAR/1 over*) OR placebo* OR ((doubl* OR singl*) NEAR/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups) OR AB=(random* OR factorial* OR crossover* OR (cross NEAR/1 over*) OR placebo* OR ((doubl* OR singl*) NEAR/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups)) AND LA=English	680	239
Cochrane Central Register of Controlled Trials	((neoadjuvant*):ab,ti,kw) AND ((((pancrea*) NEAR/6 (cancer* OR carcinoma* OR adenocarcinoma* OR neoplas* OR tumor* OR tumor*))):ab,ti,kw)	344	157
Google Scholar top 200	neoadjuvant "pancreas|pancreatic cancer|carcinoma|adeno carcinoma" trial|trials|RCT	200	108
Total		3 123	1 863

Supplementary Table 2: Full text articles excluded with reasons

No.	Study	Reason
1	Satoi S, Unno M, Motoi F, Matsuyama Y, Matsumoto I, Aosasa S, et al. The effect of neoadjuvant chemotherapy with gemcitabine and S-1 for resectable pancreatic cancer (randomized phase II/III trial; Prep-02/JSAP-05). J Clin Oncol. 2019;37.	Abstract publication of included study
2	Balzano G, Zanon S, Castoldi R, Aleotti F, Zerbi A, Falconi M, et al. A randomized phase II trial on neoadjuvant chemotherapy in resectable pancreatic adenocarcinoma. Eur J Surg Oncol. 2018;44(4):553.	Abstract publication of included study
3	Kwon W, Jang JY, Han Y, Kim SW, Heo J, Park JS, et al. Multicenter prospective randomized phase II/III study of neoadjuvant chemoradiation with gemcitabine in patients with borderline resectable pancreatic cancer. J Hepato-Biliary-Pancreatic Sci. 2017;24:A122.	Abstract publication of included study
4	Brunner TB, Golcher H, Witzigmann H, Marti L, Bechstein WO, Bruns C, et al. Preoperative chemoradiation for resectable adenocarcinoma of pancreatic head: Results of a randomized phase-II trial. Strahlenther Onkol. 2013;189:18.	Abstract publication of included study
5	Brunner T, Golcher H, Witzigmann H, Marti L, Bechstein WO, Bruns C, et al. Results of a multicenter randomized phase II trial of resection ± neoadjuvant chemoradiation therapy in pancreatic cancer. Int J Radiat Oncol Biol Phys. 2012;84(3):S90-S1.	Abstract publication of included study
6	Golcher H, Witzigmann H, Marti L, Lange J, Bechstein W, Bruns C, et al. Preoperative chemoradiation for resectable adenocarcinoma of the pancreas (isrctn 78805636): Pattern of recurrence. Ann Oncol. 2012;23:iv30.	Abstract publication of included study
7	Di Marco M, Macchini M, Di Cicilia R, Vecchiarelli S, Casadei R, Barbieri E, et al. Neoadjuvant therapy for resectable pancreatic adenocarcinoma: An interim report of a prospective randomized study. J Clin Oncol. 2010;28(15).	Abstract publication of included study
8	D'Ambra M, Casadei R, Pezzilli R, Cristina M, Marco D, Guido A, et al. Neoadjuvant therapy for resectable pancreatic adenocarcinoma: A single center prospective, randomized controlled study. Pancreatology. 2014;14(3):S6.	Abstract publication of included study
9	Schwarz L, Vernerey D, Bachet JB, Tuech JJ, Portales F, Michel P, et al. Resectable pancreatic adenocarcinoma neo-adjuvant FOLF(IRIN)OX-based chemotherapy - a multicenter, non-comparative, randomized, phase II trial (PANACHE01-PRODIGE48 study). BMC Cancer. 2018;18(1).	Protocol publication of unpublished study
10	Labori KJ, Lassen K, Hoem D, Grønbech JE, Søreide JA, Mortensen K, et al. Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1)) - study protocol for a national multicentre randomized controlled trial. BMC Surg. 2017;17(1):94.	Protocol publication of unpublished study
11	Hozaeel W, Pauligk C, Homann N, Luley K, Kraus TW, Trojan J, et al. Randomized multicenter phase II/III study with adjuvant gemcitabine versus neoadjuvant/adjuvant FOLFIRINOX in resectable pancreatic cancer: The NEPAFOX trial. J Clin Oncol. 2015;33(15).	Protocol publication of unpublished study
12	Ettrich TJ, Berger AW, Muche R, Lutz MP, Prasnikar N, Uhl W, et al. Neonax (AIO-PAK-0313): Neoadjuvant plus adjuvant or only adjuvant nab-paclitaxel plus gemcitabine for resectable pancreatic cancer: A phase II study of the AIO Pancreatic Cancer Group. J Clin Oncol. 2015;33(3).	Protocol publication of unpublished study

Supplementary Table 2. Full text articles excluded with reasons (continued)

No.	Study	Reason
13	Ettrich T, Berger A, Muche R, Lutz M, Prasnikar N, Uhl W, et al. Neonax: Neoadjuvant plus adjuvant or only adjuvant nab-paclitaxel plus gemcitabine for resectable pancreatic cancer: A phase II study of the AIO pancreatic cancer group. Ann Oncol. 2014;25:ii52.	Protocol publication of unpublished study
14	Ettrich TJ, Berger AW, Muche R, Lutz MP, Prasnikar N, Uhl W, et al. NEONAX: Neoadjuvant plus adjuvant or only adjuvant nab-paclitaxel plus gemcitabine for resectable pancreatic cancer-A phase II study of the AIO Pancreatic Cancer Group. J Clin Oncol. 2014;32(15).	Protocol publication of unpublished study
15	Heinrich S, Pestalozzi B, Lesurtel M, Berrevoet F, Laurent S, Delpero JR, et al. Adjuvant gemcitabine versus NEOadjuvant gemcitabine/oxaliplatin plus adjuvant gemcitabine in resectable pancreatic cancer: A randomized multicenter phase III study (NEOPAC study). BMC Cancer. 2011;11.	Protocol publication of unpublished study
16	Brunner T, Golcher H, Witzigmann H, Marti L, Bechstein W, Bruns C, et al. Neoadjuvant chemoradiotherapy vs surgery for pancreatic cancer. A multi-centre randomised phase II trial. Radiother Oncol. 2012;103:S182-S3.	Older publication of included study
17	D'Ambra M, Casadei R, Pezzilli R, Calculli L, Barbieri E, Di Marco MC, et al. Neoadjuvant therapy for resectable pancreatic adenocarcinoma: An interim report of a prospective controlled randomized study. Pancreatology. 2010;10(2-3):317.	Older publication of included study
18	Uhl W, Ettrich TJ, Reinacher-Schick AC, Algül H, Friess H, Kornmann M, et al. NEONAX trial: Neoadjuvant plus adjuvant or only adjuvant nab-paclitaxel plus gemcitabine for resectable pancreatic cancer, a phase II study of the AIO pancreatic cancer group (AIO-PAK-0313)? Safety interim analysis. J Clin Oncol. 2019;37.	No survival data
19	Singh A, Gupta R, Rana SS, Kang M, Sharma V, Singh H, et al. Comparison of neoadjuvant chemoradiotherapy for resectable and borderline resectable periampullary carcinoma with upfront surgery: A prospective randomised study. Gastrointest Endosc. 2018;87(6):AB575.	Includes non-PDAC

Supplementary Table 3. Unpublished randomized trials of neoadjuvant therapy and upfront surgery in patients with resectable and borderline resectable pancreatic cancer

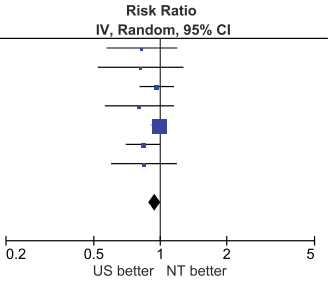
Trial	Country	Target sample size	Intervention (cycles)	Comparator (cycles)	Criteria arterial	Criteria venous	Resectability status*	Start	Trial status†
NEOPAC NCT01314027	Switzerland, Germany, France, Belgium	310	Neoadj. gemcitabine/ oxaliplatin (4) + adj. gemcitabine (6)	Adj. gemcitabine (6)	No arterial contact	Infiltration of the portal vein <180°	R	09-2009	Terminated, 38 pts randomised
NEOPA NCT01900327	Germany	410	Neadj. gemcitabine-based CRT+ adj. gemcitabine (6)	Adj. gemcitabine (6)	R: Visualizable fat plane around CA/ SMA BR: Abutment of SMA <180°	R: Patent SMV/PV BR: Substantial SMV/PV impingement	R/BR	02-2014	Terminated, 32 pts randomised
NEPAFOX NCT02172976	Germany	126	Periop. FOLFIRINOX (6+6)	Adj. gemcitabine (6)	No infiltration of SMA/CA	Venous reconstructible	R/BR	11-2014	Completed, 40 pts randomised
NEONAX NCT02047513	Germany	162	Periop. nab-paclitaxel/ gemcitabine (2+4)	Adj. nab-paclitaxel/ gemcitabine (6)	Visualizable fat planes around CA/ SMA	Patent SMV/PV	R	03-2015	Not recruiting, 127 pts randomised

Adj, adjuvant; CA, coeliac axis; CRT, chemoradiotherapy; FOLFIRINOX, fluorouracil with folinic acid, irinotecan, oxaliplatin; Neoadj, neoadjuvant; Periop, Perioperative; PV, portal vein; R, resectable; SMA, superior mesenteric artery; SMV, superior mesenteric vein.
*Resectability status according to the National Comprehensive Cancer Network (NCCN) definitions.
†Trial status according to ClinicalTrials.gov.

A: Resection rate

Study or Subgroup	NT Events	NT Total	US Events	US Total	Weight	Risk Ratio IV, Random, 95% CI
Golcher 2015	19	33	23	33	3.0%	0.83 [0.57, 1.20]
Casadei 2015	11	18	15	20	2.0%	0.81 [0.52, 1.27]
Reni 2018	27	32	49	56	12.8%	0.96 [0.81, 1.15]
Jang 2018	17	27	18	23	3.1%	0.80 [0.56, 1.15]
Unno 2019	157	182	157	180	63.0%	0.99 [0.91, 1.07]
Versteijne 2020	72	119	92	127	12.6%	0.84 [0.70, 1.00]
Ghaneh 2020	31	56	21	32	3.5%	0.84 [0.60, 1.19]
Total (95% CI)		**467**		**471**	**100.0%**	**0.94 [0.89, 1.01]**
Total events	334		375			

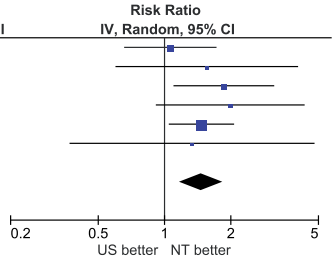
Heterogeneity: Tau² = 0.00; Chi² = 5.19, df = 6 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.74 (P = 0.08)



B: R0 resection rate

Study or Subgroup	NT Events	NT Total	US Events	US Total	Weight	Risk Ratio IV, Random, 95% CI
Golcher 2015	17	33	16	33	21.6%	1.06 [0.66, 1.72]
Casadei 2015	7	18	5	20	5.5%	1.56 [0.60, 4.04]
Reni 2018	17	32	16	56	18.2%	1.86 [1.10, 3.15]
Jang 2018	14	27	6	23	8.3%	1.99 [0.91, 4.33]
Versteijne 2020	51	119	37	127	43.3%	1.47 [1.05, 2.07]
Ghaneh 2020	7	56	3	32	3.1%	1.33 [0.37, 4.80]
Total (95% CI)		**285**		**291**	**100.0%**	**1.47 [1.17, 1.84]**
Total events	113		83			

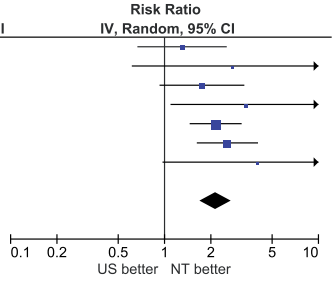
Heterogeneity: Tau² = 0.00; Chi² = 3.11, df = 5 (P = 0.68); I² = 0%
Test for overall effect: Z = 3.35 (P = 0.0008)



C: N0 resection rate

Study or Subgroup	NT Events	NT Total	US Events	US Total	Weight	Risk Ratio IV, Random, 95% CI
Golcher 2015	13	33	10	33	12.6%	1.30 [0.67, 2.54]
Casadei 2015	5	18	2	20	2.5%	2.78 [0.61, 12.59]
Reni 2018	13	32	13	56	13.9%	1.75 [0.93, 3.30]
Jang 2018	12	27	3	23	4.3%	3.41 [1.09, 10.62]
Unno 2019	63	182	29	180	37.1%	2.15 [1.46, 3.17]
Versteijne 2020	48	119	20	127	26.8%	2.56 [1.62, 4.05]
Ghaneh 2020	14	56	2	32	2.8%	4.00 [0.97, 16.49]
Total (95% CI)		**467**		**471**	**100.0%**	**2.15 [1.69, 2.72]**
Total events	168		79			

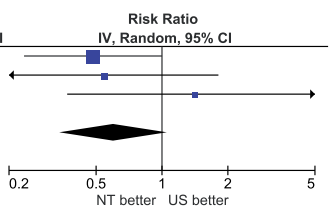
Heterogeneity: Tau² = 0.00; Chi² = 4.62, df = 6 (P = 0.59); I² = 0%
Test for overall effect: Z = 6.32 (P < 0.00001)



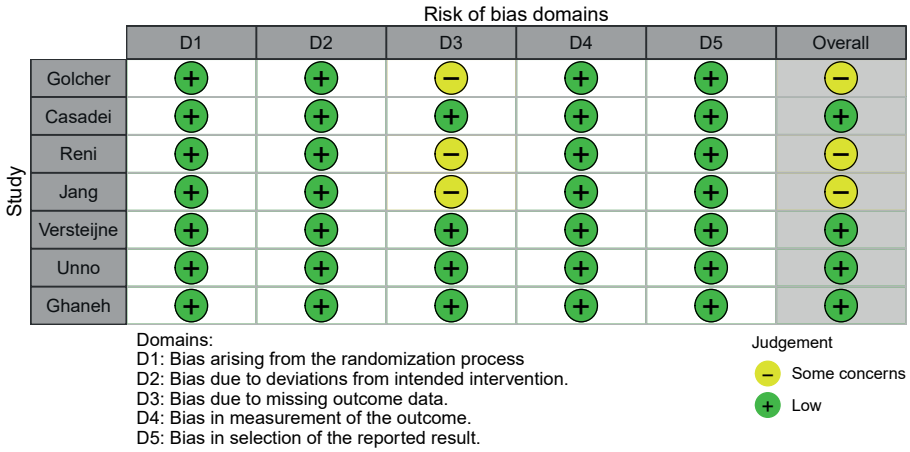
D: Major surgical complications

Study or Subgroup	NT Events	NT Total	US Events	US Total	Weight	Risk Ratio IV, Random, 95% CI
Golcher 2015	6	19	15	23	60.3%	0.48 [0.23, 1.00]
Reni 2018	3	27	10	49	22.0%	0.54 [0.16, 1.81]
Jang 2018	4	17	3	18	17.7%	1.41 [0.37, 5.40]
Total (95% CI)		**63**		**90**	**100.0%**	**0.60 [0.34, 1.05]**
Total events	13		28			

Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)



Supplementary Figure 1. Surgical and pathological outcomes
Abbreviations: NT, neoadjuvant therapy; US, upfront surgery.



Supplementary Figure 2. Risk of bias assessment

CHAPTER 7

Neoadjuvant Folfirinox in Patients With Borderline Resectable Pancreatic Cancer: A Systematic Review and Patient-Level Meta-Analysis

Quisette P. Janssen, Stefan Buettner, Mustafa Suker, Berend R. Beumer, Pietro Addeo, Philippe Bachellier, Nathan Bahary, Tanios Bekaii-Saab, Maria A. Bali, Marc G. Besselink, Brian A. Boone, Ian Chau, Stephen Clarke, Mary Dillhoff, Bassel F. El-Rayes, Jessica M. Frakes, Derek Grose, Peter J. Hosein, Nigel B. Jamieson, Amar A. Javed, Khurum Khan, Kyu-pyo Kim, Song C. Kim, Sunhee S. Kim, Andrew H. Ko, Jill Lacy, Georgios A. Margonis, Martin D. McCarter, Colin J. McKay, Eric A. Mellon, Sing Y. Moorcraft, Ken-ichi Okada, Alessandro Paniccia, Parag J. Parikh, Niek A. Peters, Hans Rabl, Jaswinder Samra, Christoph Tinchon, Geertjan van Tienhoven, Eran van Veldhuisen, Andrea Wang-Gillam, Matthew J. Weiss, Johanna W. Wilmink, Hiroki Yamaue, Marjolein Y.V. Homs, Casper H.J. van Eijck, Matthew H.G. Katz, Bas Groot Koerkamp

J Natl Cancer Inst. 2019 Aug 1;111(8):782-794.

ABSTRACT

Background

FOLFIRINOX is a standard treatment for metastatic pancreatic cancer patients. The effectiveness of neoadjuvant FOLFIRINOX in patients with borderline resectable pancreatic cancer (BRPC) remains debated.

Methods

We performed a systematic review and patient-level meta-analysis on neoadjuvant FOLFIRINOX in patients with BRPC. Studies with BRPC patients who received FOLFIRINOX as first-line neoadjuvant treatment were included. Primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), resection rate, R0-resection rate, and grade 3-4 adverse events. Patient-level survival outcomes were obtained from authors of included studies.

Results

We included 24 studies (8 prospective, 16 retrospective), comprising 313 (38%) BRPC patients treated with FOLFIRINOX. Most studies (*n*=20) presented intention-to-treat results. The median number of administered neoadjuvant FOLFIRINOX cycles ranged from 4 to 9. The resection rate was 68% (95% CI: 60.1 – 74.6), the R0-resection rate was 84% (95% CI: 76.8 – 89.1). The median OS varied from 11.0 to 34.2 months across studies. Patient-level survival data was obtained for 20 studies representing 283 BRPC patients. Patient-level median OS was 22.2 months (95% CI: 18.8 – 25.6), patient-level median PFS was 18.0 months (95% CI: 14.5 – 21.5). Neutropenia (18%), diarrhea (11%), and fatigue (11%) were the most commonly reported grade 3-4 adverse events. No deaths were attributed to FOLFIRINOX.

Conclusion

This patient-level meta-analysis of 283 BRPC patients treated with neoadjuvant FOLFIRINOX shows a favorable median OS of 22.2 months, resection rate of 68%, and R0-resection rate of 84%. Considering the heterogeneity of included studies, these results need to be assessed in a randomized trial.

INTRODUCTION

Pancreatic cancer is expected to be the second leading cause of cancer-related death by 2030.[1] Approximately 20% of patients have borderline resectable pancreatic cancer (BRPC) or upfront resectable pancreatic cancer at diagnosis.[2] Even after curative-intent surgery, cure is exceedingly rare, as demonstrated by a 10-year overall survival (OS) of 4%.[3] Upfront resection with adjuvant chemotherapy has long been the standard of care for patients with localized pancreatic cancer. However, due to postoperative complications, deteriorating performance status, and early progressive disease, only about 55% of patients receive adjuvant chemotherapy.[4-6] With a neoadjuvant approach almost all patients receive systemic chemotherapy. This approach is addressing occult metastatic disease, increasing the rate of R0 resection, and avoiding futile surgery in patients with rapidly progressive disease.[7]

Several neoadjuvant treatment regimens with or without chemoradiotherapy (CRT) have been proposed for BRPC patients.[8-10] A combination chemotherapy regimen of folinic acid (leucovorin), fluorouracil (5-FU), irinotecan, and oxaliplatin (FOLFIRINOX) seems to be the most effective regimen for patients with pancreatic cancer. In a randomized controlled trial (RCT), patients with metastatic pancreatic cancer had a superior OS with FOLFIRINOX compared to gemcitabine (median 11.1 vs. 6.8 months, $p<0.001$).[11] No RCT has been published with FOLFIRINOX in the neoadjuvant setting for BRPC patients. All published phase I - II trials and cohort studies on neoadjuvant FOLFIRINOX for BRPC patients are small and therefore report a wide range of median OS.[12-15]

The primary aim of this systematic review and patient-level meta-analysis was to determine OS after neoadjuvant FOLFIRINOX as first-line treatment for patients with BRPC. Secondary outcomes included progression-free survival (PFS), resection rate, R0 resection rate, and grade 3-4 adverse events (AEs).

METHODS

Eligibility

We searched for studies containing treatment-naïve patients with BRPC treated with FOLFIRINOX as neoadjuvant therapy, irrespective of further treatment after FOLFIRINOX. Case reports, reviews, letters to the editor, conference abstracts without full text, and studies only reporting on specific groups of patients (e.g., only patients in a specific age group) were excluded.

Search strategy

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standard guidelines.[16] In order to identify relevant studies, a comprehensive librarian-led search of Embase, MEDLINE (via OvidSP), Web of Science, Scopus, Cochrane Central, and Google Scholar was performed on September 1, 2017. Search terms included ''FOLFIRINOX", ''folinic acid", ''fluorouracil", ''irinotecan", ''oxaliplatin", ''pancreas cancer", ''drug combination", and relevant variants thereof. Only articles written in English were assessed. No restrictions on publication date were applied. Literature without formal publication was not assessed. A full description of the search is summarized in the supplementary files.

Outcome measures

The primary outcome was OS. Secondary outcomes were PFS, resection rates, R0 resection rates, and Common Terminology Criteria for Adverse Events grade 3-4.[17]

Selection procedure and data collection

After removal of duplicates, QJ and SB independently reviewed the abstracts for eligibility. The full-text article of any study that met the inclusion criteria was retrieved for further assessment. Full-text studies were excluded if only a regimen other than FOLFIRINOX was used, if the study did not include at least 1 BRPC patient, if the study was not an original report, or if the same patient cohort was presented in another study. Disagreements were resolved through discussion and consensus. QJ and SB extracted the data from selected studies with use of standardized data collection forms. Collected data included study characteristics (first author, year of publication, study design, inclusion period), study population specifications (total sample size, number of patients treated with FOLFIRINOX in total and per disease stage), details on type of intervention (FOLFIRINOX regimen, number of administered cycles, other treatments), and outcome measures (duration of follow-up, OS, PFS, (R0) resection rates, and grade 3 or 4 AEs).

For the patient-level meta-analysis, we contacted the authors of all studies to obtain (updated) patient-level data on OS and PFS. Data were collected for BRPC patients only. The authors of four studies[14, 18-20] provided patient-level data for additional BRPC patients not included in the reviewed articles. Data other than OS and PFS were not collected at patient-level, but reported as aggregate outcomes from the published studies.

Methodological assessment

All studies were assessed for risk of bias using an appraisal system developed by the Critical Appraisal Skill Program (CASP).[21] This critical appraisal tool is designed to systematically assess the methodology of individual studies. Publication bias was assessed with a funnel plot.[22]

Statistical analysis

Patient-level survival outcomes were analyzed with the Kaplan-Meier method using the *rms* and *survival* packages for R 3.5.0 (https://cran.r-project.org/). The Kaplan-Meier method was used to account for censoring of patients alive or without recurrence at last follow-up. The primary survival outcome was OS; the secondary outcome PFS. Median, 1-year, 3-year, and 5-year survival were analyzed and reported for OS; median, 1-year, 2-year, and 3-year for PFS. Patient-level survival outcomes were calculated from treatment initiation. One study only reported the date of surgery; therefore, 11 weeks were added to the date of surgery, to account for a median of 4 cycles of FOLFIRINOX (8 weeks) with an additional 3 weeks interval to surgery.[18] We performed post-hoc sensitivity analyses on patient-level survival data after exclusion of studies including only patients who underwent a resection after neoadjuvant therapy, comparing retrospective and prospective studies, comparing studies in which the number of FOLFIRINOX cycles was at least 6 or less than 6, comparing studies using full-dose or modified FOLFIRINOX regimens, comparing studies with or without granulocyte-colony stimulating factor (G-CSF) primary prophylaxis, analyzing the influence of (neo)adjuvant (chemo)radiation therapy ((C)RT) after neoadjuvant FOLFIRINOX on survival, and including only patients who were recurrence-free after 12 months. Survival distributions were compared using the logrank test.

Pooled proportions of resection and R0 resection were calculated. The I^2 statistic was estimated for both proportions to assess whether observed differences in proportions were compatible with chance alone or partly attributable to heterogeneity. The I^2 statistic estimates the percentage of variation across studies that can be ascribed to heterogeneity rather than chance.[23] An I^2 above 50% is considered substantial heterogeneity.[24] Random-effects models rather than fixed-effects models were used because heterogeneity in the definitions of disease stage across studies was anticipated to cause heterogeneity in the proportion of resection and R0 resection.[23] Studies only reporting data for BRPC patients who underwent a resection after neoadjuvant FOLFIRINOX were only included for the analysis of R0 resection rates, not for overall resection rates. Grade 3 or 4 AEs were calculated as number of events per 100 patients and pooled in random-effects models. AEs were pooled separately for prospective and retrospective studies. We performed a subgroup analysis comparing grade 3 or 4 event rates of neutropenia and febrile neutropenia in studies with or without G-CSF prophylaxis. Pooled analyses were performed using the *meta* package for R 3.5.0

RESULTS

Included studies

We identified 2659 potentially relevant studies. Based on the abstracts, 54 studies were selected for full-text assessment, of which 24 studies (representing 1802 patients) fulfilled

all inclusion criteria (Figure 1). Ten studies were excluded because only regimens other than FOLFIRINOX were used, 15 studies because no BRPC patients were included, two studies because the article was written in language other than English, one study was a protocol, and two studies overlapped with other included studies (Supplementary files).

Table 1 shows the study characteristics. Resectability status was defined by NCCN criteria[25] in eight studies, AHPBA/SSO/SSAT criteria[26] in seven studies, the ALLIANCE criteria[27] in two studies, and other criteria[28-31] in four studies. Three studies did not report staging criteria (Table 1). Most studies (*n*=20) presented intention-to-treat results of all BRPC patients who started with neoadjuvant FOLFIRINOX, regardless of subsequent resection. Four studies only included patients who underwent a resection after neoadjuvant treatment.[12, 15, 20, 32] Eight studies only included patients with BRPC, eleven studies

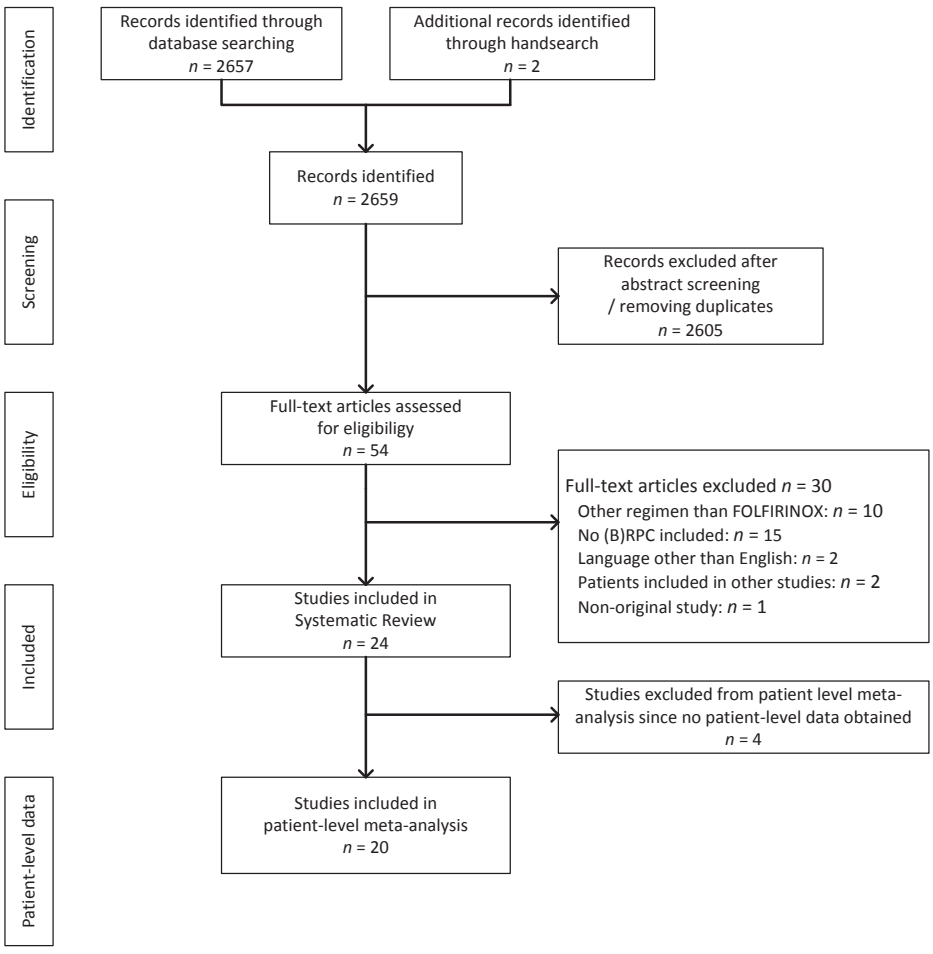


Figure 1. PRISMA flor chart showing selection of articles for systematic review and meta-analysis

Table 1. Study Characteristics

First Author	Year	Inclusion Period	Country	Resected only	Total	FOLFIRINOX	FOLFIRINOX			Definition Resectability	Study design	Multi vs. Single center
							M+	LAPC	BRPC			
Paniccia[37]	2014	2011-2013	US	No	31	18	0	0	18	NCCN	Retrospective	Single
Christians[31]	2014	2010-2012	US	No	18	18	0	0	18	MCW	Retrospective	Single
Katz[13]	2016	2013-2014	US	No	22	22	0	0	22	ALLIANCE	Phase I	Multi, *n*=14
Okada[39]	2016	2014-2015	Japan	No	10	10	0	0	10	NCCN	Phase I	Single
Shaib[36]	2016	NR	US	No	13	13	0	0	13	ALLIANCE	Phase I	Single
Yoo[38]	2017	2013-2014	Korea	No	18	18	0	0	18	NCCN	Retrospective	Single
Itchins[35]	2017	2010-2016	Australia	No	85	14	0	0	14	Australasian	Retrospective	Multi, *n*=2
Shrestha[18]	2017	2007-2012	US	No	93	13	0	0	13	AHPBA/SSO/SSAT	Retrospective	Single
Boone[43]	2013	2011-2012	US	No	21	21	0	10	11	AHPBA/SSO/SSAT	Retrospective	Single
Ferrone[15]	2015	2011-2014	US	Yes	188	40	0	25	15	AHPBA/SSO/SSAT	Retrospective	Single
Addeo[32]	2015	2007-2012	France	Yes	477	14	0	14*		MDACC	Prospective cohort	Single
Khushman[45]	2015	2008-2013	US	No	51	51	0	40	11	AHPBA/SSO/SSAT	Retrospective	Multi, *n*=2
Pietrasz[12]	2015	2010-2013	France	Yes	80	80	0	33	47†	NCCN	Prospective cohort	Multi, *n*=20
Mellon[14]	2015	2009-2014	US	No	159	23	0	21	2	NCCN	Retrospective	Single
Blazer[40]	2015	2011-2013	US	No	43	43	0	25	18	AHPBA/SSO/SSAT	Retrospective	Single
Badiyan[33]	2016	2009-2012	US	No	32	15	0	14*		AHPBA/SSO/SSAT	Retrospective	Single
Kim[20]	2016	2011-2015	US	Yes	26	26	0	7	18†	NCCN	Retrospective	Single
Vogel[34]	2017	2013-2015	Netherlands	No	93	61	0	61*		DPCG‡	Prospective cohort	Single
Grose[19]	2017	2012-2015	Scotland	No	85	65	0	30	35	NCCN	Retrospective	Single
Tinchon[44]	2013	2010-2012	Austria	No	12	12	2	0	10	AHPBA/SSO/SSAT	Phase I	Single
Peddi[46]	2012	2009-2012	US	No	61	61	38	19	4	NR	Retrospective	Multi, *n*=3
Mahaseth[41]	2013	2010-2012	US	No	60	60	36	20	4	NR	Retrospective	Single
Moorcraft[47]	2014	2010-2013	UK	No	49	49	27	13	9	NR	Retrospective	Single
Stein[42]	2016	2011-2014	US	No	75	75	44	20	11	NCCN	Phase II	Multi, *n*=5
Total: 24					**1802**	**822**	**147**	**263**	**322**			

* Locally advanced and borderline resectable pooled. † Including 4 (Pietrasz) and 5 (Kim) patients with upfront resectable pancreatic cancer. ‡ Dutch Pancreatic Cancer Group.

M+ Metastatic disease. LAPC Locally advanced pancreatic cancer. BRPC borderline resectable pancreatic cancer. NR not reported.

combined BRPC and LAPC patients, and five studies combined all disease stages. For 89 patients in three studies, no distinction could be made between BRPC or LAPC, therefore their results were only used for AEs and in patient-level analyses if BRPC was confirmed by the authors.[32-34]

FOLFIRINOX was given to 822 (46%) patients, of whom 313 (38%) patients were staged as BRPC. Only 9 patients (3%) from two studies had resectable pancreatic cancer.[12, 20] Patient-level data was obtained from 20 studies reflecting 283 BRPC patients, representing 90% of all published BRPC patients who received neoadjuvant FOLFIRINOX.

Methodological assessment

We included eight prospective and 16 retrospective studies. Six studies were multicenter studies (Table 1). Results of the methodological assessment of all included studies are reported in Supplementary Table S1. The funnel plot showed no evidence of publication bias among the included studies (Supplementary Figure S1).

Survival analysis

Seven studies [12, 13, 20, 35-38] representing 151 patients separately reported survival data for BRPC patients treated with neoadjuvant FOLFIRINOX. The median OS for BRPC patients varied across these seven studies from 11.0 to 34.2 months, and the median PFS varied from 5.7 to 21.3 months.

Patient-level data was obtained for 283 BRPC patients who received neoadjuvant FOLFIRINOX, of whom 168 (59.4%) died during follow-up. The median follow-up of patients alive at last follow-up was 22.9 months. The overall patient-level median OS was 22.2 months (95% confidence interval (CI): 18.8 – 25.6) (Figure 2a). The pooled OS at 1 year was 76.0%, at 3 years 36.2%, and at 5 years 21.2%. 115 out of 283 patients (40.6%) were censored. After excluding 21 patients from two studies[20, 32] that only included patients who underwent a resection, the patient-level median OS was similar (22.2 months, 95% CI: 18.8 – 25.7, $p = 0.79$). No statistically significant difference was observed when comparing OS of patients in prospective (21.7 months, 95% CI: 17.9 – 25.6) and retrospective studies (22.4 months, 95% CI: 17.7 – 27.2) (p = 0.36). For patients who were recurrence-free after 12 months, median OS was 43.2 months (95% CI: 37.0 – 49.4).

For studies in which patients received a median number of FOLFIRINOX cycles of 6 or higher, the median OS was 21.4 months (95% CI 16.7 – 26.0), compared to 21.7 months (95% CI 15.0 – 28.4) for patients in studies with a median of less than 6 cycles ($p = 0.46$). No statistically significant correlation was found between the reported median number of FOLFIRINOX cycles administered and the patient-level median OS (Supplementary Figure S2, $p = 0.051$). The median OS without upfront dose modification of FOLFIRINOX was 25.0 months (95% CI: 18.7 – 31.2), compared to 21.7 months (95% CI: 17.1 – 26.4) in studies with

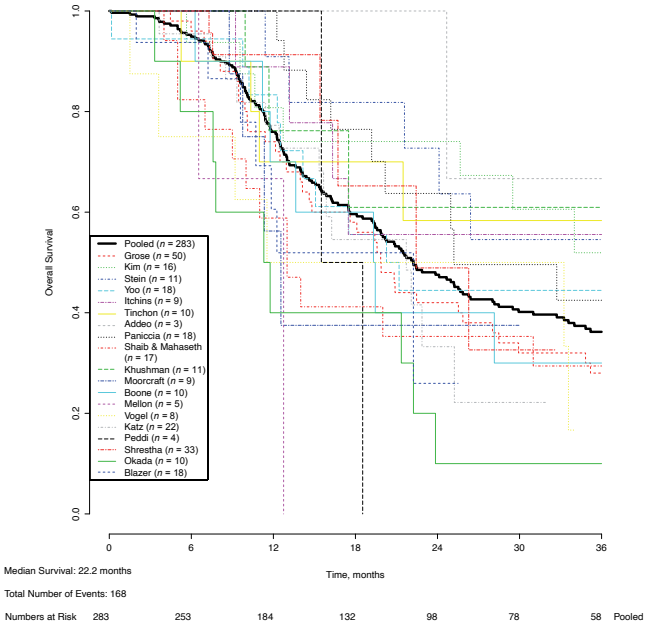


Figure 2a. Pooled and patient-level overall survival

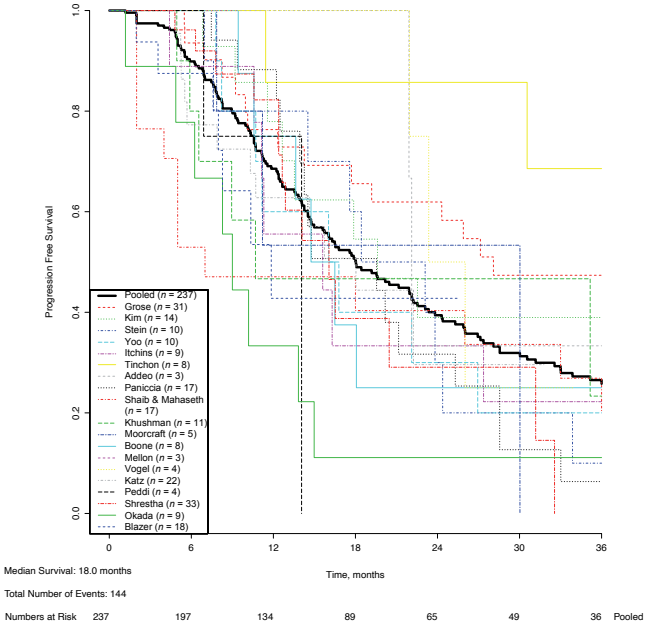


Figure 2b. Pooled and patient-level progression-free survival

any dose modification (p = 0.18). The median OS in studies with G-CSF prophylaxis was 20.8 (95% CI: 17.2 – 24.4), compared to a median OS of 18.5 months (95% CI: 13.2 – 23.8) in studies in which G-CSF was prescribed at discretion of the treating physician (p = 0.42).

Patient-level PFS was available for 237 BRPC patients (20 studies), of whom 144 patients (59.8%) showed progression or died during follow-up, with a median PFS of 18.0 months (95% CI: 14.5 – 21.5; Figure 2b). 93 out of 237 patients (39.2%) were censored. After excluding the two studies[20, 32] only reporting patients who underwent a resection (n=13), the median PFS was 18.0 months (95% CI: 14.6 – 21.4, p = 0.99). The PFS at 1 year was 68.5%, at 2 years 39.4% and at 3 years 25.8%. For prospective studies and retrospective studies, the median PFS was 18.4 months (95% CI: 12.1 – 24.8) and 17.7 months (95% CI: 14.4 – 21.0), respectively (p = 0.60).

Chemotherapy regimens

Details of the chemotherapy regimen used are shown in Table 2. Only 6 studies reported the number of planned neoadjuvant FOLFIRINOX cycles for BRPC patients only, ranging from 4 to 8 cycles. Eleven studies reported the median number of FOLFIRINOX cycles administered to BRPC patients only, ranging from 4 to 9 cycles. Of these studies, five studies reported a median number of FOLFIRINOX cycles administered of 6 or higher. Eight studies used a dose modification as compared to the FOLFIRINOX regimen described in the PRODIGE 4/ACCORD 11 trial[11]; five studies did not include a fluorouracil bolus injection,[13, 36, 39-41] four studies used a lower dose of irinotecan,[33, 39, 40, 42] three studies did not mention inclusion of leucovorin,[36, 39, 40] and one study gave fluorouracil continuous infusion with doses halved.[14] Seven studies did not specify the FOLFIRINOX regimen administered, yet mentioned either using modified FOLFIRINOX,[35] or FOLFOX / FOLFIRINOX,[18] or using FOLFIRINOX without mentioning upfront dose modifications.[15, 20, 32, 43, 44] Use of G-CSF was reported as primary prophylaxis in seven studies,[13, 19, 36, 40-42, 44] and was prescribed at discretion of the treating physician in five studies.[31, 39, 45-47]

Adverse Events

Adverse events during FOLFIRINOX were reported in 14 studies, of which nine studies reported only pooled outcomes across disease stages. In these 14 studies comprising 526 patients treated with FOLFIRINOX, 401 grade 3 or 4 AEs were reported (Table 3). No deaths were attributed to FOLFIRINOX. Neutropenia was the most commonly reported AE with a pooled event rate of 17.5 per 100 patients (95% CI: 10.3 – 28.3, I^2 = 76%). The pooled event rates per 100 patients for other common AEs were 14.5 (95% CI: 7.7 – 28.8, I^2 = 0%) for leukopenia, 10.8 (95% CI 8.1 – 14.2, I^2 = 0%) for fatigue, 11.1 (95% CI: 8.6 – 14.3, I^2 = 0%) for diarrhea, 10.4 (95% CI: 5.5 – 18.9, I^2 = 71%.) for nausea or vomiting, 8.5 (95% CI: 5.2 – 13.7, I^2 = 0%) for thromboembolism, and 8.9 (95% CI: 6.2 – 12.5, I^2 = 4%) for thrombocytopenia. The pooled event rate for neutropenia was lower in 6 studies that administered G-CSF as primary prophylaxis compared to 5 studies with prescription of G-CSF at discretion of the

Table 2. Treatment strategies for borderline resectable pancreatic cancer patients

	Chemotherapy regimen used	Neoadjuvant FOLFIRINOX			Neoadjuvant (chemo)radiation			Number of BRPC patients	Resection rates		
		Planned	Administered		Chemoradiotherapy	SBRT	IORT		Resected	R0 resection	Definition
		N	Median N	Range	N (%)	N (%)	N (%)		N (%)	N (%)	R0 resection
Paniccia[37]	FOLFIRINOX	4	4	3-5	8 (44)	0	0	18	17 (94)	17 (100)	>1mm
Christians[31]	FOLFIRINOX	4	4	3-8	18 (100)	0	0	18	12 (67)	12 (100)	UNK
Katz[13]	mFOLFIRINOX	4	4	NR	21 (95)	0	0	22	15 (68)	14 (93)	>0mm
Okada[39]	FIRINOX	4 / 8	6	4-8	0	0	0	10	7 (70)	5 (71)	>0mm
Shaib[36]	mFOLFIRINOX	4	4	4	0	12 (92)	0	13	8 (62)	8 (100)	UNK
Yoo[38]	FOLFIRINOX	NR	6	3-13	6 (34)	2 (11)	0	18	12 (67)	9 (75)	UNK
Itchins[35]	mFOLFIRINOX	NR	NR	NR	0	0	0	-	NR	NR	NR
Shrestha[18]	FOLFOX/ FOLFIRINOX	NR	NR	NR	NR	0	0	-	NR	NR	NR
Boone[43]	FOLFIRINOX	NR	NR	NR	0	4 (36)	0	11	7 (64)	6 (86)	>1mm
Ferrone[15]	FOLFIRINOX	NR	NR	NR	24 (51)*†	0	12 (30)*†	40*†	40 (100)*	35 (88)*	>0mm
Addeo[32]	FOLFIRINOX	NR	7	3-11	0	0	0	14*†	14 (100)*	34 (76)*	>0mm
Khushman[45]	FOLFIRINOX	NR	NR	NR	26 (51)*	0	0	11	10 (91)	7 (70)	>1mm
Pietrasz[12]	FOLFIRINOX	NR	5	3-7	30 (64)	0	0	47†	47 (100)	39 (83)	>0mm
Mellon[14]	mFOLFIRINOX	NR	NR	NR	0	2 (100)	0	-	NR	NR	>0mm
Blazer[40]	mFOLFIRINOX	NR	4.4	1-8	8 (44)	0	0	18	11 (61)	9 (82)	>1mm
Badiyan[33]	mFOLFIRINOX	NR	NR	NR	14 (100)*	0	0	-	NR	NR	NR
Kim[20]	FOLFIRINOX	NR	9	4-12	4 (15)*	0	2 (8)*	26*†	26 (100)*	24 (92)*	>1mm
Vogel[34]	FOLFIRINOX	NR	NR	NR	0	0	0	61*	12 (20)*	7 (58)*	>1mm
Grose[19]	FOLFIRINOX	6	6	NR	20 (47)	0	0	-	NR	NR	NR
Tinchon[44]	FOLFIRINOX	NR	NR	NR	0	0	0	10	8 (80)	NR	NR
Peddi[46]	FOLFIRINOX	NR	NR	NR	0	0	0	4	4 (100)	NR	NR
Mahaseth[41]	mFOLFIRINOX	NR	NR	2-6	4 (100)	0	0	4	2 (50)	2 (100)	UNK
Moorcraft[47]	FOLFIRINOX	NR	NR	NR	14 (29)*	0	0	9	5 (56)	4 (57)*	UNK
Stein[42]	mFOLFIRINOX	NR	NR	NR	11 (35)*	0	0	11	7 (64)	7 (100)	UNK
Total: 24								238	67.8 (60.1-74.6)	83.9 (76.8 - 89.1)	

* Locally advanced and borderline resectable pooled. † Resected patients only. SBRT = Stereotactic body radiation therapy. IORT = Intra-operative radiation therapy. NR = Not reported for BRPC specifically.

Table 3. Adverse Events Grade 3-4 following neoadjuvant FOLFIRINOX

	Paniccia	Christians	Katz	Okada	Yoo	Boone	Khushman	Blazer	Grose	Tinchon	Peddi	Mahaseth	Moorcraft	Stein	Total (events per 100 patients)
Number of patients	18	18	22	10	18	25*	51*	43*	65*	12‡	61†	60†	49†	74†	**526**
Neutropenia	1	2	3	4	15	3	10	0	..	..	12	2	14	9	**73 (18)**
Leukopenia	..	..	..	2	4	2	..	..	..	..	..	..	..	..	**8 (17)**
Diarrhea	3	2	3	0	1	1	5	6	6	1	2	8	2	12	**52 (11)**
Fatigue	2	..	..	1	1	..	3	4	5	..	3	8	9	9	**45 (11)**
Nausea / vomiting	2	5	..	2	8	..	4	2	3	..	..	5	3	2	**36 (10)**
Thrombocytopenia	2	..	..	1	0	2	8	0	..	..	2	3	5	7	**30 (9)**
Thromboembolism	1	..	3	..	..	1	..	..	..	1	..	..	6	3	**15 (9)**
Weight loss	..	3	..	..	..	1	..	..	0	..	..	..	..	..	**11 (5)**
Febrile neutropenia	1	..	..	0	1	..	6	0	2	..	3	..	7	3	**23 (7)**
Anaemia	1	..	..	0	0	..	5	..	..	..	..	..	2	4	**12 (6)**
Abdominal pain	..	1	..	..	0	..	..	..	..	..	5	..	..	..	**6 (7)**
Elevated AST/ALT	..	..	..	3	0	..	..	..	..	..	..	..	..	3	**6 (8)**
Hypoalbuminaemia	..	..	..	..	..	1	..	..	4	..	..	..	..	..	**5 (6)**
Neuropathy	4	..	..	0	0	1	2	0	..	..	..	3	2	2	**14 (5)**
Infection	..	..	..	..	..	..	..	..	2	..	..	3	..	..	**5 (4)**
Anorexia	3	1	..	1	0	..	0	..	..	..	..	..	..	..	**5 (7)**
Mucositis	1	..	..	0	..	..	0	..	..	..	..	1	2	..	**4 (3)**

* Locally advanced and borderline resectable pooled. † Metastatic, locally advanced and borderline resectable pooled. ‡ Metastatic and borderline resectable pooled.
.. Not Reported.

physician (8 per 100 patients vs. 23 per 100 patients, p = 0.01, Forest plot in Supplementary Figure S4). The results were similar for *febrile* neutropenia (3 per 100 patients vs. 10 per 100 patients, p = 0.02, Forest plot in Supplementary Figure S5).

Additional treatment modalities

Several studies reported the use of CRT (n=8), stereotactic body radiation therapy (SBRT, n=4), or intra-operative radiation therapy (IORT, n=4) besides FOLFIRINOX for at least one BRPC patient (Table 2). Neoadjuvant CRT was given as standard additional treatment for BRPC patients in three studies, [13, 31, 41] and reported as possible additional treatment in five other studies.[12, 20, 37, 38, 40] No correlation was found between the percentage of (neo)adjuvant (C)RT and patient-level median OS (Supplementary Figure S3, p = 0.14). Two studies were not included in this analysis as these studies only included patients who underwent a resection.[12, 20]

Resection and R0 resection rates

Fourteen studies reported resection rates for BRPC patients treated with neoadjuvant FOLFIRINOX (Table 2). The pooled proportion of patients who underwent resection was 67.8% (95% CI: 60.1 – 74.6, I^2 = 0%). Resection margins were reported in 13 studies (Table 2). The pooled proportion of patients who underwent R0 resection in a random-effects model was 83.9% (95% CI: 76.8 – 89.1, I^2 = 0%).

DISCUSSION

This patient-level meta-analysis of 20 studies representing 283 patients who received neoadjuvant FOLFIRINOX for BRPC showed a median OS of 22.2 months (95% CI: 18.8 – 25.6). After neoadjuvant FOLFIRINOX, 67.8% (95% CI: 60.1 – 74.6) of patients underwent a curative-intent resection with an R0 resection rate of 83.9% (95% CI: 76.8 – 89.1). The rate of grade 3 or 4 AEs was high, but no death was attributed to FOLFIRINOX.

FOLFIRINOX has been studied for patients with advanced pancreatic cancer since 2005.[48] For metastatic pancreatic cancer, palliative FOLFIRINOX has been the standard of care for patients with a good performance status since an RCT found a median OS of 11 months versus 7 months with gemcitabine.[11] In patients with locally advanced pancreatic cancer (LAPC), no RCT has been published for induction chemotherapy with FOLFIRINOX. The best available evidence of FOLFIRINOX for LAPC is a systematic review and patient-level meta-analysis of 315 patients (11 studies) that found a median OS of 24.2 months (95% CI: 21.7 – 26.8).[49] Figure 3 compares the patient-level OS of patients who received FOLFIRINOX in the setting of BRPC (present study) and LAPC.[49] OS for both groups is clearly superior to OS for patients treated with FOLFIRINOX for metastatic pancreas cancer in the RCT of Conroy et al.[11] It is remarkable that the median OS of 22.2 months for BRPC patients in

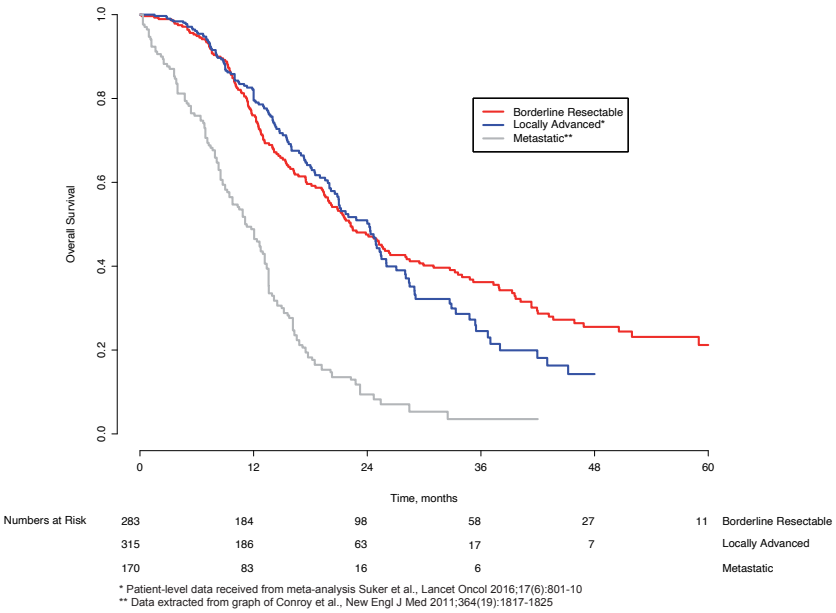


Figure 3. Pooled overall survival for BRPC, LAPC, and metastatic pancreatic cancer
Abbreviations: BRPC = borderline resectable pancreatic cancer, LAPC = locally advanced pancreatic cancer

this study is similar to the 24.2 months in the LAPC setting. The survival curves of LAPC and BRPC overlap for the initial two years, after which they diverge. OS after three years was 36.2% for BRPC versus 23.0% for LAPC patients. The difference in local extent of the disease between BRPC and LAPC appears to be irrelevant for about half of the patients who die within 2 years. The difference in OS after 2 years probably reflects both less advanced disease and a higher resection rate for BRPC (68% versus 27% in the LAPC setting).[49]

The use of radiation therapy after neoadjuvant FOLFIRINOX varied across studies. At the study-level, no association was found between the percentage of patients who received neoadjuvant (chemo)radiation and median OS (Supplementary Figure 3). Versteijne et al. performed a meta-analysis of intention-to-treat outcomes of any neoadjuvant approach versus upfront resection for (borderline) resectable pancreatic cancer ((B)RPC). In a subgroup analysis comparing neoadjuvant approaches with and without radiation therapy, they also found no difference in OS.[50] The interim analysis of the Dutch PREOPANC-1 trial, as presented at the ASCO annual meeting in 2018, showed a twofold increase in R0-resection rate, with 31% after upfront resection versus 65% after neoadjuvant CRT ($p<0.001$).[51] Although the impact of RT on local control is convincing, it remains uncertain whether this translates into superior OS.

Many studies have found favorable OS for patients who undergo a resection of BRPC after neoadjuvant chemo(radio)therapy.[52] However, some studies overestimated OS with neoadjuvant treatment, because OS was only reported for patients who underwent a curative-intent resection after neoadjuvant treatment, whilst patients who had progressive disease prior to resection were excluded. A recent meta-analysis resolved this selection bias by including only studies that adhered to the intention-to-treat principle: all patients who started neoadjuvant treatment were included in the analyses, regardless of whether they underwent a resection.[50] Only 3% of these patients received neoadjuvant FOLFIRINOX. The authors found a superior median OS for any neoadjuvant approach (18.8 months) compared to upfront surgery (14.8 months) in (B)RPC patients. In 2018, the first two RCTs for neoadjuvant treatment of (B)RPC completed accrual.[51, 53] A Korean trial was closed prematurely, when interim analysis found a superior median OS of 21 months for neoadjuvant CRT versus 12 months with upfront surgery and adjuvant CRT (p = 0.028).[53] The previously mentioned interim analysis of the PREOPANC-1 trial found a median OS of 17.1 months with neoadjuvant gemcitabine-based CRT versus 13.7 months with upfront surgery and adjuvant gemcitabine (p = 0.074).[51] However, neither RCTs investigated neoadjuvant FOLFIRINOX.

Because FOLFIRINOX is a more effective regimen than gemcitabine alone in the metastatic setting, it is expected that it further improves OS for patients with (B)RPC in the neoadjuvant setting. Four RCTs evaluating neoadjuvant FOLFIRINOX are currently accruing patients: the phase II ALLIANCE A021501 trial (NCT02839343) initially compared neoadjuvant mFOLFIRINOX with or without hypofractioned radiation therapy for BRPC, but recently closed the radiation therapy arm as it met the predetermined futility boundary for R0 resection;[54] the phase III NorPACT-1 trial (NCT02919787) for resectable pancreatic cancer comparing neoadjuvant FOLFIRINOX to upfront surgery, both followed by adjuvant gemcitabine and capecitabine;[55] the phase II PANACHE01-PRODIGE48 trial (NCT02959879) for resectable pancreatic cancer comparing neoadjuvant FOLFIRINOX to neoadjuvant FOLFOX chemotherapy and upfront surgery, all followed by adjuvant chemotherapy;[56] and the phase III PREOPANC-2 trial (NTR7292) comparing neoadjuvant FOLFIRINOX to neoadjuvant gemcitabine-based chemoradiotherapy for (B)RPC.[57] Final results of these trials are not anticipated within the next five years.

Median OS estimates after neoadjuvant treatment for BRPC may appear inferior to outcomes with adjuvant chemotherapy. For example, the ESPAC-4 trial reported a median OS of 28.0 months in the adjuvant gemcitabine-capecitabine arm.[58] Moreover, the recent PRODIGE 24/CCTG PA.6 trial reported a median OS of 54.4 months in the adjuvant FOLFIRINOX arm.[59] However, the patient populations of a neoadjuvant and an adjuvant trial are highly different and cannot be compared directly. To be eligible for an adjuvant trial, a patient has to overcome several hurdles. A small percentage of patients will never make it to the operating room, often because of a combination of drainage-related complications

(e.g., cholangitis or pancreatitis) and frailty. Moreover, about 20% of radiographically BRPC patients will never undergo resection because of occult metastatic disease at staging laparoscopy, or unexpected LAPC during surgical exploration.[60, 61] And finally, most adjuvant trials require a complete macroscopic resection, a CA 19-9 level below 180 U/ml, and full recovery from surgery within 12 weeks after resection. In large nation-wide studies, only about 55% of patients received adjuvant chemotherapy.[4-6] Neoadjuvant trials include all those patients that drop out during treatment; only about a third of these patients would be eligible for adjuvant trials after undergoing a resection and remaining fit for adjuvant chemotherapy. Excluding the worst two-thirds of patients will obviously have a major impact on the median OS.

After neoadjuvant FOLFIRINOX, resection rates ranged between 50 and 100% across studies. This substantial heterogeneity may be explained by the lack of consensus regarding resectability criteria and criteria to proceed with surgery after neoadjuvant treatment. Reaching consensus on resectability criteria is needed to improve comparison in future studies. In the pooled analysis of the present study, we found a resection rate of 68%. A similar resection rate of 66% was found in an intention-to-treat meta-analysis of (B)RPC patients treated with any neoadjuvant CRT regime.[50] The pooled R0 resection rate of 84% in the present study was higher compared to the intention-to-treat R0 resection rate of 67% with upfront surgery.[50]

Some limitations of the present study should be considered. While the present study represents the best available estimate of survival after neoadjuvant FOLFIRINOX for BRPC patients, it might be an overestimate because of the retrospective nature of most included studies. Similarly, secondary study endpoints such as AEs and PFS were prone to selection and information bias. Heterogeneity across studies also might have biased the results; studies used different resectability criteria, FOLFIRINOX regimens, and additional treatment (e.g., CRT).

In conclusion, neoadjuvant FOLFIRINOX for BRPC has a favorable median OS of 22.2 months in a patient-level meta-analysis of 283 patients.

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SUPPLEMENTARY FILES

Supplementary Methods

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 (Ovid)

((Leucovorin/ AND fluorouracil/ AND irinotecan.mp. AND oxaliplatin.mp. AND Drug Combinations/ AND (exp Pancreatic 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

Web-of-science

TS=(Folfirinox)

Scopus

TITLE-ABS-KEY(Folfirinox)

Google scholar

Folfirinox

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Only other regimen than FOLFIRINOX, n=10

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Non-original studie, n=1

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Patients included in other studies, n=2

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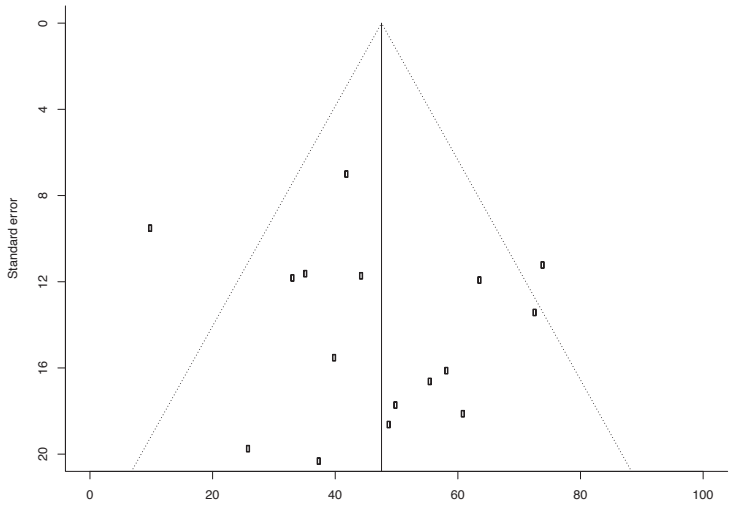
Supplementary Table 1. Methodological quality assessment according to Critical Appraisal Skill Program (CASP)

Study [reference]	Clear aim	Re cruit ment	Accurately measured exposure	Accurately measured outcome	Confounding factors identified	Confounding factors accounted	Follow-up complete enough	Follow-up long enough	Precise statistical results presented	Do you believe results	Ability to generalize results	In accordance with existing evidence	Implications of study in practice
Paniccia et al. 2014[1]	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	Yes	No
Christians et al. 2014[2]	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	Yes	No
Katz et al. 2016[3]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Okada et al. 2016[4]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Shaib et al. 2016[5]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yoo et al. 2017[6]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Itchins et al. 2017[7]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No
Shrestha et al. 2017[8]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Boone et al. 2013[9]	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No
Ferrone et al. 2015[10]	Yes	Yes	Yes	No	No	No	Yes	No	Yes	No	No	No	No
Addeo et al. 2015[11]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes
Khushman et al. 2015[12]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No	No
Pietrasz et al. 2015[13]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes
Mellon et al. 2015[14]	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No	Yes	No
Blazer et al. 2015[15]	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No
Badiyan et al. 2016[16]	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	No	Yes	No
Kim et al. 2016[17]	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	No	No	No	No
Vogel et al. 2017[18]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes	No
Grose et al. 2017[19]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Tinchon et al. 2013[20]	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	Yes	No
Peddi et al. 2012[21]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	Yes	No
Mahaseth et al. 2013[22]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	Yes	No
Moorcraft et al. 2014[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Stein et al. 2016[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes

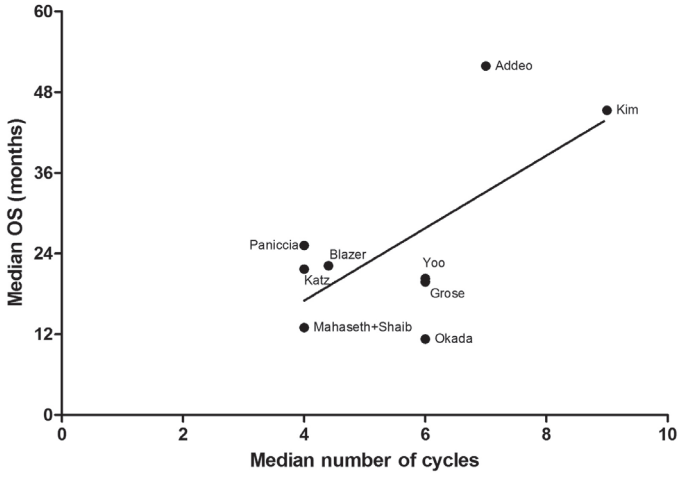
Supplementary Table 2. Survival outcomes reported for BRPC patients treated with neoadjuvant FOLFIRINOX

Study [reference]*	Number of patients	Median follow-up* (months; IQR)	Median OS (months; 95% CI)	Median PFS (months; 95% CI)
Paniccia et al. 2014 [1]	18	14.5 (10-17)	25.0	14.0
Katz et al. 2016 [3]	22	NR	21.7 (16-nr)	NR
Shaib et al. 2016 [5]	13	18.0	11.0 (6-nr)	5.7 (3-33)
Yoo et al. 2017 [6]	18	24.1 (14-32)	21.2 (14-28)	16.8 (9-24)
Itchins et al. 2017 [7]	14	34.8	25.9 (12-nr)	NR
Pietrasz et al. 2015 [13]	47	38.2 (29-47)†	nr	16.5†
Kim et al. 2016 [17]	19	41.4†	34.2†	21.3†

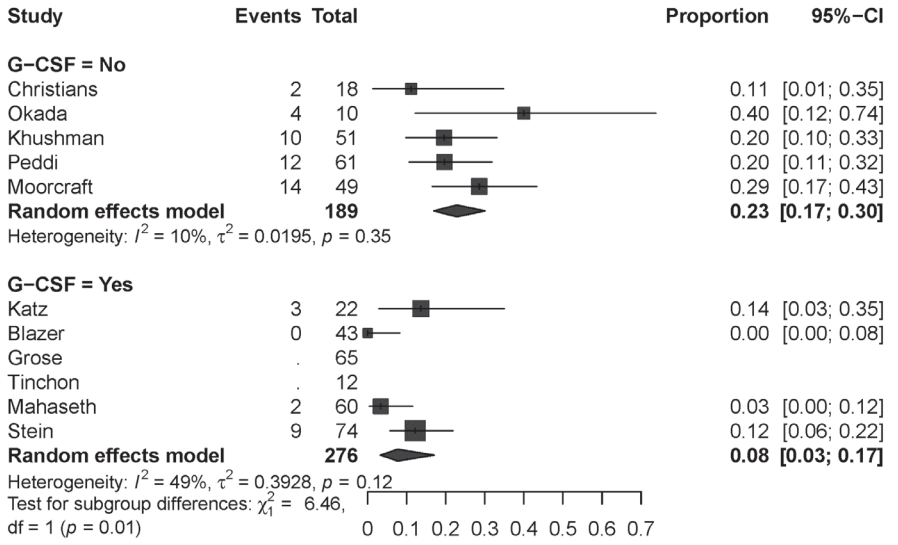
* Studies not shown in this table did not report survival outcomes for BRPC patients specifically, or did not report survival at all.
IQR = interquartile range. CI = confidence interval. OS = overall survival. PFS = progression-free survival. NR = Not Reported. nr = not reached.
† = resected patients only.



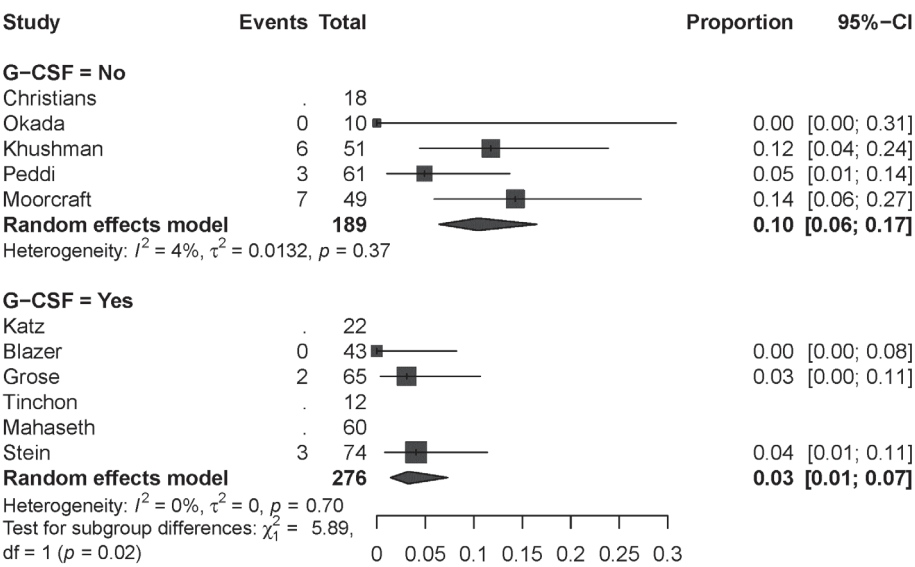
Supplementary Figure 1. Funnel plot of the 2-year OS of studies
Kaplan-Meier analysis of patient-level OS was used for estimation of median study OS, including only patients with BRPC. Three studies are not shown in this funnel plot as Peddi et al.[21] and Mellon et al.[14] included no patients surviving at least 2 years, and Addeo et al.[11] did not have a sufficient number of events to calculate the standard error. OS = overall survival. BRPC = borderline resectable pancreatic cancer.



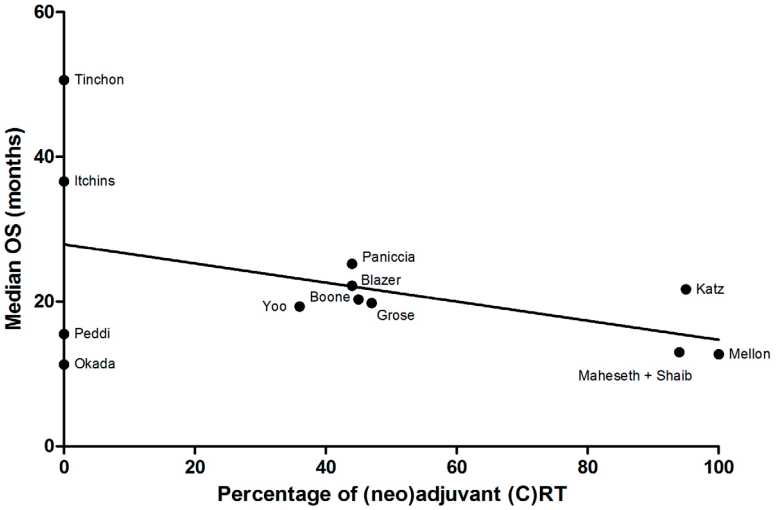
Supplementary Figure 2. Median number of administered neoadjuvant FOLFIRINOX cycles and median OS of studies
Kaplan-Meier analysis of patient-level OS was used for estimation of median study OS, including only patients with BRPC. (p = 0.05).
Linear regression analysis was performed. P-value was calculated using a two-sided F test.
OS = overall survival. BRPC = borderline resectable pancreatic cancer.



Supplementary Figure 3. Forest plots showing reported grade 3 or 4 adverse event rates in studies with and without G-CSF prophylaxis: neutropenia (p = 0.01)
p-value was calculated using a two-sided Q-test and a random effects model. G-CSF = granulocyte-colony stimulating factor. CI = confidence interval.



Supplementary Figure 4. Forest plots showing reported of grade 3 or 4 adverse event rates in studies with and without G-CSF prophylaxis: febrile neutropenia. (p = 0.02)
p-value was calculated using a two-sided Q-test and a random effects model. G-CSF = granulocyte-colony stimulating factor. CI = confidence interval.



Supplementary Figure 5. (Neo)adjuvant (C)RT after neoadjuvant FOLFIRINOX and median OS of studies

Kaplan-Meier analysis of patient-level OS was used for estimation of median study OS, including only BRPC patients. Two studies are not shown in this figure as Addeo et al.[11] and Kim et al.[17] only included patients who underwent a resection. (p = 0.14). Linear regression analysis was performed. P-value was calculated using a two-sided F test. OS = overall survival. BRPC = borderline resectable pancreatic cancer.

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CHAPTER 8

FOLFIRINOX as Initial Treatment for Localized Pancreatic Adenocarcinoma: A Retrospective Analysis by the Trans-Atlantic Pancreatic Surgery (TAPS) Consortium

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ABSTRACT

Background

Large pragmatic studies of patients who received (m)FOLFIRINOX as initial treatment for localized pancreatic ductal adenocarcinoma (PDAC) are lacking. This study aimed to provide realistic estimates of oncologic outcomes in these patients.

Methods

This international retrospective cohort study included all consecutive patients presenting with localized PDAC who received at least one cycle of (m)FOLFIRINOX as initial treatment in five referral centers from the United States and the Netherlands (2012-2019). Primary outcome was median overall survival (OS), calculated from the date of tissue diagnosis, assessed using Kaplan-Meier estimates. Log-rank test was used to compare OS between groups. A Cox proportional hazards regression model was used to assess prognostic baseline factors for OS. All statistical tests were 2-sided.

Results

Overall, 1,835 patients were included, of whom 958 (52.2%) had locally advanced (LA), 531 (28.9%) had borderline resectable (BR), and 346 (18.9%) had potentially resectable (PR) PDAC. The median number of (m)FOLFIRINOX cycles was 6 (interquartile range = 4-8). Subsequent treatment included second chemotherapy (12.9%), radiotherapy (49.0%), and resection (37.9%). Resection rate was 17.6% for LA, 53.1% for BR, and 70.5% for PR PDAC ($p<0.001$). Margin-negative resection rate (>1mm) was 55.2% for LA, 62.6% for BR, and 79.2% for PR PDAC ($p<0.001$). Median OS was 18.7 months (95% confidence interval [CI] = 17.7-19.9) for LA, 23.2 months (95% CI = 21.0-25.7) for BR, and 31.2 months (95% CI = 26.2-36.6) for PR PDAC ($p<0.001$). Median OS for 695 patients who underwent a resection was 38.3 months (95% CI = 36.1-42.0). Independent prognostic factors at baseline for worse OS were more advanced stage, worse performance status, baseline CA 19-9 >500 U/mL, and BMI ≤18.5 kg/m^2.

Conclusion

This large international cohort study provides realistic estimates of resection rates and survival in patients with LA, BR, and PR PDAC who started (m)FOLFIRINOX treatment in PDAC referral centers.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal solid cancers. Even after curative-intent resection, the 10-year overall survival (OS) is only approximately 4% due to high rates of disease recurrence.[1] PDAC could be considered a systemic disease, even without evidence of distant metastases on initial imaging. Therefore, it has been suggested that systemic therapy should be the initial treatment modality for all patients diagnosed with PDAC, followed by surgery in selected patients.[2]

The multi-drug combination regimen of 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin ([m]FOLFIRINOX) has been shown to be superior to gemcitabine in two randomized controlled trials (RCTs) in the metastatic and adjuvant settings.[3, 4] Extrapolating these data, guidelines recommend (m)FOLFIRINOX as the preferred initial treatment for patients with locally advanced (LA) or borderline resectable (BR) PDAC with a good performance status. For patients with potentially resectable (PR) PDAC, adjuvant mFOLFIRINOX is recommended and neoadjuvant (m)FOLFIRINOX can be considered, especially in patients with poor prognostic features.[5] In the absence of RCTs, two patient-level meta-analyses of nonrandomized studies demonstrated favorable outcomes for patients with LA and BR PDAC treated with (m)FOLFIRINOX.[6, 7] Moreover, several cohort studies reported favorable survival in the subgroup of patients who underwent a resection after preoperative (m)FOLFIRINOX.[8, 9] However, that subgroup represents only a minority of all non-selected patients. International series including all patients who started (m)FOLFIRINOX regardless of subsequent treatment (i.e., 'denominator' data) are lacking.

Within this context, the Trans-Atlantic Pancreatic Surgery (TAPS) Consortium was assembled to investigate the treatment course and oncologic outcome after (m)FOLFIRINOX as initial treatment for localized PDAC. The TAPS consortium combined all consecutive patients to fill the gap in knowledge on real-world outcomes beyond RCTs with restrictive inclusion criteria and small retrospective series with inherent selection bias. The aim of this study was to provide realistic estimates of resection rates and OS after initial (m)FOLFIRINOX for localized PDAC to better inform clinicians and patients.

METHODS

Consortium creation and study design

This was an international retrospective cohort study, which was the first study from the TAPS Consortium including five high-volume pancreatic cancer referral centers from the United States (Memorial Sloan Kettering Cancer Center, New York City, NY; University of Pittsburgh Medical Center, Pittsburgh, PA; University of Texas MD Anderson Cancer Center, Houston, TX) and the Netherlands (Erasmus MC University Medical Center and Amsterdam UMC,

location Academic Medical Center). The rationale behind this consortium was to create a large uniform database including patients from referral centers with comparable high-quality care and only minor differences in patient characteristics and treatment approaches. Consequently, a number of research questions regarding the treatment and outcomes of patients with localized PDAC can be addressed with generalizable results for other referral centers and benchmarks for community practices. While diverse in geographic location, all TAPS centers share common features. These include high referral volumes for patients in need of both surgical and non-surgical therapies, specialty-trained pancreatic surgeons, medical and radiation oncologists with experience in collaborative research studies, institutions recognized as comprehensive multi-modality cancer care centers, and prospective databases run by surgeons monitoring data fidelity. The name and purpose of the TAPS Consortium were finalized at the 2020 Americas Hepato-Pancreato-Biliary Association (AHPBA) meeting by principal investigators from all TAPS centers. All participating centers hence obtained ethical approval from local Institutional Review Boards as well as legal approval of data sharing agreements for de-identified data to be uploaded and analyzed in a cloud-based digital research environment (Microsoft Azure DRE, Nijmegen, the Netherlands). The requirement to obtain informed consent was waived because of the retrospective nature of the study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[10]

Patients

All consecutive patients diagnosed with localized biopsy-confirmed PDAC between January 1, 2012 and December 31, 2019, who received at least one cycle of (m)FOLFIRINOX as initial treatment were included. Inherently, patients not eligible for (m)FOLFIRINOX were not included, although no direct selection was made on performance score or age. Patients who started with a modified regimen were included if the primary intention was to give the complete four-drug regimen of (m)FOLFIRINOX and they received at least one cycle of this complete regimen for localized PDAC. For patients who received part of their treatment outside the five TAPS centers, at least one follow-up visit and consultation before initiating (m)FOLFIRINOX were required. Patients with all subtypes of PDAC, including PDAC arising from precursor lesions, were included.

Primary and secondary outcomes

The primary outcome was OS from the date of tissue diagnosis. Secondary outcomes included resection rate and postoperative outcomes such as margin-negative (R0) resection rate, pathological TNM staging, lymphovascular invasion, perineural invasion, and histologic differentiation grade. Furthermore, details and sequence of treatment after (m)FOLFIRINOX were evaluated, including surgery, second chemotherapy, radiotherapy, adjuvant therapy, and cancer-directed palliative therapy.

Data collection and definitions

Predefined data on baseline, radiologic, treatment, and pathological characteristics, in addition to survival data were collected locally. Demographics on sex were based on self-report. No data on race and ethnicity were collected. The stage at diagnosis (i.e., PR, BR, or LA PDAC) was based on radiographic imaging before initiating (m)FOLFIRINOX, as assessed by the local multidisciplinary team. The MDACC Clinical Classification System was used by the MD Anderson Cancer Center[11]. The other four centers used the National Comprehensive Cancer Network (NCCN) criteria applicable at the time of diagnosis. The main difference is that PR PDAC requires venous contact <180° without contour irregularity for NCCN criteria, while the MDACC system allows for any degree of venous contact in the absence of occlusion. Tumor marker levels (i.e., carbohydrate antigen [CA] 19-9 and carcinoembryonic antigen [CEA]) closest to the start of FOLFIRINOX were included, preferably measured at the time of normalized bilirubin levels (i.e., <1.2 m/dL). If no measurement was conducted simultaneously with normalized bilirubin levels, the value at the time of the lowest bilirubin level within 4 weeks before initiating (m)FOLFIRINOX was used.

Full-dose FOLFIRINOX consisted of oxaliplatin (85mg/m^2), leucovorin (400mg/m^2), irinotecan (180mg/m^2), and fluorouracil (2400mg/m^2) with/without bolus (400mg/m^2) over 46-hours every two weeks. Dosage modifications were allowed. The number of (m)FOLFIRINOX cycles was defined as all continuous cycles with or without modifications until metastatic disease, change in chemotherapy regimen, or change of treatment modality. Second chemotherapy was defined as any change in the chemotherapy regimen because of toxicity or local progression before radiotherapy or surgery.

R0 resection was defined as the absence of tumor within 1 mm of any resection or dissection margin, including the pancreatic neck, common bile duct, superior mesenteric artery and vein, enteric margins, and the posterior and anterior surfaces.[12] All centers used the axial slicing or bivalve dissection technique for pancreatoduodenectomy specimens.[13, 14] Pathological TNM staging was converted to the 8th edition of the American Joint Committee on Cancer Staging (AJCC) Manual based on pathological tumor size, the number of positive lymph nodes, and arterial involvement.[15] Histologic differentiation grade was categorized into three levels (grade 1, well differentiation; grade 2, moderate differentiation; and grade 3, poor differentiation). Adjuvant therapy was defined as at least one cycle of postoperative chemotherapy. Palliative therapy included any cancer-directed therapy (e.g., chemotherapy, immunotherapy, or radiotherapy for local recurrent disease) for metastatic or recurrent disease after start of neoadjuvant or induction treatment. OS was defined as the time between the date of tissue diagnosis and the date of death. To enable comparison with resection cohort studies, a secondary analysis was performed for the subgroup who underwent resection with OS calculated from the date of surgery. The date of final follow-up was December 31, 2020. Patients still alive were censored at their last follow-up date.

Statistical analysis

Outcomes were presented for the complete cohort and by stage at diagnosis. Baseline characteristics were presented as medians with interquartile ranges (IQRs) for continuous variables and frequencies with proportions for categorical variables. Differences between groups were calculated using the chi-square test for categorical variables and Mann-Whitney U test for continuous variables. OS was assessed using Kaplan-Meier estimates and presented as median with corresponding 95% confidence interval (CI). Difference in survival outcomes between groups was tested using the log-rank test. The median follow-up time of patients alive at last follow-up was calculated using the reverse Kaplan-Meier method. A Cox proportional hazards regression model was used to assess the potential prognostic baseline factors for OS. Known prognostic factors and factors with a p-value <0.20 in univariable analysis were included in the multivariable model.[16] The proportional hazards assumption was assessed by visualization of the Schoenfeld residuals and the log(-log(survival)) versus log of survival time plot. The proportional hazards assumption was not violated for any of the factors. Multiple imputation was used to account for missing data in multivariable analysis, including WHO (n=7), BMI (n=23), tumor size (n=61), and CA 19-9 (n=102). All tests were two-sided and p-values <0.05 were considered statistically significant. All analyses were performed using R software, version 3.4.3.

RESULTS

Baseline characteristics

From 2012 through 2019, 1,835 patients were diagnosed with localized PDAC and started (m)FOLFIRINOX as initial treatment. At diagnosis, 958 (52.2%) were staged as LA, 531 (28.9%) as BR, and 346 (18.9%) as PR PDAC. Patient and treatment characteristics are summarized in **Table 1**. Most patients were men (54.6% male, 45.4% female), median age was 64 years, and 95.6% had a performance score of 0 or 1. Initial FOLFIRINOX was started at centers other than the five TAPS centers in 106 patients (5.8%) and 35 patients (1.9%) received initial (m)FOLFIRINOX after aborted upfront surgery.

Table 1. Baseline characteristics of included patients and treatment specifications

Patient and treatment characteristics[a]	Overall (n = 1,835)	LA (n = 958)	BR (n = 531)	PR (n = 346)	*P*[b]
Sex, No. (%)	1,002 (54.6)	502 (52.4)	293 (55.2)	207 (59.8)	0.06
Male	833 (45.4)	456 (47.6)	238 (44.8)	139 (40.2)	
Female					
Median age (IQR), years	64 (57, 69)	63 (56, 68)	64 (57, 70)	65 (58, 70)	0.003
Performance status, No. (%)					<0.001
WHO 0	718 (39.3)	305 (32.1)	254 (47.8)	159 (46.0)	
WHO 1	1,036 (56.7)	605 (63.6)	261 (49.2)	170 (49.1)	
WHO 2-3	74 (4.0)	41 (4.3)	16 (3.0)	17 (4.9)	

Table 1. Baseline characteristics of included patients and treatment specifications (continued)

Patient and treatment characteristics[a]	Overall (n = 1,835)	LA (n = 958)	BR (n = 531)	PR (n = 346)	*P*[b]
Median BMI, kg/m² (IQR)	26 (23, 29)	26 (23, 29)	26 (23, 30)	27 (24, 30)	<0.001
Location, No. (%)					<0.001
Head/uncinate	1,223 (66.6)	555 (57.9)	422 (79.5)	246 (71.1)	
Body/tail	612 (33.4)	403 (42.1)	109 (20.5)	100 (28.9)	
Median Tumor size on CT (IQR), mm	36 (28, 46)	39 (32, 49)	34 (27, 42)	30 (24, 38)	<0.001
Median pre-treatment CA 19-9 (IQR), U/mL	208 (46, 774)	236 (51, 858)	219 (48, 720)	148 (42, 490)	0.003
Median pre-treatment CA 19-9, No. (%)					0.004
Non-secretor (<5 U/mL)	124 (7.3)	64 (7.2)	42 (8.6)	18 (5.6)	
5-500 U/mL	1,016 (59.8)	508 (57.4)	285 (58.0)	223 (69.0)	
>500 U/mL	559 (32.9)	313 (35.4)	164 (33.4)	82 (25.4)	
Median pre-treatment CEA (IQR), ng/mL	3.8 (2.2, 7.3)	3.9 (2.2, 8.2)	3.5 (2.1, 6.4)	3.7 (2.4, 6.3)	0.17
Median number of cycles (IQR)	6 (4, 8)	7 (4, 8)	6 (4, 8)	5 (4, 8)	<0.001
Number of cycles, No. (%)					<0.001
1-4 cycles	646 (35.2)	295 (30.8)	203 (38.2)	148 (42.8)	
5-8 cycles	868 (47.3)	423 (44.2)	265 (49.9)	180 (52.0)	
>8 cycles	320 (17.4)	239 (25.0)	63 (11.9)	18 (5.2)	
Second chemotherapy, No. (%)	236 (12.9)	126 (13.2)	77 (14.6)	33 (9.5)	0.09
Radiotherapy[c], No. (%)	888 (49.0)	546 (57.7)	222 (42.7)	120 (34.9)	<0.001
Multidisciplinary recommendation after systemic treatment with or without radiotherapy, No. (%)					<0.001
Surgical exploration	868 (47.9)	252 (26.7)	340 (64.4)	276 (81.2)	
Pall. tx / BSC for metastases	351 (19.4)	219 (23.2)	93 (17.6)	39 (11.5)	
Pall. tx / BSC for unresectable disease	504 (27.8)	418 (44.2)	71 (13.4)	15 (4.4)	
BSC for clinical decline / comorbidities	90 (5.0)	56 (5.9)	24 (4.5)	10 (2.9)	
Surgery with intent of resection, No. (%)	854 (46.5)	247 (25.8)	335 (63.1)	272 (78.6)	<0.001
Resection, No. (%)	695 (37.9)	169 (17.6)	282 (53.1)	244 (70.5)	<0.001
Surgical procedure, No. (%)					<0.001
Pancreatoduodenectomy	514 (74.3)	98 (58.7)	238 (84.7)	178 (73.0)	
Distal pancreatectomy	145 (21.0)	57 (34.1)	30 (10.7)	58 (23.8)	
Central pancreatectomy	27 (3.9)	9 (5.4)	12 (4.3)	6 (2.5)	
Total pancreatectomy	6 (0.9)	3 (1.8)	1 (0.4)	2 (0.8)	
Adjuvant treatment, No. (% of resections)	411 (59.2)	73 (43.5)	177 (62.8)	161 (66.0)	<0.001
Palliative cancer-directed treatment[d], No. (%)	1,022 (58.6)	575 (62.8)	279 (55.1)	168 (51.9)	<0.001

[a] Missing data: age (n=1), WHO (n=7), BMI (n=21), size (n=61), CA 19-9 (n=113), CEA (n=761), cycles (n=1), second chemotherapy (n=9), radiotherapy (n=24), recommendation (n=22), procedure (n=3), adjuvant (n=1), palliative (n=90). BMI, body mass index; BR, borderline resectable; BSC, best supportive care; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CT, computed tomography; IQR, interquartile range; LA, locally advanced; No, Number; Pall. Tx, palliative treatment; PR, potentially resectable; WHO, World Health Organization.

[b] Differences between groups were calculated using the chi-square test for categorical variables and Mann-Whitney U test for continuous variables. All tests were 2-sided.

[c] Preoperative radiotherapy only.

[d] Any cancer-directed treatment (e.g., chemotherapy, immunotherapy, or radiotherapy for local recurrent disease) for metastatic or recurrent disease after start of neoadjuvant or induction treatment).

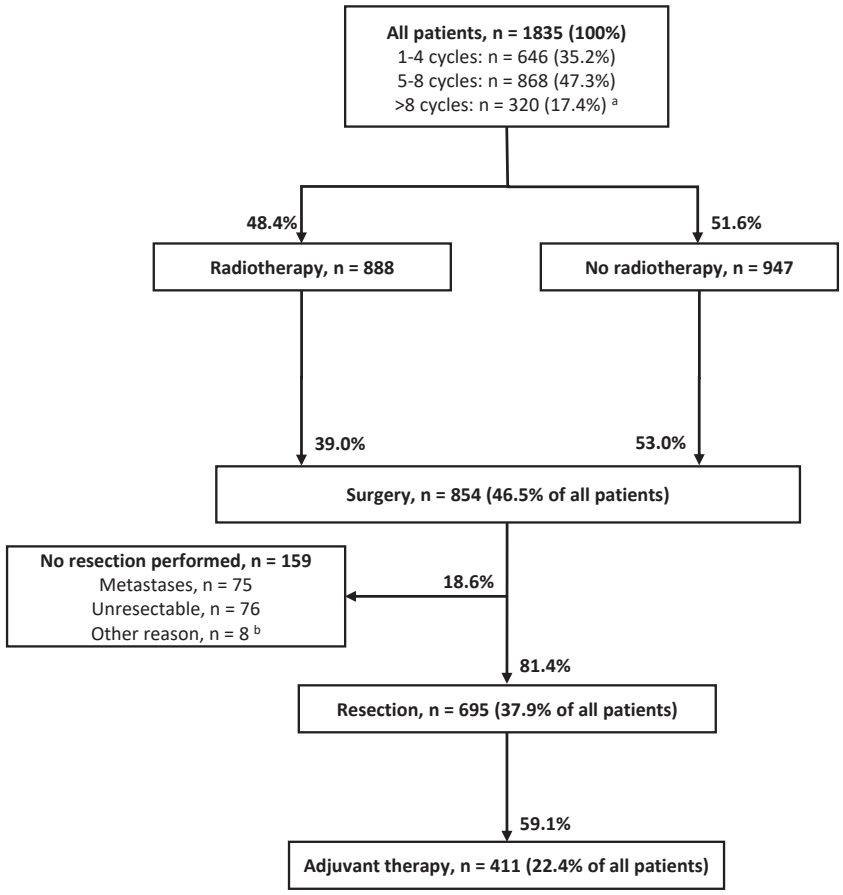
Treatment characteristics

Figure 1 shows the flow chart of subsequent treatments after (m)FOLFIRINOX for all patients. A separate flow chart for each stage (i.e., LA, BR, and PR) is included in the **Supplementary Figure 1A-C**. The median number of initial (m)FOLFIRINOX cycles was 6 (IQR = 4-8). Second chemotherapy was administered to 236 patients (12.9%). Furthermore, systemic chemotherapy was followed by radiotherapy (i.e., excluding adjuvant radiotherapy) in 888 patients (49.0%), including 546 patients with LA (57.7%), 222 with BR (42.7%), and 120 with PR (34.9%) PDAC (**Table 1**).

Treatment evaluation

At multidisciplinary evaluation after all systemic treatment with or without radiotherapy, 51.5% of patients were ineligible for surgery. This was due to *anatomy* (definitively unresectable disease on imaging in 504 patients [27.5%]), *biology* (metastases in 351 patients

A)



B)

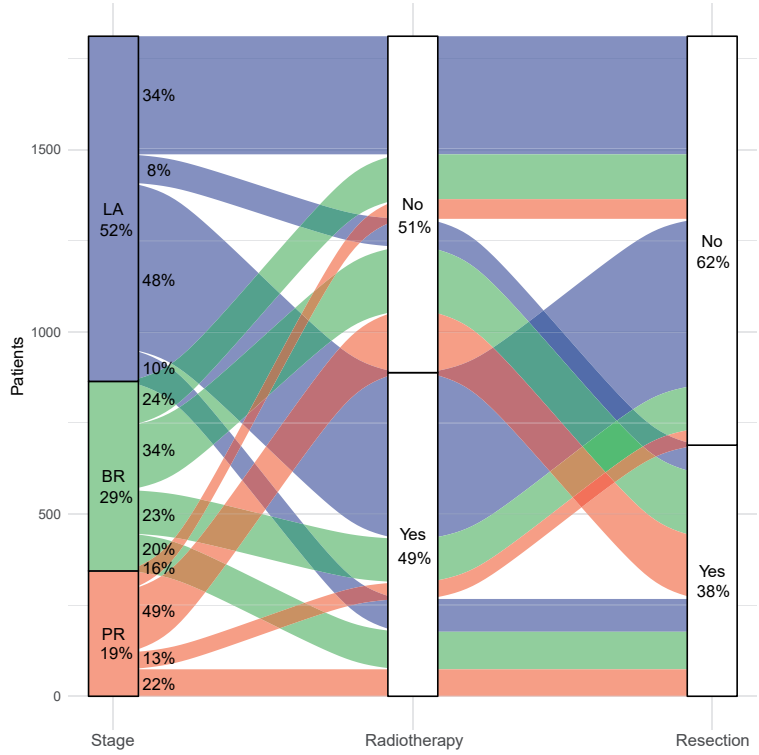


Figure 1. Flow chart and alluvial diagram of treatment for all patients with localized pancreatic adenocarcinoma who started treatment with (m)FOLFIRINOX. **A)** [a] 236 patients (13%) also received second chemotherapy. [b] Other reasons for not performing a resection were a cirrhotic liver in three, peripancreatic fibrosis in three, and an unknown reason for not performing a resection in two patients. **B)** In the alluvial diagram, the first column shows the stage at baseline prior to start of (m)FOLFIRINOX, the second column shows whether patients received radiotherapy to the primary tumor after initial (m)FOLFIRINOX, and the last column shows whether patients underwent a surgical resection. Percentages in columns represent the percentages of the total cohort. Percentages in the blue, green, and red stream fields represent the stage-specific percentages for subsequent radiotherapy and surgery. For example, 52.2% of the total cohort was diagnosed with LA PDAC. Of those LA PDAC patients, 34.2% received radiotherapy and did not undergo resection after start of (m)FOLFIRINOX, 8.1% did not receive radiotherapy but did undergo a resection, 48.1% received radiotherapy but did not undergo a resection, and 9.5% received both radiotherapy and resection. Due to rounding, total stage-specific percentages may not exactly add up to 100%. BR, borderline resectable; LA, locally advanced; PR, potentially resectable

[19.1%]), or *condition* (clinical decline without metastases or other medical conditions precluding surgery in 90 patients [4.9%]). The remaining 868 patients (47.3%) were considered for surgical exploration (**Figure 1, Table 1**). Fourteen patients (1.6%) ultimately did not undergo surgery because of the patient's preference (n=7) or unknown reason (n=7).

Surgical cohort

Overall, 854 patients (46.5%) underwent surgical exploration, of whom 159 (8.7%) did not undergo resection because of occult metastatic disease in 77 (4.2%), unresectable disease in 78 (4.3%), or other reasons encountered during surgical exploration (e.g., unrecognized cirrhosis) in 8 (0.1%) (Figure 1A). The remaining 695 patients (81.4%; 37.8% of the total cohort) underwent resection. Resection rates were 17.6% for LA, 53.1% for BR, and 70.5% for PR PDAC (p<0.001) (**Table 1**). Median time from diagnosis to resection was 175 (IQR = 135-225) days. Vascular resection was performed in 292 of 695 patients (42.0%). Arterial resection and reconstruction was performed in 128 of 695 (18.4%) patients. The 30- and 90-days postoperative mortality rates were 1.0% and 2.0%, respectively.

Following resection, 411 patients (59.1%) received adjuvant therapy, of whom 149 of 411 (36.3%) received (m)FOLFIRINOX with a median of 6 (IQR = 4-6) cycles. Other adjuvant regimens included gemcitabine-based therapy in 203 of 411 patients (49.4%), 5-fluoro-uracil-based therapy other than (m)FOLFIRINOX in 27 of 411 patients (6.6%), and (chemo) radiotherapy in 66 of 411 patients (16.1%) (data not shown).

Pathology outcomes

Pathology outcomes for patients who underwent a resection are shown in **Table 2**. The R0 resection rate was 405 of 613 (66.1%) for patients with known margin-status; 55.2% for LA, 62.6% for BR, and 79.2% for PR PDAC (p<0.001). In total, 33/597 (5.5%; 1.8% of the total cohort) patients with known pathologic response had a complete response and 302/684 (44.2%; 16.5% of the total cohort) patients with known nodal status had node-negative disease.

Survival outcomes

After a median follow-up time of 36.5 months, 1,202 patients (65.6%) had died. The median OS for all patients was 21.4 months (95% CI = 20.1-22.7) (**Supplementary Figure 2A**). The median OS was 18.7 months (95% CI = 17.7-19.9) for LA, 23.2 months (95% CI = 21.0-25.7) for BR, 31.2 months (95% CI = 26.2-36.6) for PR PDAC (p<0.001) (**Figure 2A**). The 5-year OS rate was 15.8% (95% CI = 13.6-18.4%) for all patients, including 9.5% (95% CI = 7.2-12.6%) for LA, 18.4% (95% CI = 14.1-23.9%) for BR, and 33.7% (95% CI = 27.1-42.0%) for PR PDAC.

The median OS from diagnosis for patients who did not undergo a resection was 16.3 months (95% CI = 15.6-17.2). Median OS from diagnosis for patients who underwent a resection was 38.3 months (95% CI = 36.1-42.0) (**Figure 2B**). From the date of surgery, the median OS was 32.6 months (95% CI = 29.2-37.0). The 5-year OS rates for patients who underwent a resection were 33.4% (95% CI = 28.7-39.0%) for all patients, including 24.9% (95% CI = 16.9-36.5%) for LA, 31.5% (95% CI = 24.6-40.3%) for BR, and 44.6% (95% CI = 36.3-54.9%) for PR PDAC. The 5-year OS rates for patients who did not undergo a resection

Table 2. Pathological outcomes of patients who underwent a resection

Pathological outcomes[a]	Overall (n = 695)	LA (n = 169)	BR (n = 282)	PR (n = 244)	*P*[b]
Tumor size, No. (%)					0.17
0-20 mm	231 (34.1)	45 (28.5)	98 (35.0)	88 (36.7)	
21-40 mm	333 (49.1)	77 (48.7)	140 (50.0)	116 (48.3)	
>40 mm	114 (16.8)	36 (22.8)	42 (15.0)	36 (15.0)	
T stage[c], No. (%)					0.04
ypT0	33 (4.9)	9 (5.7)	9 (3.2)	15 (6.2)	
ypT1-2	493 (72.5)	102 (64.2)	215 (76.8)	176 (73.0)	
ypT3-4	154 (22.6)	48 (30.2)	56 (20.0)	50 (20.7)	
N stage[c], No. (%)					0.92
ypN0	302 (44.2)	75 (46.6)	119 (42.3)	108 (44.6)	
ypN1	245 (35.8)	56 (34.8)	105 (37.4)	84 (34.7)	
ypN2	137 (20.0)	30 (18.6)	57 (20.3)	50 (20.7)	
Resection margin status[d], No. (%)					<0.001
R0	405 (66.1)	85 (55.2)	164 (62.6)	156 (79.2)	
R1	208 (33.9)	69 (44.8)	98 (37.4)	41 (20.8)	
Tumor differentiation, No. (%)					0.11
Well (G1)	21 (3.4)	7 (4.9)	8 (3.1)	6 (2.9)	
Moderate (G2)	402 (65.8)	81 (57.0)	182 (70.3)	139 (66.2)	
Poor (G3)	188 (30.8)	54 (38.0)	69 (26.6)	65 (31.0)	
Perineural invasion, No. (%)	512 (75.6)	111 (70.7)	219 (78.2)	182 (75.8)	0.21
Lymphovascular invasion, No. (%)	370 (55.2)	80 (51.3)	157 (56.5)	133 (56.4)	0.53
Pathologic response, No. (%)					0.23
Complete response	33 (5.5)	9 (6.9)	9 (3.6)	15 (6.9)	
<5% viable tumor cells	58 (9.7)	17 (13.1)	24 (9.6)	17 (7.8)	
≥5% viable tumor cells	506 (84.8)	104 (80.0)	216 (86.7)	186 (85.3)	

[a] Missing data: tumor size (n=17), ypT (n=15), ypN (n=11), margin (n=82), differentiation (n=84), perineural (n=18), lymphovascular (n=25), pathologic response (n=98).
[b] Differences between groups were calculated using the chi-square test. All tests were 2-sided.
[c] 8th edition of the American Joint Committee on Cancer Staging.
[d] 1mm definition of the Royal College of Pathologists.
BR, borderline resectable; LA, locally advanced; No, number; PR, potentially resectable.

was 4.8% (95% CI = 3.3-7.2%) and the 2-year OS rate was 27.6% (95% CI = 24.9-30.6%). The median OS from diagnosis for 888 patients (49.0%) who received radiotherapy after initial (m)FOLFIRINOX (i.e., excluding adjuvant radiotherapy) was 23.6 months (95% CI = 22.4-25.7); the median OS from diagnosis for 923 patients who did not receive additional radiotherapy was 18.4 months (95% CI = 17.5-20.1) (hazard ratio [HR] = 0.77, 95% CI = 0.69-0.87, p<0.001).

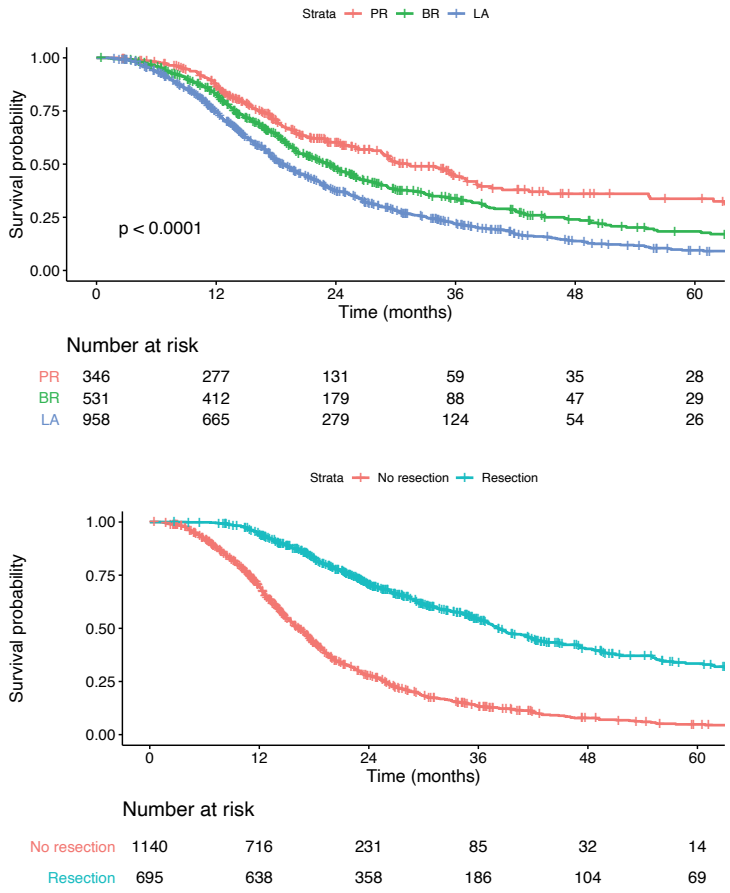


Figure 2. Overall survival of patients with localized pancreatic adenocarcinoma treated with (m) FOLFIRINOX as initial treatment by radiographic stage at diagnosis and by resection status
A) MD Anderson Cancer Center (MDACC) classification was used for patients from MDACC. National Comprehensive Cancer Network (NCCN) classification applicable at time of diagnosis was used for patients from the other centers. Difference in survival outcomes between groups was tested using the log-rank test. The test was 2-sided. *P* <.001. **B)** Survival was measured from the time of diagnosis in patients who did and did not undergo resection. BR, borderline resectable; LA, locally advanced; PR, potentially resectable.

Baseline factors prognostic for OS

Independent prognostic factors at baseline for worse OS were more advanced stage, worse performance status, baseline CA 19-9 level >500 U/mL, and BMI ≤18.5 kg/m^2 (**Table 3**). All factors were measured before start of (m)FOLFIRINOX. **Supplementary Figures 2B-D** show the survival curves of the three prognostic factors besides stage.

Table 3. Univariable and multivariable cox proportional hazards regression analysis of overall survival using baseline factors for all patients[a]

Baseline factors	No. of patients	Univariable analysis		Multivariable analysis	
		HR (95% CI)	*P*[b]	HR (95% CI)	*P*[b]
Sex					
Male	1,002	1 [Reference]	NA	-	-
Female	833	0.95 (0.85-1.07)	0.41		
Age, years					
<65	990	1 [Reference]	NA	-	-
65-74	711	1.04 (0.92-1.17)	0.57		
≥75	133	1.15 (0.91-1.45)	0.24		
Location					
Head/uncinate	1,223	1 [Reference]	NA	-	-
Body/tail	612	0.97 (0.86-1.09)	0.58		
Performance status					
WHO 0	718	1 [Reference]	NA	1 [Reference]	NA
WHO 1	1,036	1.39 (1.23-1.56)	<0.001	1.31 (1.16-1.48)	<0.001
WHO 2-3	74	1.74 (1.31-2.32)	<0.001	1.78 (1.33-2.37)	<0.001
BMI, kg/m^2					
18.5-30	1,374	1 [Reference]	NA	1 [Reference]	NA
≤18.5	53	1.66 (1.21-2.27)	0.002	1.46 (1.06-2.01)	0.02
>30	387	0.98 (0.85-1.13)	0.77	1.03 (0.90-1.19)	0.67
Radiographic stage at baseline					
PR PDAC	346	1 [Reference]	NA	1 [Reference]	NA
BR PDAC	531	1.44 (1.19-1.73)	<0.001	1.43 (1.18-1.72)	<0.001
LA PDAC	958	1.94 (1.63-2.30)	<0.001	1.81 (1.20-2.16)	<0.001
Tumor size on baseline CT					
0-20 mm	97	1 [Reference]	NA	1 [Reference]	NA
21-40 mm	1,036	1.33 (0.98-1.79)	0.06	0.99 (0.73-1.35)	0.97
>40 mm	641	1.56 (1.15-2.11)	0.004	1.05 (0.77-1.44)	0.75
Pre-treatment CA 19-9					
5-500 U/mL	1,016	1 [Reference]	NA	1 [Reference]	NA
Non-secretor (<5 U/ml)	124	1.19 (0.95-1.49)	0.13	1.16 (0.93-1.44)	0.19
>500 U/mL	559	1.42 (1.25-1.61)	<0.001	1.39 (1.23-1.58)	<0.001

[a] Imputed data for multivariable analysis: WHO (n=7), BMI (n=21), tumor size (n=61), and CA 19-9 (n=136).
[b] A Cox proportional hazards regression model was used to assess the potential prognostic baseline factors for OS. Known prognostic factors and factors with a p-value <0.20 in univariable analysis were included in the multivariable model.[16]

BMI, body mass index; BR, borderline resectable; CA 19-9, carbohydrate antigen 19-9; CI, confidence interval; CT, computed tomography; HR, hazard ratio; LA, locally advanced; NA, not applicable; No, number; PR, potentially resectable; WHO, World Health Organization.

DISCUSSION

This large international multicenter retrospective cohort study assessed the treatment course and outcomes of 1,835 patients who received (m)FOLFIRINOX as initial treatment for localized PDAC. Following (m)FOLFIRINOX, 49.0% received radiotherapy and 37.9% underwent a resection of whom 59.2% started adjuvant treatment. The resection rate was 17.6% for LA, 53.1% for BR, and 70.5% for PR PDAC. The median OS was 18.7 months for LA, 23.2 months for BR, and 31.2 months for PR PDAC. In a multivariable analysis of baseline factors, more advanced stage, worse performance status, baseline CA 19-9 level >500 U/mL, and BMI ≤18.5 kg/m^2 were independently associated with worse OS.

This study is the largest reported series on (m)FOLFIRINOX for localized PDAC to date. In the past decade, two patient-level meta-analyses of small cohort studies and several phase II trials investigated (m)FOLFIRINOX as initial treatment for LA, BR, and/or PR PDAC.[6, 7, 17-30] In **Supplementary Table 1**, the resection rate and median OS of some key studies are presented. The broad range of outcomes across studies is partly explained by the small sample size of most studies. In addition, heterogeneity reflects differences in patient characteristics, staging, whether all consecutive patients were captured, the duration of systemic treatment, and subsequent treatments. Based on the large number of patients, the inclusion of all 'denominator' data, and the international group of centers, our results are generalizable to pancreatic cancer referral centers. The results can be used as reference data for other experienced centers treating patients with localized PDAC with initial (m)FOLFIRINOX.

Initial (m)FOLFIRINOX was the focus of the present study; however, no RCT has been published that shows superiority of (m)FOLFIRINOX over other regimens beyond the metastatic and adjuvant setting. Several ongoing RCTs compare initial FOLFIRINOX with gemcitabine-based regimens. For the Dutch PREOPANC-2 trial, comparing neoadjuvant FOLFIRINOX to neoadjuvant gemcitabine-based chemoradiotherapy for BR and PR PDAC, accrual was completed in January 2021.[31] A Chinese RCT compares initial mFOLFIRINOX to gemcitabine/nab-paclitaxel for LA and BR PDAC (NCT04617821).

The available evidence on neoadjuvant (m)FOLFIRINOX for PR PDAC is limited. The phase 2 SWOG S1505 trial is the largest prospective study to date, including 102 patients.[18] This study compared 12 weeks of pre- and postoperative mFOLFIRINOX (n=55) to gemcitabine/nab-paclitaxel (n=47), showing a resection rate of 73% and median OS of 23.2 months for mFOLFIRINOX, with no difference in outcomes between the treatment arms. The present study included 346 patients with PR PDAC, showing a similar resection rate of 70.5% and a median OS of 31.2 months. In comparison, the PRODIGE24/CCTG PA.6 trial found a median OS of 54.4 months for patients who received adjuvant mFOLFIRINOX. An adjuvant trial, however, includes only the selected subgroup of patients who underwent a resection, without evidence of early recurrence on CT, a low postoperative CA 19-9 level, and a

good performance score within three months after resection. Currently, four RCTs directly compare neoadjuvant to adjuvant (m)FOLFIRINOX, including the NorPACT-1[32], ALLIANCE A021806 (NCT04340141), PREOPANC-3 (NCT04927780), and PANACHE01-PRODIGE48.[33]

Almost half of all patients received radiotherapy after initial (m)FOLFIRINOX, whereas no RCT has been published to support radiotherapy after (m)FOLFIRINOX in LA, BR, or PR PDAC. Recently, the ALLIANCE A021501 trial did not demonstrate a benefit in OS of SBRT after initial mFOLFIRINOX for BR PDAC.[25] A recent meta-analysis comparing neoadjuvant (m) FOLFIRINOX alone or followed by radiotherapy for BR and PR PDAC showed an improved R0 resection rate but no difference in OS.[34] In the present study, patients who received additional radiotherapy following systemic treatment showed superior OS compared to those who did not. However, both selection bias and guarantee-time bias may have influenced this comparison.[35] Future studies are needed to further elucidate the role of radiotherapy for PDAC. Ongoing trials investigating the role of radiotherapy after multi-drug systemic treatment include the CONKO-007 trial[36] for LA PDAC and the PANDAS-PRODIGE44 trial (NCT02676349) for BR PDAC. With the literature available to date, no strong recommendation for or against radiotherapy after initial (m)FOLFIRINOX is possible at this time.

Four factors at diagnosis were independently associated with worse OS: radiographic stage (i.e., LA, BR, PR), baseline CA 19-9 level >500 U/mL, performance status, and BMI ≤18.5 kg/m^2. Conventional staging systems (e.g., NCCN) are based only on the radiographic stage determined by the apparent abutment of the tumor to the vasculature.[5] The difference in anatomical tumor-vessel contact may also represent a biological difference. In addition, the poor prognostic value of serum CA 19-9 level >500 U/mL has been acknowledged in the biological definition of BR PDAC of the MDACC classification introduced in 2008 and subsequently adapted by the International Association of Pancreatology.[11, 37, 38] These classifications upstaged patients with a performance status ≥2. The present study found that even a performance status of 1 (compared to 0) was associated with worse OS. Although not common, underweight (BMI ≤18.5 kg/m^2) at diagnosis, another measure of poor clinical condition, was one of the worst prognostic factors.

This international multicenter retrospective cohort study has some inherent limitations. First, no centralized histopathological or radiologic review was conducted and the staging criteria (e.g., NCCN, MDACC) differed somewhat across centers. Moreover, the NCCN criteria have changed slightly over time. Second, the participating centers varied in terms of subsequent treatment after (m)FOLFIRINOX. All centers, however, are experienced referral centers and heterogeneity in subsequent treatment makes the study results more generalizable to everyday patients in pancreatic cancer referral centers. Third, community practices may care for a patient population that is different from the present study and consequently have different outcomes. Finally, no detailed data on radiographic treatment response or timing

and site of disease progression (e.g., local vs. distant, primary site of distant progression) were collected.

The results of this TAPS cohort allow for improved discussion between patients and clinicians regarding resection rates and survival outcomes by clinical stage after initial (m)FOLFIRINOX for localized PDAC. Moreover, the results can be used as robust real-world estimates for sample size calculations for studies investigating new treatments for PDAC when initial (m)FOLFIRINOX is the standard arm. Future research should determine the optimal number of cycles of (m)FOLFIRINOX treatment prior to definitive local therapy. Moreover, future studies may investigate which patients benefit from subsequent treatments, including second systemic regimens, radiotherapy, surgical resection, and adjuvant chemotherapy.

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Supplementary Table 1. Resection rates and overall survival of selected studies on (m)FOLFIRINOX for localized pancreatic adenocarcinoma

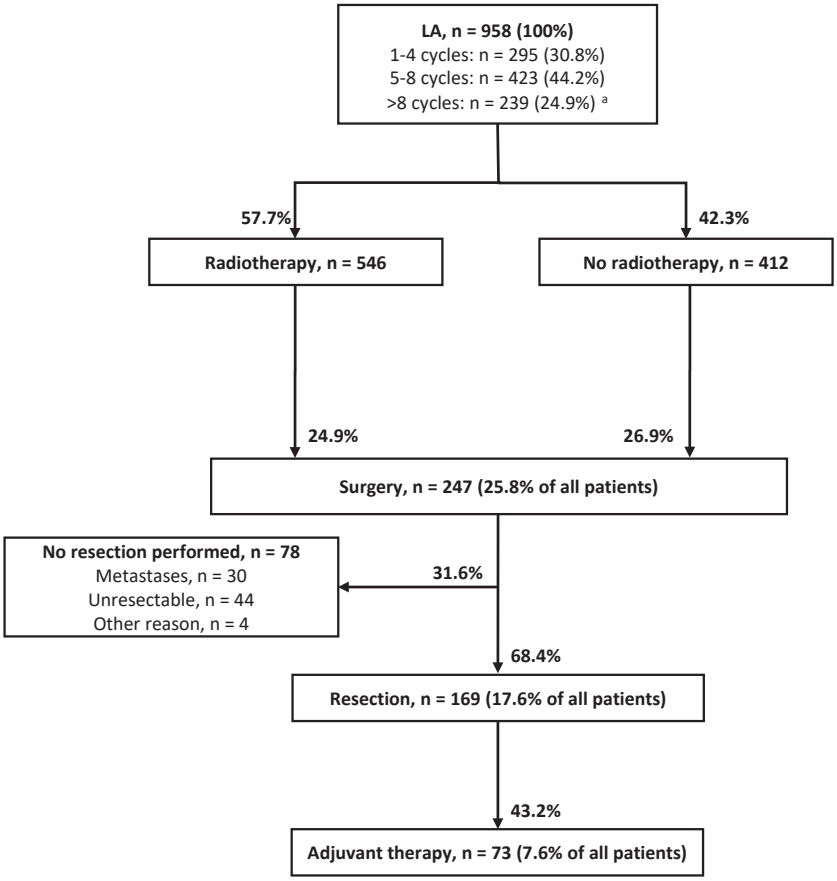
Trial / First Author	Year	Country	Design	No. of patients receiving (m) FOLFIRINOX	Resection rate[a]	Median OS in months[a]
PR PDAC						
De Marsh[1]	2018	USA	Prospective cohort	21	81%	34
SWOG S1505 [2]	2021	USA	Randomized phase II trial	55	73%	23.2
TAPS cohort	2021	USA + The Netherlands	Retrospective	346	71%	31.2
BR PDAC						
Murphy [3]	2018	USA	Nonrandomized Phase II trial	48	67%	37.7
Janssen [4]	2019	USA, The Netherlands, France, UK, Scotland, Austria, Japan, Korea, Australia	Patient-level meta-analysis	283	68%	22.2
Maggino [5]	2019	Italy	Prospective cohort	107	34%	20.0
Yoo [6]	2020	South-Korea	Retrospective	75	36%	18.4
Garnier [7]	2020	France	Retrospective	199	45%	22 (BR and LA combined)
ESPAC-5F (abstract only) [8]	2020	UK	Randomized phase II trial	20	55%	NR 1 year OS 84%
Auclin [9]	2021	France	Retrospective	102	42%	26.8
ALLIANCE A021501 (abstract only) [10]	2021	USA	Randomized phase II trial	70 without RT 56 with RT	48% without RT 35% with RT	31.0 without RT 17.1 with RT
TAPS cohort	2021	USA + The Netherlands	Retrospective	531	53%	23.2
LA PDAC						

Supplementary Table 1. Resection rates and overall survival of selected studies on (m)FOLFIRINOX for localized pancreatic adenocarcinoma (continued)

Trial / First Author	Year	Country	Design	No. of patients receiving (m) FOLFIRINOX	Resection rate[a]	Median OS in months[a]
Suker [11]	2016	USA, France, UK, Austria	Patient-level meta-analysis	315	26%	24.2
Murphy [12]	2019	USA	Nonrandomized Phase II trial	49	69%	31.4
Maggino [5]	2019	Italy	Prospective cohort	153	12%	16.2
Yoo [6]	2020	South-Korea	Retrospective	124	29%	17.1
Garnier [7]	2020	France	Retrospective	59	14%	22 (BR and LA combined)
Walma [13]	2020	The Netherlands	Prospective	252	13%	14.0
Auclin [9]	2021	France	Retrospective	226	16%	18.9
JCOG1407 (abstract only) [14]	2021	Japan	Randomized phase II trial	62	NR	24.0
TAPS cohort	2021	USA + The Netherlands	Retrospective	958	18%	18.7

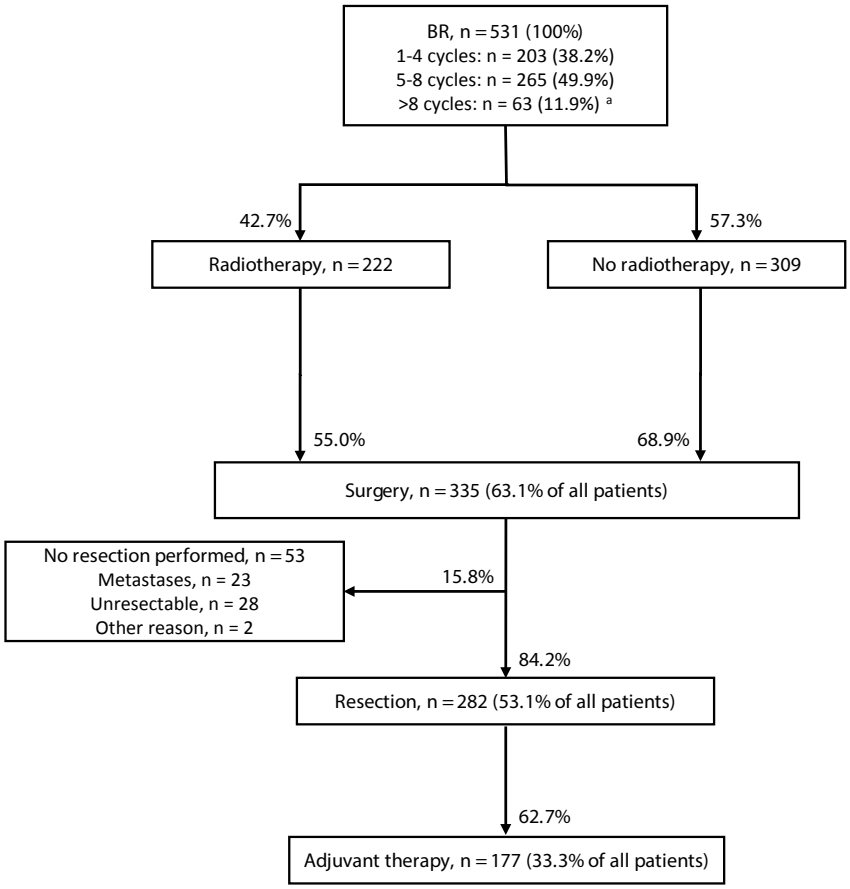
[a] Resection rate and survival for all enrolled patients in each study. BR = borderline resectable; LA = locally advanced; OS = overall survival; PDAC = pancreatic ductal adenocarcinoma; NR = not reported; PR = potentially resectable; RT = radiotherapy; UK = United Kingdom; US = United States of America

A)



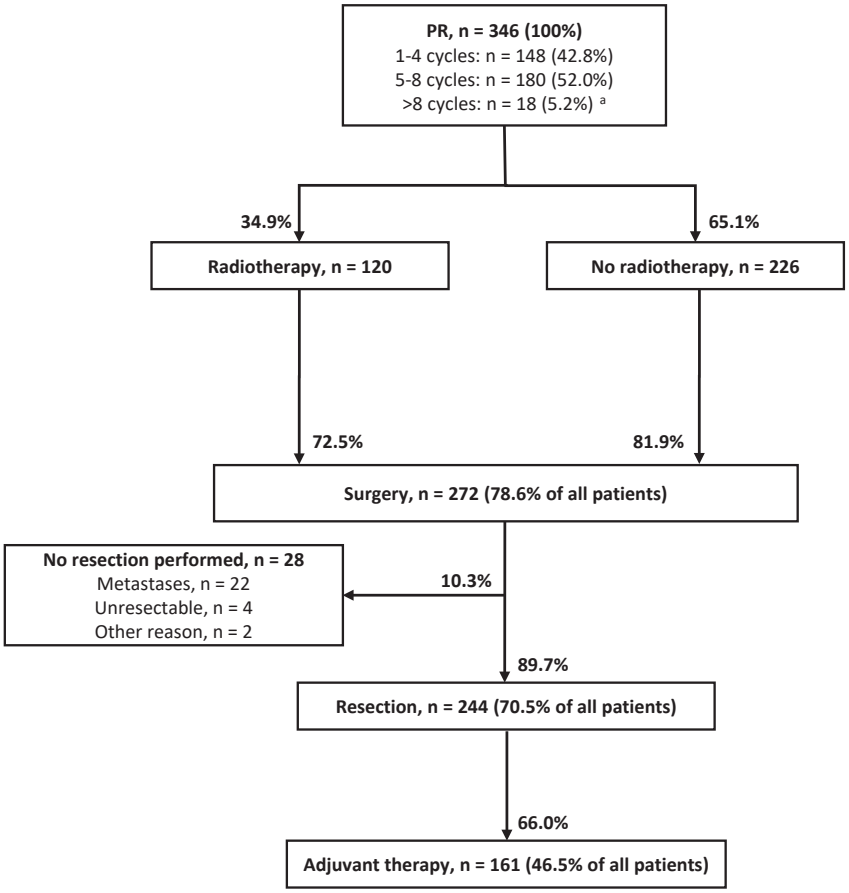
[a] = 126 patients (13%) also received second chemotherapy. LA = locally advanced.

B)



[a] = 77 patients (15%) also received second chemotherapy. BR = borderline resectable.

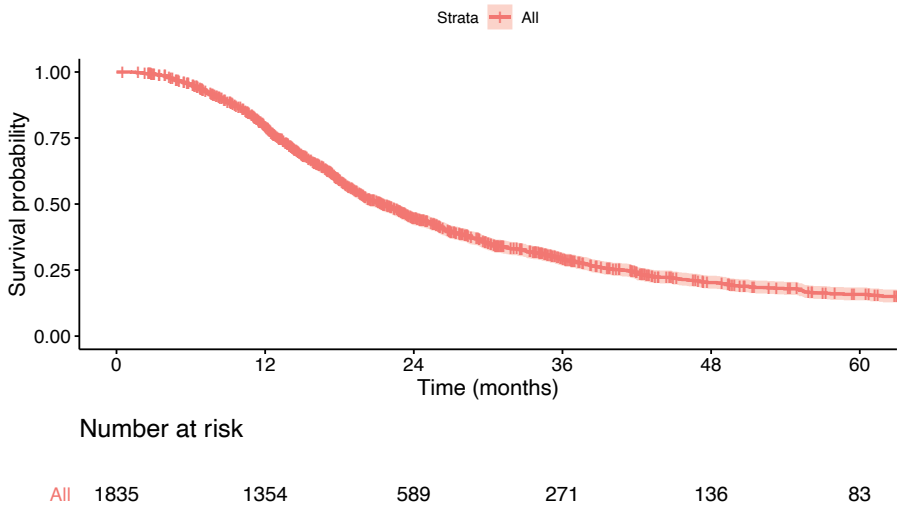
C)



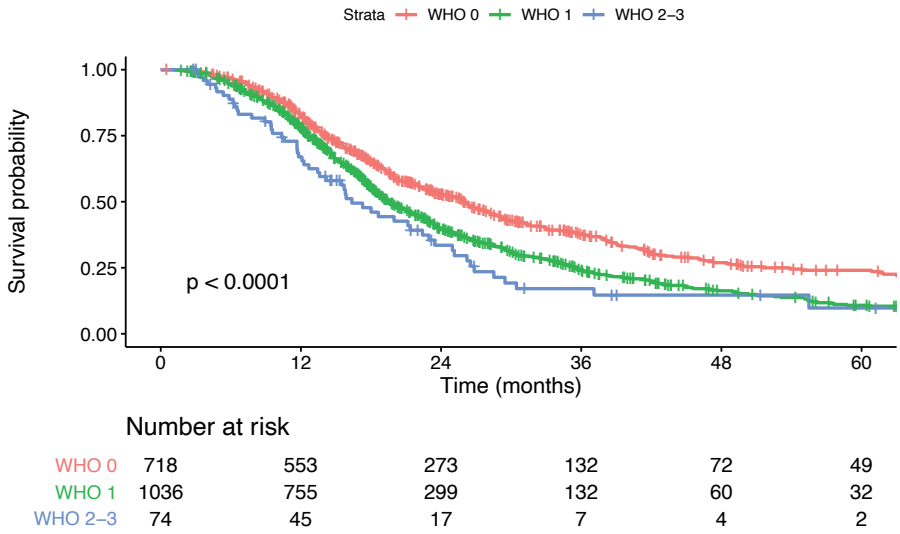
[a] = 33 patients (10%) also received second chemotherapy. PR = potentially resectable.

Supplementary Figure 1. Flow chart and alluvial diagram of treatment for patients with localized pancreatic adenocarcinoma who started treatment with (m)FOLFIRINOX by stage

A)

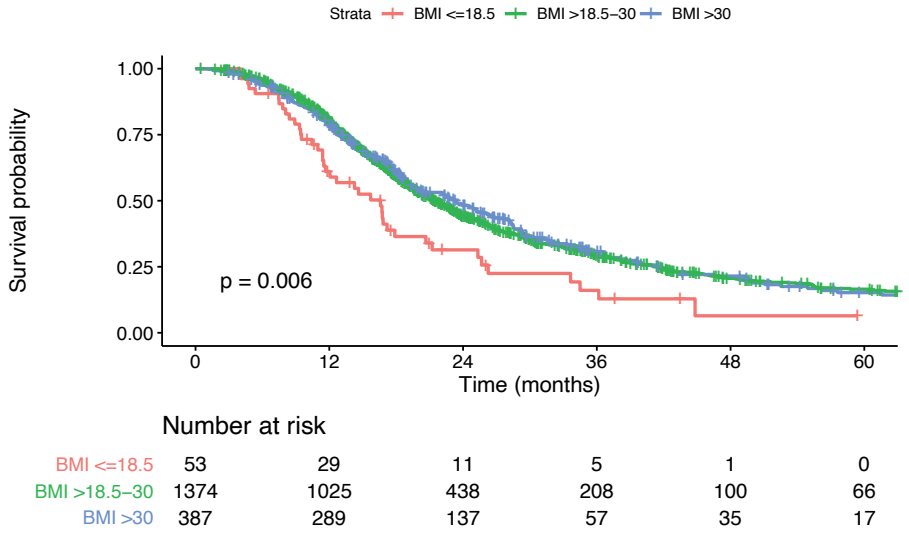

Strata All
Survival probability
1.00
0.75
0.50
0.25
0.00
0
12
24
36
48
60
Time (months)
Number at risk
All 1835 1354 589 271 136 83

B)

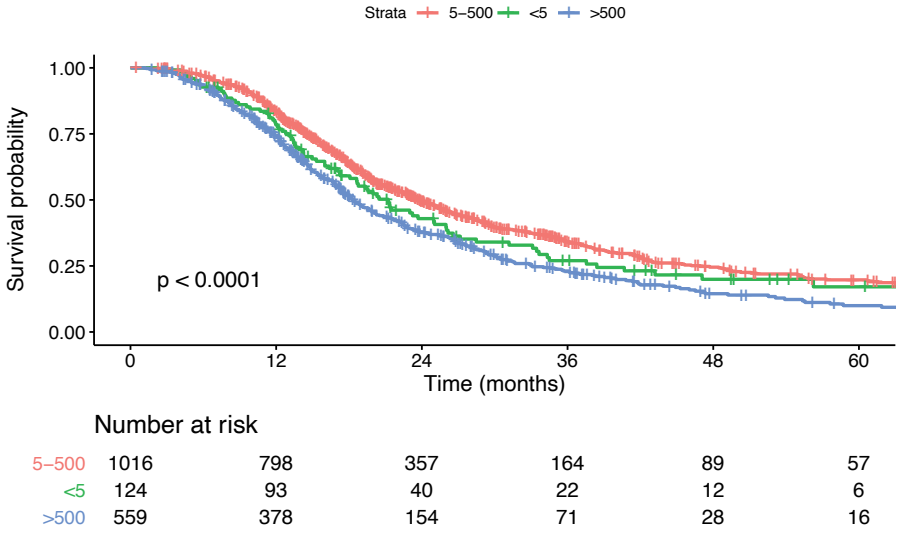

Strata WHO 0 WHO 1 WHO 2–3
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
12
24
36
48
60
Time (months)
Number at risk
WHO 0 718 553 273 132 72 49
WHO 1 1036 755 299 132 60 32
WHO 2–3 74 45 17 7 4 2

8

C)



D)



Supplementary Figure 2. Overall survival of all patients with localized pancreatic adenocarcinoma treated with (m)FOLFIRINOX as initial treatment, by World Health Organization (WHO) performance status, by Body Mass Index (BMI), and by Carbohydrate Antigen (CA) 19-9 level in U/mL prior to start of (m)FOLFIRINOX treatment. Difference in survival outcomes between groups was tested using the log-rank test. All tests were 2-sided

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CHAPTER 9

Total neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine for resectable and borderline resectable pancreatic cancer (PREOPANC-2 trial): study protocol for a nationwide multicenter randomized controlled trial.

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BMC Cancer. 2021 Mar 23;21(1):300.

ABSTRACT

Background

Neoadjuvant therapy has several potential advantages over upfront surgery in patients with localized pancreatic cancer; more patients receive systemic treatment, fewer patients undergo futile surgery, and R0 resection rates are higher, thereby possibly improving overall survival (OS). Two recent randomized trials have suggested benefit of neoadjuvant chemoradiotherapy over upfront surgery, both including single-agent chemotherapy regimens. Potentially, the multi-agent FOLFIRINOX regimen (5-fluorouracil with leucovorin, irinotecan, and oxaliplatin) may further improve outcomes in the neoadjuvant setting for localized pancreatic cancer, but randomized studies are needed. The PREOPANC-2 trial investigates whether neoadjuvant FOLFIRINOX improves OS compared with neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine in resectable and borderline resectable pancreatic cancer patients.

Methods

This nationwide multicenter phase III randomized controlled trial includes patients with pathologically confirmed resectable and borderline resectable pancreatic cancer with a WHO performance score of 0 or 1. Resectable pancreatic cancer is defined as no arterial and ≤90 degrees venous involvement; borderline resectable pancreatic cancer is defined as ≤90 degrees arterial and ≤270 degrees venous involvement without occlusion. Patients receive 8 cycles of neoadjuvant FOLFIRINOX chemotherapy followed by surgery without adjuvant treatment (arm A), or 3 cycles of neoadjuvant gemcitabine with hypofractionated radiotherapy (36 Gy in 15 fractions) during the second cycle, followed by surgery and 4 cycles of adjuvant gemcitabine (arm B). The primary endpoint is OS by intention-to-treat. Secondary endpoints include progression-free survival, quality of life, resection rate, and R0 resection rate. To detect a hazard ratio of 0.70 with 80% power, 252 events are needed. The number of events is expected to be reached after inclusion of 368 eligible patients assuming an accrual period of 3 years and 1.5 years follow-up.

Discussion

The PREOPANC-2 trial directly compares two neoadjuvant regimens for patients with resectable and borderline resectable pancreatic cancer. Our study will provide evidence on the neoadjuvant treatment of choice for patients with resectable and borderline resectable pancreatic cancer.

INTRODUCTION

Pancreatic ductal adenocarcinoma is often diagnosed at an advanced stage. Only 10-20% of patients present with resectable or borderline resectable pancreatic cancer, for which a potentially curative resection can be performed. Despite surgery, cure remains exceptional, as is demonstrated by a 10-year overall survival (OS) after resection of less than 4%.[1] Most patients die of distant progression rather than local recurrence. Apparently, the vast majority of patients with local disease on imaging already have occult metastatic disease. This underlines the importance of systemic therapy.

Upfront surgery with adjuvant gemcitabine has long been the standard of care for patients with resectable pancreatic cancer.[2] Over the past decade, multiple randomized trials have focused on adjuvant therapy, with gradually improving OS.[3-5]. Unfortunately, only a subgroup of patients with localized pancreatic cancer receive the intended upfront surgery and adjuvant therapy. First, 10-20% of patients who are scheduled for surgical exploration do not undergo resection, because metastatic or locally unresectable disease is found at surgery that was not anticipated on imaging.[6] An exploratory laparotomy without resection has considerable mortality, morbidity, and a prolonged reduced quality of life. Most of these patients fail to receive palliative chemotherapy.[7] Second, many patients (40-50%) do not recover from a resection sufficiently or in time to tolerate adjuvant chemotherapy.[8, 9] Third, recurrence within 6 months after surgery can occur in up to 50% of patients who do not receive adjuvant chemotherapy.[3] It is unlikely that these patients derived any benefit from surgery. Hence, with upfront surgery, too many patients with the initial diagnosis of resectable or borderline resectable pancreatic cancer undergo futile surgery and too few patients receive systemic chemotherapy, while the majority of patients have occult metastatic disease at presentation.

Neoadjuvant therapy has been proposed to overcome the drawbacks associated with upfront surgery. Single-arm studies on neoadjuvant chemotherapy, with or without radiotherapy, have reported favorable outcomes. A meta-analysis of 38 studies with 3843 patients with resectable and borderline resectable pancreatic cancer found superior OS by intention-to-treat (ITT) (18.8 vs. 14.8 months) and higher R0 resection rates (87% vs. 67%; $p<0.001$) after neoadjuvant therapy compared with upfront surgery.[6] The addition of radiotherapy to chemotherapy has been suggested to improve R0 resection rate and decrease local recurrence rate, with the potential to improve OS. A recent Korean randomized phase II-III trial was closed early after inclusion of 50 patients because of superior survival with neoadjuvant versus adjuvant gemcitabine-based chemoradiotherapy at interim analysis (21 vs. 12 months, $p=0.028$).[10] The Dutch PREOPANC-1 randomized controlled trial (RCT) compared neoadjuvant gemcitabine-based chemoradiotherapy to upfront surgery, both arms followed by adjuvant gemcitabine.[11, 12] Although this study did not meet the primary endpoint of OS by ITT (16.0 vs. 14.3 months, $p=0.096$), all secondary outcomes found

superiority of the neoadjuvant arm: R0 resection rate (71% vs. 40%; $p<0.001$), disease free survival (8.1 vs. 7.7 months, $p=0.032$), and locoregional recurrence free interval (not reached vs. 13.4 months, $p=0.003$).

In 2011, the multi-drug regimen FOLFIRINOX, consisting of 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin, was superior to gemcitabine in patients with metastatic pancreatic cancer (median OS 11.1 vs. 6.8 months, $p<0.001$).[13] For locally advanced pancreatic cancer (LAPC), no RCT has been conducted, yet a favorable median OS with FOLFIRINOX of 24 months was found in a patient-level meta-analysis including 315 patients.[14] In comparison, the median OS with gemcitabine for LAPC ranged from 8 to 13 months in previous studies.[15] In the neoadjuvant setting, a patient-level meta-analysis of FOLFIRINOX for borderline resectable pancreatic cancer found a median OS of 22.2 months.[16] In recent years, FOLFIRINOX has become the most commonly used neoadjuvant chemotherapy in observational studies and ongoing phase II trials.[17]

Neoadjuvant therapy appears the most appropriate choice for most patients with localized disease. A direct comparison of FOLFIRINOX to gemcitabine-based chemoradiotherapy in the neoadjuvant setting has not yet been performed in a phase III trial. Our primary objective is to determine if total neoadjuvant FOLFIRINOX results in superior OS compared with neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine for patients with resectable and borderline resectable pancreatic cancer.

METHODS

Design

The PREOPANC-2 trial is a multicenter randomized phase III superiority trial, initiated by the Dutch Pancreatic Cancer Group (DPCG). A list of all participating centers is added as Supplementary file. Eligible patients are randomly assigned to either receive neoadjuvant FOLFIRINOX followed by surgery without adjuvant treatment (intervention; arm A) or neoadjuvant gemcitabine-based chemoradiotherapy followed by surgery and adjuvant gemcitabine (comparator; arm B) (Figure 1). Randomization in a 1:1 ratio is performed centrally using a web-based system, with stratification according to center and by resectability status (resectable vs. borderline resectable).

Study population

Patients are eligible if they have histologically or cytologically confirmed resectable or borderline resectable pancreatic cancer, without distant metastases. Resectability is assessed by a multiphase computed tomography (CT) scan within 4 weeks before randomization. A tumor without arterial (common hepatic artery, superior mesenteric artery, or celiac trunk) involvement and with venous (portal vein and/or superior mesenteric vein) involvement ≤90°

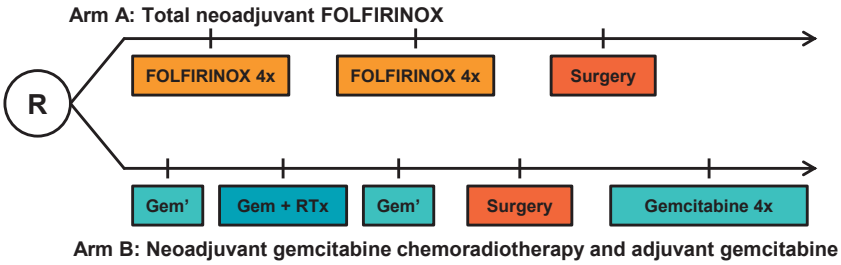

Figure 1. Treatment schedule

is considered resectable; a tumor with arterial involvement ≤90° and/or venous involvement >90° and ≤270° without occlusion is considered borderline resectable. Other inclusion criteria are a World Health Organization (WHO) performance status of 0 or 1, ability to undergo surgery, chemoradiotherapy, and chemotherapy, age ≥18 years, adequate bone marrow function (i.e. hemoglobin ≥ 6 mmol/l; leucocytes ≥ $3.0x10^9$/l; platelet count ≥ $100x10^9$/l), adequate renal function (e-GFR ≥ 50 ml/min), and written informed consent.

Exclusion criteria are prior treatment for pancreatic cancer, comorbidity or previous treatment precluding surgery, chemoradiotherapy, and chemotherapy, and pregnancy. Furthermore, patients are ineligible in case of previous malignancy, unless no evidence of disease and diagnosed more than 3 years before diagnosis of pancreatic cancer, or with a life expectancy of more than 5 years from date of inclusion. A past medical history of non-melanoma skin cancer, pancreatic neuroendocrine tumor (pNET) <2 cm, and gastrointestinal stromal tumor (GIST) <2 cm are not exclusion criteria. Lesions on chest CT that are too small to characterize are not considered metastatic disease.

Patients with hyperbilirubinemia may be randomized, but biliary drainage with a metal stent should be performed before start of neoadjuvant therapy if bilirubin is higher than 1.5 times the upper limit of normal.

Treatment

Arm A: total neoadjuvant FOLFIRINOX

Treatment in arm A starts with four cycles of neoadjuvant FOLFIRINOX, followed by a re-staging CT-scan. Patients with treatment response or stable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria are scheduled for an additional four cycles of neoadjuvant FOLFIRINOX. Restaging CT-scan is repeated and when appropriate followed by surgical exploration with intended resection. No adjuvant chemotherapy is scheduled. Cycles are repeated every two weeks (Figure 1). The dosages are identical to that of the phase III trial (PRODIGE 4/ACCORD 11 trial) for metastatic pancreatic can-

cer.[13] Starting with a modified regimen is allowed in patients older than 75 years or at the discretion of the treating physician, including withholding of the fluorouracil bolus or dose reduction of irinotecan and oxaliplatin to 80%. Fluorouracil dose should be adjusted or withheld in patients with a (partial) deficiency of the dihydropyrimidine dehydrogenase (DPD) enzyme. Primary prophylaxis with (Peg)Filgrastim (G-CSF) after every cycle of FOLFIRINOX is strongly recommended. Dose adjustments during treatment should be based on the maximum graded toxicity within the previous cycle.

Arm B: neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine

Treatment in arm B starts with three cycles of neoadjuvant gemcitabine, adding hypofractionated radiotherapy (36 Gy in 15 fractions during three weeks) to the second cycle. Gemcitabine is given weekly for 3 weeks (day 1, 8, and 15) in subsequent 4-week courses, at a dose of 1000 mg per square meter of body-surface area. The first and third cycle are modified to a 3-week course (day 1 and 8). After neoadjuvant therapy, a restaging CT-scan is performed and when appropriate followed by surgical exploration with intended resection. After resection, four cycles of adjuvant gemcitabine are administered (Figure 1). Adjuvant chemotherapy should start after the patient has recovered from surgery, but no later than 12 weeks after surgery.

Surgery: both groups

Patients are eligible for a surgical exploration if they have non-metastatic resectable or borderline resectable disease on restaging CT-scan of the chest and abdomen. Surgery is performed 3 to 6 weeks after completion of chemotherapy. Surgery starts with a staging laparoscopy (during the same surgical procedure), followed by the standard surgical exploration and resection depending on the location of the tumor. Postoperative complications are defined according to the Clavien-Dindo classification and definitions of post-pancreatic surgery complications (i.e. pancreatic fistula, delayed gastric emptying, and bleeding) according to the International Study Group of Pancreatic Surgery (ISGPS), recorded until 90 days after surgery.[18-21] If chemotherapy is discontinued because of toxicity or in case of local progression at restaging, patients may also proceed to surgical exploration. Patients with distant metastasis or unresectable disease at restaging or surgery continue with standard palliative care according to the national guideline.

Outcomes

The primary endpoint is OS by intention-to-treat, calculated from date of randomization. Secondary endpoints include progression-free survival, locoregional progression-free interval, distant metastases-free interval, resection rate, R0 resection rate, chemotherapy start rate, chemotherapy completion rate, toxicity, postoperative complications, radiologic response, tumor marker response (serum carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA)), pathologic response, and quality of life.

Progression-free survival is defined as survival without any locoregional progressive disease, distant metastases, recurrence, or secondary pancreatic cancer, calculated from the date of randomization. Death from any cause is also considered an event for this endpoint. Patients alive and free of these events will be censored at the last follow-up. For locoregional progression-free interval and distant metastases-free interval, only progression is considered an event and patients are censored at death or at the date of last follow-up for patients alive and free of these events. Resection is considered R0 if the distance between the inked margin and tumor cells is ≥1 mm.[22] Radiologic response is defined according to RECIST criteria version 1.1 comparing pre-randomization and restaging imaging after 4 and 8 cycles of FOLFIRINOX (arm A) or after chemoradiotherapy (arm B). These time points are also used to assess tumor marker response. Pathologic response is defined using the modified 3-tier histologic tumor regression grading (HTRG) scheme.[23]

Quality of life

Quality of life is assessed using questionnaires at multiple time points throughout the study and during follow-up: every 3 months in the first year, every 6 months in the second year, and annually in year 3 to 5.

Follow-up

After randomization, follow-up takes place every 3 months during the first 2 years and every 6 months during year 3 to 5. Follow-up CT-scans of the chest and abdomen combined with tumor marker analysis (CA 19-9 and CEA) take place at 6, 12, 18, and 24 months from randomization and yearly thereafter, until disease recurrence or up to a maximum of 5 years after randomization in patients without recurrence.

Data collection and management

The web-based software tool ALEA (FormsVision BV, Abcoude, The Netherlands) is used for randomization, clinical data collection, and central data management. Data management is coordinated by the Clinical Trial Center Rotterdam and data collection is performed by The Netherlands Comprehensive Cancer Organization (Integraal Kankercentrum Nederland). Data entry is done according to study specific data entry guidelines, promoting a uniform and standardized way of data entry and providing procedures for exceptions (i.e. missing values, unknowns). Data managers are trained in using the ALEA electronic case report form system prior to data entry start.

Monitoring

Throughout the trial, a trained, qualified, and independent monitor will periodically visit each participating center in order to randomly check compliance with the protocol, compliance with in- and exclusion criteria, proper implementation, conduct of Informed Consent procedures, Source Data Verification (i.e. crosscheck data in ALEA with patient dossier and vice versa), and reporting of serious adverse events (SAEs). Adverse events are graded

using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3.[24] SAE's defined as adverse events grade 3, 4, or 5 are collected. Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to the Competent Authority and Ethics Committee according to national regulation. In addition to the expedited reporting of SUSARs, the sponsor submits a safety report to the Competent Authority and Ethics Committee once a year during the clinical trial. An independent Data Safety Monitoring Board (DSMB) monitors the safety of the trial subjects by qualitative analyses of feasibility, accrual rate, mortality, and SAE'S after 50 and 100 patients have completed treatment.

Statistical analysis

Sample size calculation was performed for the primary endpoint of OS. The median OS of 17 months for the chemoradiotherapy arm of the PREOPANC-1 trial (preliminary results, 149/176 events) was used as estimate for the comparator arm.[25] In order to detect a hazard ratio (HR) of 0.70 with 80% power (2-sided significance level alpha=0.05), a total of 252 events (deaths) need to be observed. This HR translates into a median OS of about 24 months in the intervention arm, which is consistent with a large patient-level meta-analysis on neoadjuvant FOLFIRINOX treatment for borderline resectable pancreatic cancer.[16] The number of events is expected to be reached after inclusion of 368 eligible patients assuming an accrual rate of 10 patients per month with an accrual period of 3 years and an additional follow up of 1.5 years after the last patient has been randomized. Dropouts were rare in PREOPANC-1 and are therefore not accounted for. No interim analysis for the primary outcome is planned.

All main analyses will be performed by intention-to-treat. Cox regression analysis will be performed to calculate the hazard ratio and corresponding 95% confidence interval. Kaplan-Meier method will be used to estimate OS probabilities at appropriate time points, using the Greenwood estimate to construct corresponding 95% confidence intervals (CIs). A p-value of 0.05 is considered statistically significant.

Prespecified subgroup analyses include: patients that received at least one cycle of neoadjuvant treatment, patients that underwent a resection, patients that underwent an R0 resection, patients that completed all scheduled treatment, for the subgroups resectable and borderline resectable pancreatic cancer, patients younger vs. older than 65 years, patients with high and low CA 19-9, and patients with performance score 0 vs. 1.

DISCUSSION

Herein, we describe the protocol of the PREOPANC-2 trial, a multicenter randomized phase III trial conducted by the Dutch Pancreatic Cancer Group in the Netherlands, which was designed to compare the efficacy of two neoadjuvant treatment strategies for patients with

resectable and borderline resectable pancreatic cancer. This study builds upon the results of the previously conducted PREOPANC-1 trial.[11] If the PREOPANC-2 trial demonstrates superior OS for patients receiving neoadjuvant FOLFIRINOX, this treatment should be implemented as neoadjuvant treatment of choice for patients with resectable and borderline resectable pancreatic cancer.

Based on the available evidence, we believe that neoadjuvant therapy is the best approach for the majority of patients with both resectable and borderline resectable pancreatic cancer. This paradigm shift was confirmed by a recently published study by Cloyd and colleagues.[26] This meta-analysis of six RCTs comparing neoadjuvant treatment to upfront surgery for resectable and borderline resectable pancreatic cancer patients showed that neoadjuvant treatment significantly improved OS by intention-to-treat compared with upfront surgery (HR 0.73, 95% CI: 0.61 – 0.86). The pooled HR remained in favor of neoadjuvant treatment in all subgroup analyses, thus independent on anatomic classification (resectable: HR 0.73, 95% CI: 0.59 – 0.91; borderline resectable: HR 0.51, 95% CI: 0.28 – 0.93) or neoadjuvant treatment type (chemoradiotherapy: HR 0.77, 95% CI: 0.61 – 0.98; chemotherapy alone: HR 0.68, 95% CI: 0.54 – 0.87) In addition, neoadjuvant treatment increased the likelihood of an R0 resection (RR 1.51, 95% CI: 1.18 – 1.93).

Since the design of the PREOPANC-2 trial, two RCTs showed superiority of gemcitabine combined with capecitabine (ESPAC-4 trial) and modified (m)FOLFIRINOX (PRODIGE 24/CCTG PA.6 trial) when compared to gemcitabine monotherapy in the adjuvant setting.[5, 27] Based on these studies, both mFOLFIRINOX and gemcitabine with capecitabine have become preferred regimens in the adjuvant setting for patients with adequate performance status. It remains unclear what the best adjuvant regimen is after neoadjuvant chemoradiotherapy and resection.

Trial status

The PREOPANC-2 trial is a nationwide multicenter randomized phase III trial, conducted in 15 centers that provide multidisciplinary treatment for pancreatic cancer throughout the Netherlands. The study opened for accrual on June 5th, 2018. At the time of submission of this paper, all centers were actively recruiting and treating patients. A total of 294 patients were included in the trial on September 1st, 2020.

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SUPPLEMENTARY FILES

List of participating centers:

Amphia Hospital, Breda, The Netherlands
Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
Amsterdam UMC, VU University, Amsterdam, The Netherlands
Catharina Hospital, Eindhoven, The Netherlands
Erasmus MC University Medical Center, Rotterdam, The Netherlands
Isala Hospital, Zwolle, The Netherlands
Jeroen Bosch Hospital, Den Bosch, The Netherlands
Leiden University Medical Center, Leiden, The Netherlands
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PART III

RADIOTHERAPY AND ADJUVANT TREATMENT OF PANCREATIC CANCER

CHAPTER 10

The added value of radiotherapy following neoadjuvant FOLFIRINOX for resectable and borderline resectable pancreatic cancer: a systematic review and meta-analysis.

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ABSTRACT

Background

The added value of radiotherapy following neoadjuvant FOLFIRINOX chemotherapy in patients with resectable or borderline resectable pancreatic cancer ((B)RPC) is unclear. The objective of this meta-analysis was to compare outcomes of patients who received neoadjuvant FOLFIRINOX alone or combined with radiotherapy.

Methods

A systematic literature search was performed in Embase, Medline (ovidSP), Web of Science, Scopus, Cochrane, and Google Scholar. The primary endpoint was pooled median overall survival (OS). Secondary endpoints included resection rate, R0 resection rate, and other pathologic outcomes.

Results

We included 512 patients with (B)RPC from 15 studies, of which seven were prospective nonrandomized studies. In total, 351 patients (68.6%) were treated with FOLFIRINOX alone (8 studies) and 161 patients (31.4%) were treated with FOLFIRINOX and radiotherapy (7 studies). The pooled estimated median OS was 21.6 months (range 18.4 – 34.0) for FOLFIRINOX alone and 22.4 months (range 11.0 – 37.7) for FOLFIRINOX with radiotherapy. The pooled resection rate was similar (71.9% vs. 63.1%, $p = 0.43$) and the pooled R0 resection rate was higher for FOLFIRINOX with radiotherapy (88.0% vs. 97.6%, $p = 0.045$). Other pathological outcomes (ypN0, pathologic complete response, perineural invasion) were comparable.

Conclusion

In this meta-analysis, radiotherapy following neoadjuvant FOLFIRINOX was associated with an improved R0 resection rate as compared with neoadjuvant FOLFIRINOX alone, but a difference in survival could not be demonstrated. Randomized trials are needed to determine the added value of radiotherapy following neoadjuvant FOLFIRINOX in patients with (B)PRC.

INTRODUCTION

Pancreatic ductal adenocarcinoma is one of the most aggressive solid tumors.[1] Although it is only the 12th most common cancer globally, it is one of the leading causes of cancer-related death in developed countries.[2] Around 20-30% of patients have resectable or borderline resectable pancreatic cancer ((B)RPC) at diagnosis. In the most recent National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines, neoadjuvant treatment is recommended for patients with BRPC. For patients with resectable tumors, neoadjuvant treatment is considered an alternative to upfront surgery, especially in patients with biochemical findings suggesting systemic disease (e.g., elevated tumor markers).[3-5]

In the past two decades, numerous studies on neoadjuvant chemoradiotherapy for pancreatic cancer have been performed.[6,7] The rationale behind adding radiotherapy to neoadjuvant chemotherapy is to improve locoregional control by sterilizing vessel margins and enhancing the likelihood of a radical (R0) resection, thereby potentially preventing or postponing locoregional recurrence. Indeed, before the era of FOLFIRINOX (5-fluorouracil with leucovorin, irinotecan, and oxaliplatin), several phase 2 and phase 3 studies of neoadjuvant radiotherapy combined with single- or double-agent chemotherapy have consistently shown high R0 resection rates.[8-13]

Multi-drug regimens including FOLFIRINOX and gemcitabine with nab-paclitaxel have shown superiority to gemcitabine in randomized trials in the metastatic and adjuvant settings.[14-16] Based on extrapolation of these results, FOLFIRINOX is commonly used in the neoadjuvant setting in many centers worldwide nowadays. Two patient-level meta-analyses of observational studies in patients with locally advanced pancreatic cancer (LAPC) and BRPC treated with FOLFIRINOX ± radiotherapy indeed showed promising results.[17,18] Due to limited high-level evidence, current guidelines do not draw final conclusions on whether these multi-drug regimens should be combined with radiotherapy.[3-5] The role of neoadjuvant radiotherapy in addition to neoadjuvant FOLFIRINOX in patients with (B)RPC remains unclear. Published prospective and retrospective observational studies on this topic are small, precluding definitive conclusions on outcomes.

The aim of this systematic review and meta-analysis was to compare outcomes of (B)RPC patients who received neoadjuvant FOLFIRINOX alone versus FOLFIRINOX with neoadjuvant radiotherapy.

METHODS

Search Strategy

This systematic review and meta-analysis was performed according to the PRISMA guidelines.[19] An extensive librarian-led literature search of Embase, MEDLINE (via OvidSP), Web-of-Science, Scopus, Cochrane Central, and Google Scholar was performed on December 18, 2020. The search strategy included the following terms: "FOLFIRINOX", "folinic acid", "fluorouracil", "irinotecan", "oxaliplatin", "drug combination", "pancreatic cancer", and relevant variants. A full description of the search strategy is outlined in Suppl. Table 1. No restrictions on publication dates were applied.

Eligibility

Eligible studies reported outcomes for treatment-naïve patients with resectable or borderline resectable pancreatic cancer ((B)RPC) as defined within each study, and whom were either treated with neoadjuvant FOLFIRINOX alone (FOLFIRINOX alone group) or with neoadjuvant FOLFIRINOX followed by any type of radiotherapy (FOLFIRINOX with radiotherapy group). In order to adequately compare the treatment strategies, additional eligibility criteria were applied. Prospective studies were eligible if patients were scheduled to receive either FOLFIRINOX alone or FOLFIRINOX combined with radiotherapy. Retrospective studies were eligible as FOLFIRINOX with radiotherapy study if at least 90% of patients received radiotherapy following FOLFIRINOX, and studies were eligible as FOLFIRINOX alone study if less than 10% of patients received additional radiotherapy. Reviews, letters to the editor, case reports, conference abstracts, and articles written in language other than English were excluded.

Selection Procedure and Data Collection

After removal of duplicates, two authors (QJ and IK) independently screened the abstracts for eligibility. Full-text assessment was performed for all studies that met the inclusion criteria. Articles were excluded if none of the primary or secondary outcomes were reported or if the same cohort was presented in another study. Discordant judgments were addressed through discussion until consensus was achieved. Data were extracted from the articles separately by the first and second author using a standardized data extraction form.

Methodological Assessment

Risk of bias was assessed using the Critical Appraisal Skill Program (CASP) appraisal system, which is designed to systematically assess the methodological quality of studies.[20] Publication bias was assessed using a funnel plot.[21]

Statistical Analysis

The primary outcome was median OS, as reported by the included articles or extracted from the survival curves. The weighted pooled estimate of median OS was calculated using

Table 1. Study characteristics

Study (Reference)	Country	Evidence	Inclusion period	Total [a]	Total (B) RPC + FFX	Definition resectability	Radiotherapy, No. (%)	Chemotherapy		Radiotherapy			Adjuvant therapy, No. (%)
								Regimen	Neoadj. cycles, median (range)	Type	CRT regimen	Dose, fractions	
FOLFIRINOX alone													
Barenboim[22]	Israel	Retrospective	2008-2017	100	23	NCCN	2 (8.7)	FOLFIRINOX	8 (5 - 14)	-	-	-	16 (70.0)
Dhir[36]	United States	Retrospective	2011-2017	193	73 [b]	NCCN	0 (0.0)	FOLFIRINOX	3 (IQR 3 - 4)	-	-	-	54 (73.9)
Okada[23]	Japan	Prospective	2014-2015	10	10	NCCN	0 (0.0)	mFOLFIRINOX [e]	6 (4 - 8)	-	-	-	8 (80.0)
Tinchon[24]	Austria	Prospective	2010-2012	12	10	AHPBA/ SSO/SSAT	0 (0.0)	FOLFIRINOX	4 (4 - 6)	-	-	-	0
De Marsh[34]	United States	Prospective	2013-2015	21	21 [c]	NCCN	0 (0.0)	mFOLFIRINOX	4 (NR - 4)	-	-	-	15 (71.4)
Kim[35]	United States	Retrospective	2011-2015	26	18 [d]	NCCN	0 (0.0)	FOLFIRINOX	9 (4 - 12)	-	-	-	7 (38.9)
Medrano[25]	France	Retrospective	2011-2018	139	121	NCCN	0 (0.0)	FOLFIRINOX	4 (4 - 16)	-	-	-	76 (62.8)
Yoo[26]	South Korea	Retrospective	2013-2017	199	75	NCCN	0 (0.0)	(m)FOLFIRINOX	7 (1 – 41)	-	-	-	NR
Total				700	351		2 (0.6)		5 (3 - 9)				176 (58.2)
FOLFIRINOX with radiotherapy													
Christians[27]	United States	Retrospective	2010-2012	18	18	MCW	18 (100.0)	FOLFIRINOX	4 (3 - 8)	CRT	Gemcitabine/ Capecitabine	50.4 Gy, 28	1 (5.6)
Katz[28]	United States	Prospective	2013-2014	22	22	ALLIANCE	21 (95.5)	mFOLFIRINOX	4 (NR)	CRT	Capecitabine	50.4 Gy, 28	10 (45.5)
Murphy[29]	United States	Prospective	2012-2016	48	48	NR	44 (91.7)	FOLFIRINOX	8 (NR)	CRT	Capecitabine/5-Fluorouracil	25.0 Gy, 5 / 30.0 Gy, 10 / 50.4 Gy, 28 [g]	5 (10.4)
Shaib[30]	United States	Prospective	NR	13	13	ALLIANCE	12 (92.3)	mFOLFIRINOX	4 (NR)	SBRT	-	36 - 45 Gy, 3	0
Tran[31]	United States	Prospective	2011-2017	25	25	NCCN	19 (76.0)	(m)FOLFIRINOX	6 (NR)	CRT	Gemcitabine	50.0 Gy, 25	0
Bolton[32]	United States	Retrospective	2008-2015	195	31	AHPBA/ SSO/SSAT	28 (90.3) [f]	FOLFIRINOX	4 (3 - 5)	CRT	5-Fluorouracil	NR	NR
Mahaseth[33]	United States	Retrospective	2010-2012	60	4	NR	4 (100.0)	mFOLFIRINOX	NR (2 - 6)	CRT	Gemcitabine/ Capecitabine	NR	NR
Total				381	161		146 (90.7)		4 (4 - 8)				16 (6.0)

[a] Total patients included in study, [b] Including upfront resectable pancreatic cancer (n=15), [c] All upfront resectable pancreatic cancer, [d] Including upfront resectable pancreatic cancer (n = 5), [e] Modified FOLFIRINOX without bolus 5-fluorouracil and leucovorin, and with reduced dose of irinotecan, [f] Estimation based on percentage mentioned in manuscript, [g] Depending on evaluation by multidisciplinary team; short-course chemotherapy with protons or photons for clearly resectable disease, long-course chemoradiotherapy using intensity modulated radiotherapy in case of persistent vascular involvement. Abbreviations: *AHPBA/SSO/SSAT* Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract, *(B)RPC* resectable or borderline resectable pancreatic cancer, *CRT* chemoradiotherapy, *FFX* FOLFIRINOX, *MCW* Medical College of Wisconsin, *MDACC* MD Anderson Cancer Center, *NCCN* National Comprehensive Cancer Network, *No.* number, *NR* not reported, *Neoadj.* Neoadjuvant, *SBRT* stereotactic body radiation therapy.

the formula proposed in a previous meta-analysis, with a study-specific weight function based on the number of patients of interest.[6] For the primary analysis, the median OS by intention to treat was used (e.g., excluding studies only reporting outcomes for patients who underwent a resection). Furthermore, the pooled weighted median OS in patients who ultimately underwent resection was calculated. For studies reporting the latter outcome from time of resection, the median OS time was increased with the estimated duration of neoadjuvant treatment based on the reported median number of cycles plus 1 month as estimated time between the end of chemotherapy and surgery date. Confidence intervals for median survival estimates were not calculable and therefore the range of medians was provided.

Secondary outcomes were progression free survival (PFS) in patients who underwent resection, resection rate, adjuvant therapy rate, and postoperative outcomes including R0 resection rate (i.e. among patients who underwent resection and among all patients who started neoadjuvant treatment), ypN0 rate, perineural invasion rate, and pathologic complete response rate. For the adjuvant therapy rate, all patients from prospective studies were included in the denominator, since it is likely that this outcome will be known and reported for prospective studies. Patients from retrospective studies were only included in the denominator for the adjuvant therapy rate if this outcome was reported, since the lack of reporting may be due to information bias. Studies only reporting outcomes for patients who ultimately underwent resection were excluded for calculation of the pooled resection rate, yet included for the pooled R0 resection rate and other pathologic outcomes. Random-effects rather than fixed-effects models were used for all pooled analyses to account for potential between-study heterogeneity and I^2 was used as a measure of consistency across studies. Pooled analyses were performed using the meta package for R 3.5.0. All tests were two-sided and a p-value less than .05 was considered statistically significant.

RESULTS

Included Studies

The literature search identified 6,160 records. After removal of duplicates, 2,947 records were screened for eligibility. Based on title and abstract, 97 studies were selected for full-text assessment of which 15 fulfilled all inclusion criteria (Figure 1). The reason for exclusion based on full-text assessment is outlined in Supplementary Table 3.

Table 1 shows the study characteristics of the 15 included studies. In total, 1081 patients with pancreatic cancer were included, of whom 512 met eligibility criteria based on stage and treatment. Eight studies included 351 patients (68.6%) who received neoadjuvant FOLFIRINOX alone and 7 other studies included 161 patients (31.4%) who received neoadjuvant FOLFIRINOX followed by radiotherapy. Twelve studies reported outcomes for BRPC patients

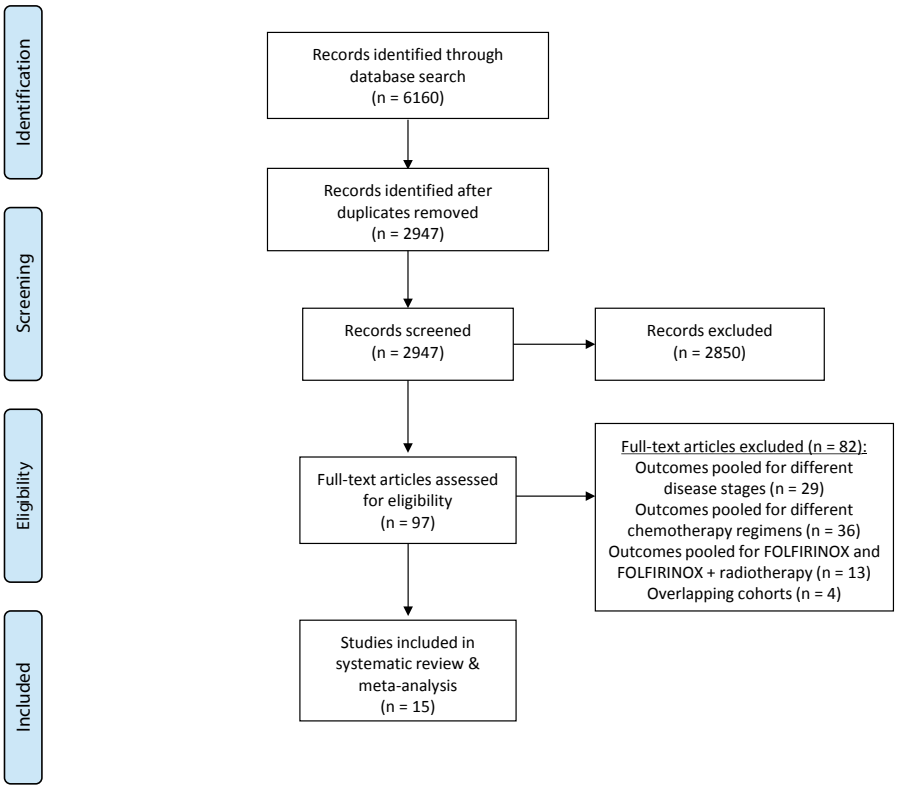

Figure 1. PRISMA flow chart showing selection of articles for systematic review and meta-analysis

specifically.[22-33] Three studies also or solely reported outcomes for patients with resectable pancreatic cancer.[34-36] In total, the FOLFIRINOX alone studies included 310 patients (88.3%) with BRPC and 41 patients (11.7%) with resectable pancreatic cancer, whereas all 161 patients (100.0%) in the FOLFIRINOX with radiotherapy studies had BRPC. Four studies included only patients who underwent a resection after neoadjuvant treatment, [25,32,35,36] while the other 11 studies included all patients who started neoadjuvant treatment.

Methodological Assessment

Seven studies were prospective nonrandomized studies and 8 studies had a retrospective design (Table 1). No randomized controlled trials were identified. Results of the methodological assessment and funnel plot assessing publication bias are shown in the supplementary section. No study was assessed to contain high risk of bias (Suppl. Table 2). Based on the 8 studies reporting the primary outcome, there was no convincing evidence of publication

bias, though 2 studies may be considered an outlier (Suppl. Figure 1). Since there were no randomized studies, confounding by indication cannot be ruled out.

Chemotherapy Regimens and Radiotherapy

Details of the chemotherapy and radiotherapy regimens are presented in Table 1. FOLFIRINOX was administered in 9 studies, modified FOLFIRINOX (mFOLFIRINOX) in 5 studies, and 2 studies administered both [(m)FOLFIRINOX]. Dose modifications consisted of the exclusion of 5-fluorouracil bolus in all 7 studies, 2 studies decreased the dose of irinotecan,[23,37] and one study also left out leucovorin.[23] The median number of administered neoadjuvant FOLFIRINOX cycles ranged from 3 to 9 cycles. Adjuvant therapy was administered to 176 patients (58.2%) in the FOLFIRINOX only group (6 studies) and 16 patients (6.0%) in the FOLFIRINOX with radiotherapy group (3 studies). Additional single-agent chemotherapy as radiosensitizer was administered to 133 patients (82.6%) in the FOLFIRINOX with radiotherapy group (6 studies).

In the FOLFIRINOX with radiotherapy group, 146 patients (90.7%) received radiotherapy following FOLFIRINOX, compared with 2 patients (0.6%) in the FOLFIRINOX alone group. Patients were treated with radiation and concurrent chemotherapy (CRT) in 6 studies, whilst a dose-escalating stereotactic body radiation therapy (SBRT) scheme was used in one study. Total administered dose ranged from 25.0 to 50.4 Gy.

Survival Analysis

The pooled median OS for all studies was 22.0 months (range 11.0 – 37.7). By treatment group, the estimated median OS was 21.6 months (range 18.4 – 34.0) in the FOLFIRINOX only group (3 studies) versus 22.4 months (range 11.0 – 37.7) in the FOLFIRINOX with radiotherapy group (5 studies) (Table 2). In a sensitivity analysis excluding one study in which a dose-escalating SBRT regimen rather than chemoradiotherapy was used, the median OS for the FOLFIRINOX with radiotherapy group (4 studies) was 25.4 months (range 15.8 – 37.7).

Eight studies reported the median OS specifically for those patients who underwent a resection after neoadjuvant treatment. For this subgroup, the estimated median OS was 40.4 months (range 34.2 – 45.0) in the FOLFIRINOX alone group (5 studies) versus 33.5 months (range 23.1 – 42.5) in the FOLFIRINOX with radiotherapy group (3 studies). Median OS was not reached in four studies.

Median PFS in patients who underwent a resection after neoadjuvant treatment is shown in Table 2. The pooled estimated median PFS was 22.1 (range 13.7 – 28.0) in the FOLFIRINOX alone group (4 studies) versus 28.4 months (range 18.0 – 48.6) in the FOLFIRINOX with radiotherapy group (4 studies).

Table 2. Survival outcomes for (B)RPC patients treated with (m)FOLFIRINOX as first-line treatment with or without additional radiotherapy

Study (Reference)	No. of (B)RPC patients	Median FU, months	Baseline for OS and PFS calculations	Median OS, months (95% CI)		Median PFS, months (95% CI)
				All patients	*Resected patients*	*Resected patients*
FOLFIRINOX alone						
Barenboim[22]	23	17.0	Start treatment	27.9 (NR)	34.3 (NR)	13.7 (NR)
Dhir[36]	73 [a]	35.8	Diagnosis	#	38.7 (25.7-50.6)	NR
Okada[23]	10	NR	NR	NR	NR	NR
Tinchon[24]	10	15.4	Start treatment	not reached	not reached	not reached
De Marsh[34]	21 [b]	27.7	Start treatment	34 (12.3-57.6)	35.5 (15.0-59.2)	15.2 (10.5 - 24.1)
Kim[35]	13 [c]	41.4 [c]	Start treatment	#	34.2 (NR) [c]	19.6 (NR) [c]
Medrano[25]	121	mean 39	Diagnosis	#	45.0 (NR)	28.0 (NR)
Yoo[26]	75	40.3	Start treatment	18.4 (16.1 – 20.8)	NR	NR
Estimated Median Survival	351	33.3		21.6 (range 18.4 – 34.0)	40.4 (range 34.2 – 45.0)	22.1 (range 13.7 – 28.0)
FOLFIRINOX with radiotherapy						
Christians[27]	18	22.0	Diagnosis	15.8 (NR) [d]	not reached	NR
Katz[28]	22	NR	Trial registration	21.7 (15.7 - not reached)	23.1 (NR) [d]	At 12 mo: 53% (33 - 86); At 18 mo: 40% (19 - 84)
Murphy[29]	48	18.0	Start treatment	37.7 (19.4 - not reached)	not reached	48.6 (14.4 - not reached)
Shaib[30]	13	18.0	Trial registration	11.0 (5.8 - not reached)	not reached (9.3 - not reached)	29.6 (5.1 - not reached)
Tran[31]	25	NR	Trial registration	24.4 (12.6 - 40.0)	37.1 (15.4 - not reached)	21.6 (8.2 - 31.7)
Bolton[32]	31	NR	Resection	#	42.5 (NR) [e]	NR
Mahaseth[33]	4	NR	Start treatment	NR	NR	NR
Estimated Median Survival	161	18.8		22.4 (range 11.0 – 37.7)	33.5 (range 23.1 – 42.5)	28.4 (range 18.0 – 48.6) [f]

[a] Including upfront resectable pancreatic cancer (n=15), [b] All upfront resectable pancreatic cancer, [c] Survival outcomes for subgroup of BRPC patients specifically, [d] Estimation based on Kaplan Meier results, [e] Based on Kaplan Meier results of BRPC patients who received 4 or more cycles of neoadjuvant FOLFIRINOX, with 3 months added for duration of neoadjuvant treatment and time to surgery, [f] Pooled estimate including a median PFS of 18 months for Katz et al., since the median PFS certainly did not exceed 18 months. # Study only included patients who underwent resection. Abbreviations: *(B)RPC* resectable or borderline resectable pancreatic cancer, *CI* confidence interval, *FU* follow-up, *No.* number, *NR* not reported, *OS* overall survival, *PFS* progression free survival

Surgical and pathological outcomes

Surgical and pathological outcomes are reported in Table 3. Forest plots of pooled resection and R0 resection rates are shown in Figures 2 and 3, respectively. The pooled resection rate was 71.9% (79/139 patients, 95% CI: 49.9% – 86.8%) in the FOLFIRINOX alone group (5 studies) versus 63.1% (82/130 patients, 95% CI: 54.5 – 70.9) in the FOLFIRINOX with radiotherapy group (6 studies) (I^2 = 61%, p = 0.43) (Figure 2).

Among the patients who underwent a resection, the pooled R0 resection rate was 88.0% (210/256 patients, 95% CI: 75.2% – 94.7%) in the FOLFIRINOX alone group (6 studies) versus 97.6% (80/82 patients, 95% CI: 90.8% – 99.4%) in the FOLFIRINOX with radiotherapy group (6 studies) (I^2 = 69%, p = 0.045) (Figure 3a). The pooled R0 resection rate in all patients starting with FOLFIRINOX was 79.9% (210/266 patients, 95% CI: 71.9% – 86.1%) in the FOLFIRINOX alone group (6 studies) versus 61.5% (80/130 patients, 95% CI: 52.9% – 69.5%) in the FOLFIRINOX with radiotherapy group (6 studies) (I^2 = 54%, p = 0.002) (Figure 3b).

The pooled ypN0 rate was 52.5% (99/232 patients, 95% CI: 34.0% – 70.4%) in the FOLFIRINOX alone group (4 studies) versus 67.1% (55/82 patients, 95% CI: 56.2% – 76.4%) in the FOLFIRINOX with radiotherapy group (6 studies) (I^2 = 73%, p = 0.18). The pooled perineural invasion rate was 75.1% (178/232 patients, 95% CI: 63.9% – 83.7%) in the FOLFIRINOX alone group (4 studies) versus 72.5% (29/40 patients, 95% CI: 56.8% – 84.1%) in the FOLFIRINOX with radiotherapy group (2 studies) (I^2 = 23%, p = 0.77). Pathologic complete response was rare, considering a pooled estimate of 3.9% (10/256 patients, 95% CI: 2.1% – 7.1%) in the FOLFIRINOX alone group (6 studies) versus 2.9% (6/111 patients, 95% CI: 0.3% – 21.2%) in the FOLFIRINOX with radiotherapy group (6 studies) (I^2 = 33%, p = 0.80).

DISCUSSION

In this systematic review and meta-analysis including 512 patients with (B)RPC, no difference in survival could be demonstrated between treatment with neoadjuvant FOLFIRINOX with radiotherapy or neoadjuvant FOLFIRINOX alone. The pooled resection rate was also similar, but the pooled R0 resection rate was higher for patients receiving FOLFIRINOX with radiotherapy. These findings support the hypothesis that systemic control remains the most important factor for survival in pancreatic cancer in the era of neoadjuvant FOLFIRINOX. However, these results should be interpreted with caution, since they are based on non-randomized comparisons of small studies. Considering the small subset of patients with upfront resectable disease, the results of our study are mostly applicable to BRPC patients. A patient-level meta-analysis including 283 BRPC patients who received neoadjuvant FOLFIRINOX found a similar median OS of 22.2 months and a similar resection rate of 67.8%.[18]

Table 3. Surgical and pathological outcomes for (B)RPC patients treated with (m)FOLFIRINOX as first-line treatment, with or without additional radiotherapy

Study (Reference)	No. of (B)RPC patients	Resection rates		ypN0, No. (%) [f]	Perineural invasion, No. (%) [f]	Pathological complete response, No. (%) [f]
		Resection, No. (%)	R0 resection, No. (%) [e]			
FOLFIRINOX alone						
Barenboim[22]	23	20 (87.0)	20 (100.0)	16 (80.0) [d]	13 (65.0) [d]	3 (15.0) [d]
Dhir[36]	73 [a]	#	62 (84.9)	32 (43.8)	57 (78.1)	3 (4.1)
Okada[23]	10	7 (70.0)	5 (71.4)	NR	NR	0
Tinchon[24]	10	8 (80.0)	NR	NR	NR	NR
De Marsh[34]	21 [b]	17 (81.0)	16 (94.1)	NR	NR	1 (5.9)
Kim[35]	18 [c]	#	17 (94.4)	11 (61.1) [e]	10 (55.6) [e]	0
Medrano[25]	121	#	90 (74.4)	40 (33.1)	98 (81.0)	3 (2.5)
Yoo[26]	75	27 (36.0)	NR	NR	NR	NR
Total	276	79 (71.9)	210 (88.0)	99 (52.5)	178 (75.1)	10 (3.9)
FOLFIRINOX with radiotherapy						
Christians[27]	18	12 (66.7)	12 (100.0)	10 (83.3)	NR	0
Katz[28]	22	15 (68.0)	14 (93.3)	10 (66.7)	NR	2 (13.3)
Murphy[29]	48	32 (66.7)	31 (96.9)	20 (62.5)	22 (68.8)	0
Shaib[30]	13	8 (61.5)	8 (100.0)	7 (87.5)	7 (87.5)	0
Tran[31]	25	13 (52.0)	13 (100.0)	6 (46.2)	NR	0
Bolton[32]	31	#	NR	NR	NR	4 (12.9)
Mahaseth[33]	4	2 (50.0)	2 (100.0)	2 (100.0)	NR	NR
Total	161	82 (63.1)	80 (97.6)	55 (67.1)	29 (72.5)	6 (2.9)

[a] Including upfront resectable pancreatic cancer (n=15), [b] All upfront resectable pancreatic cancer, [c] Including upfront resectable pancreatic cancer (n=5), [d] Estimated based on percentage of pooled results for borderline resectable (n=20) and locally advanced pancreatic cancer (n=3), [e] Estimated based on percentage of pooled results for resectable and borderline resectable (n=18) and locally advanced pancreatic cancer (n=4), [f] Percentage of patients who underwent a resection. # Studies included only patients who underwent a resection.
Abbreviations: *(B)RPC* resectable or borderline resectable pancreatic cancer, *No.* number, *NR* not reported, *ypN0* absence of positive lymph nodes

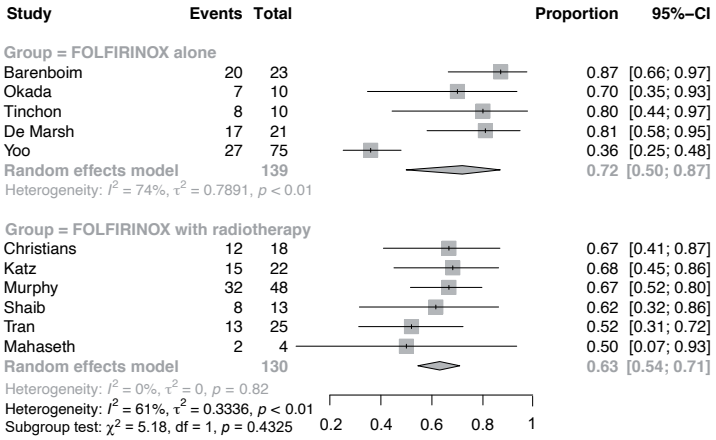

Figure 2. Forest plot showing resection rates in studies with FOLFIRINOX alone versus FOLFIRINOX and radiotherapy: (p = 0.43)
P-value was calculated using a two-sided Q-test and a random effects model. *CI* confidence interval, *df* degrees of freedom.

The pooled resection rate was comparable between the treatment groups. In contrast, the pooled R0 resection rate among patients undergoing resection, which is most commonly reported in the literature, was superior for the FOLFIRINOX with radiotherapy group. This is consistent with a large retrospective multicentric cohort study from France including BRPC and LAPC patients who underwent a resection after induction FOLFIRINOX combined with chemoradiotherapy (n = 102) or FOLFIRINOX alone (n = 101). This cohort showed higher R0 (89% vs. 76%, p = 0.017) and ypN0 (77% vs. 49%, p < 0.001) resection rates in patients who received both FOLFIRINOX and chemoradiotherapy. In addition, patients with additional chemoradiotherapy had significantly longer OS (median OS: 57.8 vs. 35.5 months; p = 0.007), which could not be demonstrated in the current meta-analysis.[38] This may be explained by the inclusion of LAPC patients in the French study.

Focusing on chemotherapy regimens other than FOLFIRINOX with or without radiotherapy, a large Japanese multicentric cohort study included a prospensity matched analysis of 376 patients with BRPC who received chemotherapy with radiotherapy (mostly gemcitabine- or S1-based chemoradiotherapy) or neoadjuvant chemotherapy alone (mostly gemcitabine + S1). This study showed a higher ypN0 rate (62.2% vs. 34.0%; p < 0.001) and lower locoregional recurrence rate (20.4% vs. 44.6%; p = 0.002) in the chemotherapy with radiotherapy group, yet no difference in R0 resection rate (87.2% vs. 84.1%, p = 0.50) and survival (median OS: 22.5 vs. 29.2 months; p = 0.130) could be demonstrated.[39]

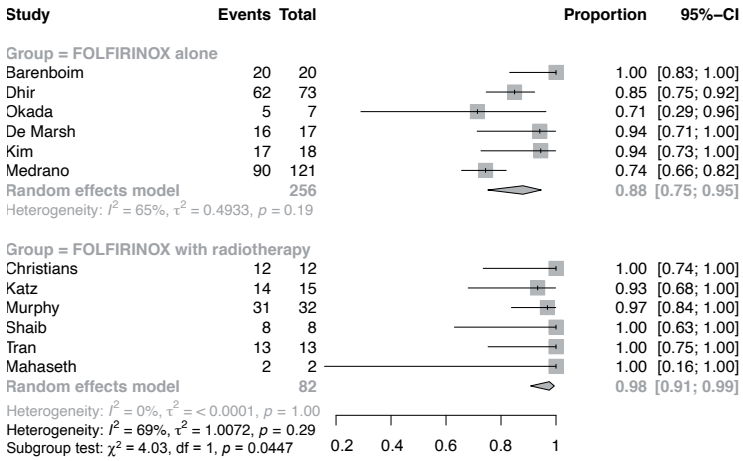

Figure 3a. Forest plot showing R0 resection rates among patients who underwent a resection in studies with FOLFIRINOX alone versus FOLFIRINOX and radiotherapy: (p = 0.04)
P-value was calculated using a two-sided Q-test and a random effects model. *CI* confidence interval, *df* degrees of freedom.

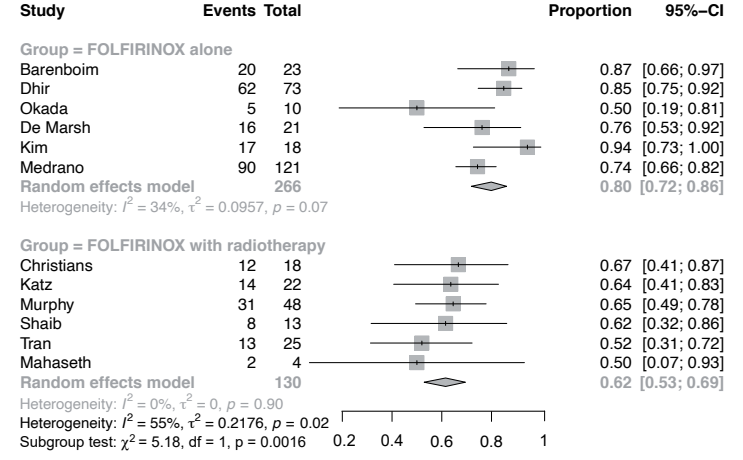

Figure 3b. Forest plot showing R0 resection rates among all patients starting with neoadjuvant treatment in studies with studies with FOLFIRINOX alone versus FOLFIRINOX and radiotherapy: (p < 0.01)
P-value was calculated using a two-sided Q-test and a random effects model. *CI* confidence interval, *df* degrees of freedom.

No difference in pathological complete response rate could be demonstrated. However, a clinically relevant impact of radiotherapy after FOLFIRINOX on pathologic response cannot be ruled out due to the small number of patients. Two recent retrospective studies found a pathologic complete response rate ranging from 6.8 to 16.3% after systemic chemotherapy and radiotherapy.[40,41] A large study from the National Cancer Database showed that preoperative radiation was independently associated with a pathologic complete response on multivariable analysis.[42] However, it has not been shown that complete response for a few patients translates into an improvement of survival for all patients who receive neoadjuvant radiation.

Patients in the FOLFIRINOX alone studies have clearly received more adjuvant therapy as compared with patients in the FOLFIRINOX with radiotherapy studies. On the other hand, additional single-agent chemotherapy was used as radiosensitizer in 6 out of the 7 FOLFIRINOX with radiotherapy studies. Since both the neoadjuvant chemoradiotherapy and adjuvant therapy mostly included single-agent chemotherapy regimens, the total systemic treatment may have been comparable in the two groups, yet this remains uncertain.

SBRT is a new development in the field of radiotherapy.[43] By applying image guidance, the tumor can be followed during the radiation (tracking) or radiation can be interrupted when the tumor moves out of the beam (gating). This allows high doses of radiation in a very short period of time with less toxicity than conventional chemoradiotherapy. Several systematic reviews and large epidemiological studies found good results in LAPC.[44-46] Moreover, a recent study in the National Cancer Data Base (NCDB) of over 2000 patients with resected upfront resectable pancreatic cancer who received neoadjuvant multi-agent chemotherapy without radiotherapy (n=1355), with conventional radiotherapy (n=552), or with SBRT (n=175), showed superior outcomes for the patients receiving SBRT.[47] In the propensity matched analysis, SBRT was associated with a significantly better survival than chemotherapy alone (HR 0.65, 95% CI: 0.47 – 0.90, $p = 0.01$) and chemotherapy plus conventional radiotherapy (HR 0.53, 95% CI: 0.37 – 0.76, $p = 0.001$). Furthermore, SBRT was associated with a better R0 resection rate (chemotherapy alone 81% vs. chemotherapy + conventional radiotherapy 86% vs. chemotherapy + SBRT 91%; $p = 0.0001$) and pathologic complete response rate (respectively 2.2% vs. 4.9% vs. 6.1%; $p = 0.0002$).[47] In line with the current study, this suggests that future randomized studies of neoadjuvant treatment should focus on modern, multi-agent chemotherapy in combination with SBRT rather than conventional radiotherapy.

Another new development in the field of radiotherapy for pancreatic cancer is combining radiotherapy with immunotherapeutic agents.[48,49] Both *in vitro* and *in vivo* studies have shown that radiotherapy may act as an “in situ vaccine” by increasing the expression of cell surface receptors such as major histocompatibility complex class I (MHC-I) and by increasing tumor antigen presentation.[50-52] However, due to the immune suppressive tumor microenvironment

in pancreatic cancer, the anti-tumor immune response induced by radiotherapy alone may not be sufficient.[53] When combined, the increased release of tumor specific antigens by radiotherapy may enhance the efficacy of immotherapeutic drugs, potentially resulting in a robust and targeted anti-tumor immune response.[48,54]

Four ongoing randomized controlled trials may provide better insights in the individual contributions of systemic chemotherapy and radiotherapy for BRPC patients.[55-57] In the ALLIANCE trial A021501, 134 BRPC patients are randomized to neoadjuvant mFOLFIRINOX (8 cycles) or neoadjuvant mFOLFIRINOX (7 cycles) plus SBRT, with surgery and adjuvant FOLFOX in both arms.[55] In the French PANDAS-PRODIGE 44 trial (NCT02676349), 90 BRPC patients are randomized to neoadjuvant mFOLFIRINOX (8 cycles) or neoadjuvant mFOLFIRINOX (8 cycles) with subsequent capecitabine-based chemoradiotherapy, followed by surgery and adjuvant gemcitabine or 5-FU in both arms. Results of these two studies are expected in 2021. The Chinese BRPCNCC-1 trial is a three-arm trial that randomizes 150 BRPC patients to neoadjuvant gemcitabine plus nab-paclitaxel alone, neoadjuvant gemcitabine plus nab-paclitaxel with SBRT, or neoadjuvant S1 plus nab-paclitaxel with SBRT, with expected results in 2022.[56] Finally, the Dutch PREOPANC-2 trial has completed accrual of 368 (B)RPC patients who were randomized to total neoadjuvant FOLFIRINOX (8 cycles) or neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine, with results expected in 2022.[57]

Some limitations should be taken into account when interpreting the results of our study. First, no randomized trial was included that directly compared FOLFIRINOX with or without radiotherapy. Half of the studies were retrospective studies with potential confounding by indication and information bias. Furthermore, many studies included only small numbers of patients with (B)RPC. Together, these factors have limited the quality of the included studies. Second, our primary endpoint was the estimated median survival time, whereby studies were weighted based on the number of study participants. This weighted estimate of median OS is an imperfect analytical method, but a conventional meta-analytical method in the absence of hazard ratios or patient-level data. Third, only one study focused primarily on the addition of radiotherapy to FOLFIRINOX in a dose finding phase 1 design. This was the only study concerning SBRT. All other studies included conventional chemoradiotherapy, which, as suggested earlier, may not be ideal in this setting. Fourth, heterogeneity across the included studies might have influenced the results, with differences in neoadjuvant FOLFIRINOX treatment (e.g., number of cycles and dose modifications), radiotherapy treatment (e.g., doses, fractions, and concurrent chemotherapy), and different definitions for (B)RPC. This heterogeneity was anticipated by using random-effects for all pooled analyses. Last, not all endpoints were reported in several studies, resulting in less precise and potentially biased estimates. Despite these unavoidable limitations, considering the available evidence, the results of the present meta-analysis currently provide the best available comparison of FOLFIRINOX with or without additional radiotherapy in patients with (B)RPC.

In conclusion, radiotherapy following neoadjuvant FOLFIRINOX was associated with an improved R0 resection rate as compared with neoadjuvant FOLFIRINOX alone, but a difference in survival could not be demonstrated. Randomized trials are needed to determine the added value of radiotherapy following neoadjuvant FOLFIRINOX in patients with (B)PRC.

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SUPPLEMENTARY FILES

Supplementary Table 1. Search strategy and results

Database	Search query	Number of records	After deduplication
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)	2314	2143
Medline (Ovid)	((Leucovorin/ AND fluorouracil/ AND irinotecan.mp. AND oxaliplatin.mp. AND Drug Combinations/ AND (exp Pancreatic Neoplasms/ OR (pancrea* ADJ3 (cancer* OR neoplas* OR tumo* OR adenocarcinom* OR carcinom* OR adenom*)).ab,ti.)) OR (Folfirinox).ab,ti.)	815	48
Web of Science	(TI=(neoadjuvant*) OR AB=(neoadjuvant*)) AND (TI=((pancrea*) NEAR/5 (cancer* OR carcinoma* OR adenocarcinoma* OR neoplas* OR tumor* OR tumour*)) OR AB=((pancrea*) NEAR/5 (cancer* OR carcinoma* OR adenocarcinoma* OR neoplas* OR tumor* OR tumour*))) AND (TI=(random* OR factorial* OR crossover* OR (cross NEAR/1 over*) OR placebo* OR ((doubl* OR singl*) NEAR/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups) OR AB=(random* OR factorial* OR crossover* OR (cross NEAR/1 over*) OR placebo* OR ((doubl* OR singl*) NEAR/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups)) AND LA=English	1587	527
Scopus	TITLE-ABS-KEY(Folfirinox)	923	55
Cochrane Central	(Folfirinox):ab,ti	321	111
Google Scholar	Folfirinox	200	63
Total		**6160**	**2947**

Supplementary Table 2. Methodological quality assessment according to Critical Appraisal Skill Program (CASP)

Study	Clear question	Recruitment	Accurately measured exposure	Accurately measured outcome	Confounding factors identified	Confounding factors accounted	Follow-up complete enough	Follow-up long enough	Precise statistical results presented	Do you believe results	Ability to generalize results	In accordance with existing evidence	Implications of study in practice
Barenboim	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Dhir	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Okada	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Tinchon	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	Yes	No
De Marsh	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kim	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No
Medrano	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Yoo	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Christians	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No
Katz	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Murphy	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Shaib	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tran	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bolton	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Mahaseth	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	Yes	No

Supplementary Table 3. References excluded studies after full text assessment, n=82

Outcomes pooled for different disease stages, n=29

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Outcomes pooled for different chemotherapy regimens, n=36

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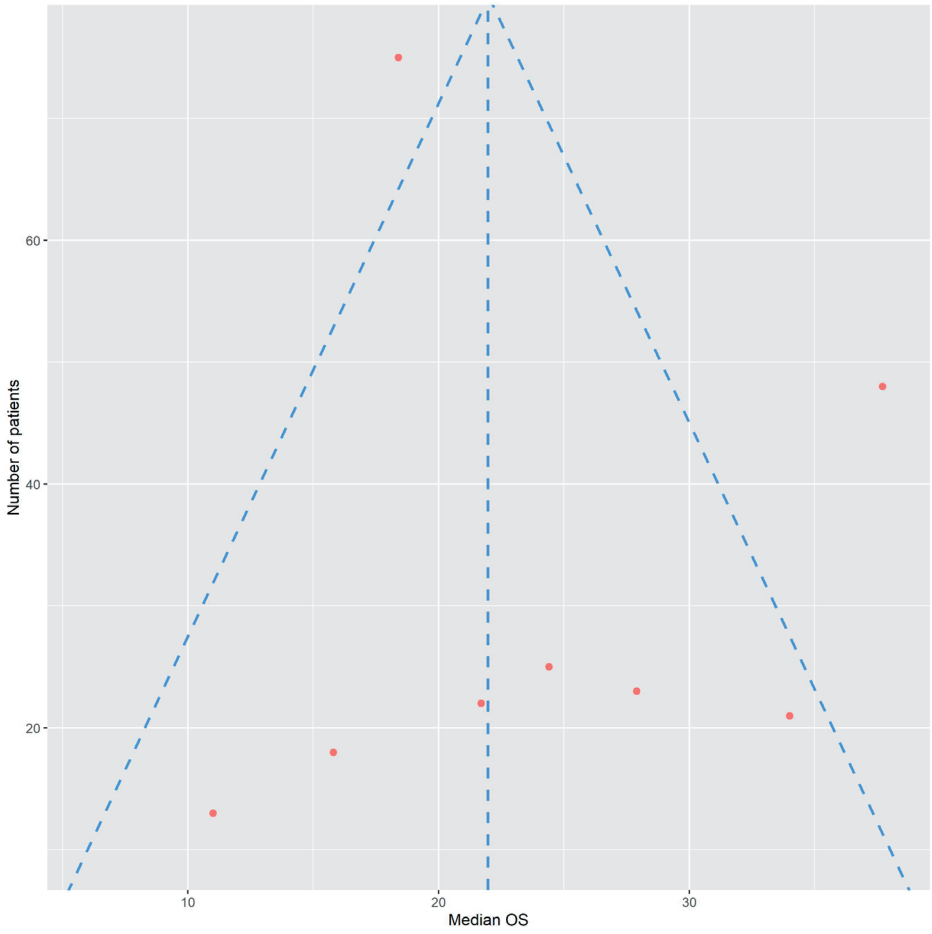

Supplementary Figure 1. Funnel plot assessing risk of publication bias using primary outcome of overall survival

CHAPTER 11

Neoadjuvant radiotherapy following (m) FOLFIRINOX for borderline resectable pancreatic adenocarcinoma – a TAPS Consortium study

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ABSTRACT

Background

The value of neoadjuvant radiotherapy following (m)FOLFIRINOX for patients with borderline resectable (BR) pancreatic ductal adenocarcinoma (PDAC) is uncertain.

Methods

We conducted an international retrospective cohort study including consecutive patients with BR PDAC who received (m)FOLFIRINOX as initial treatment (2012-2019) from the Trans-Atlantic Pancreatic Surgery Consortium. Since the decision for radiotherapy is made after chemotherapy, patients with metastases or deterioration after (m)FOLFIRINOX or a performance score ≥2 were excluded. Patients who received radiotherapy following (m) FOLFIRINOX were matched 1:1 by nearest neighbor propensity scores with patients who did not. Propensity scores were calculated using sex, age (≤70 versus >70), performance score (0 versus 1), tumor size (0-20 versus 21-40 versus >40mm), tumor location (head/uncinate versus body/tail), number of cycles (1-4 versus 5-8 versus >8), and baseline carbohydrate antigen (CA) 19-9 (≤500 versus >500 U/mL). Primary outcome was overall survival (OS) from diagnosis.

Results

Of 531 patients who received neoadjuvant (m)FOLFIRINOX for BR PDAC, 424 met inclusion criteria and 300 (70.8%) were propensity score matched. After matching, median OS was 26.2 months (95% confidence interval [CI]: 24.0-38.4) with radiotherapy versus 32.8 months (95% CI: 25.3-42.0) without radiotherapy (p=0.71). Radiotherapy was associated with a lower resection rate (55.3% versus 72.7%, p=0.002). In patients who underwent a resection, radiotherapy was associated with a comparable margin-negative resection rate (>1mm) (70.6% versus 64.8%, p=0.51), more node-negative disease (57.3% versus 37.6%, p=0.01), and more major pathologic response with <5% tumor viability (24.7% versus 8.3%, p=0.006). The OS of conventional and stereotactic body radiation approaches was similar (median OS: 25.7 versus 26.0 months, p=0.92).

Conclusion

In patients with BR PDAC, neoadjuvant radiotherapy following (m)FOLFIRINOX was associated with more node-negative disease and better pathologic response in patients who underwent resection, yet no difference in OS was found. Routine use of radiotherapy cannot be recommended based on these data.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) represents one of the most aggressive solid tumors. Localized PDAC is classified into radiographic stages as potentially resectable (PR), borderline resectable (BR), or locally advanced (LA) disease, based on the extent of venous and arterial involvement.[1,2] Although several staging criteria are currently used, patients with BR PDAC are generally considered technically resectable, but with increased risk of a microscopic margin-positive (R1) resection. The National Comprehensive Cancer Network (NCCN) guideline recommends neoadjuvant therapy for patients with BR PDAC to increase the likelihood of a microscopically radical (R0) resection.[2] Moreover, a neoadjuvant approach allows for early treatment of occult micro-metastatic disease and ensures systemic treatment for all patients without the risk of postoperative complications precluding adjuvant treatment.[3] Last, it allows tumor biology to declare itself for patients with elevated tumor markers, thereby improving patient selection for surgery.[4]

In the current NCCN guideline, neoadjuvant chemotherapy may be followed by radiotherapy, without clear specification on when this may be considered.[2] Cohort studies reported that neoadjuvant radiotherapy is associated with better locoregional control compared with chemotherapy alone. However, a benefit in overall survival (OS) has not been clearly demonstrated.[5-8] The long-term results of the PREOPANC trial found better OS with neoadjuvant chemoradiotherapy compared with upfront surgery in patients with BR and PR PDAC.[9,10] However, this study did not directly compare neoadjuvant chemotherapy with or without radiation. Moreover, the PREOPANC trial used gemcitabine alone that was shown inferior to FOLFIRINOX (i.e. 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin) in the metastatic and adjuvant setting.[11,12] By extrapolation of these results, the NCCN guideline has included neoadjuvant (m)FOLFIRINOX as one of the preferred first-line treatments for patients with BR PDAC with a good performance status.[2] Several retrospective studies have already shown promising results using neoadjuvant (m)FOLFIRINOX with or without additional radiotherapy.[13-16]

This study aimed to assess the effectiveness of neoadjuvant radiotherapy following (m) FOLFIRINOX in patients with BR PDAC. In the absence of published phase III trials, we performed propensity score matched analysis of a large observational cohort to minimize known confounding biases.[17]

METHODS

2.1 Study design and patients

The international Trans-Atlantic Pancreatic Surgery (TAPS) Consortium includes five PDAC referral centers from the United States (University of Pittsburgh Medical Center; MD An-

derson Cancer Center; Memorial Sloan Kettering Cancer Center) and the Netherlands (Amsterdam UMC; Erasmus MC University Medical Center). All participating centers obtained ethical approval from local Institutional Review Boards. Due to the retrospective nature of the study, the requirement to obtain informed consent was waived. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline, modified for reporting propensity score analysis.[17]

The consortium centers aggregated a consecutive cohort of patients diagnosed with clinically localized PDAC between 2012 and 2019, who started with (m)FOLFIRINOX as initial treatment. Radiographic stage was based on the MDACC classification system[4] or the NCCN criteria applicable at time of diagnosis (the other four centers). For patients from the Netherlands, stage according to NCCN criteria was reconstructed based on the exact extent of vascular contact with and possible occlusion of surrounding vasculature after radiologic review of the CT scan prior to start of treatment.

For the present study, all patients diagnosed with BR PDAC were identified from the TAPS total cohort of 1835 patients. Since the decision for radiotherapy is generally made after completion of chemotherapy, patients were excluded in case of metastatic disease or clinical decline at restaging following (m)FOLFIRINOX, or in case of a baseline World Health Organization (WHO) performance score of ≥2. Furthermore, patients were excluded if it was unknown whether they had received neoadjuvant radiotherapy. The decision to proceed with and the type of neoadjuvant radiotherapy was based on the discussions at each institution's local multidisciplinary meeting. Radiotherapy options included conventional regimens (typically 30 Gy in 10 fractions or 50.4 Gy in 28 fractions, often with concurrent chemotherapy) or stereotactic body radiation therapy (SBRT) regimens of ≥ 5 Gy per fraction in 5 fractions.

2.2 Data collection and definitions

Prespecified data on patient demographics, tumor characteristics, treatment details, and clinical and pathological outcomes were collected locally and merged after de-identification. OS was defined from date of tissue diagnosis to date of death, with censoring at the date of last follow-up for patients with no event. The date of final analysis for the cohort was December 31st, 2020. The 8th edition of the American Joint Committee on Cancer Staging (AJCC) Manual was used for tumor-node-metastasis (TNM) staging,[18] the 1mm definition for resection margin status,[19] and pathologic response was categorized as major/complete (<5% tumor viability) or not (≥5%).[20] One biweekly treatment of (m)FOLFIRINOX was considered one cycle.

2.3 Statistical analysis

Clinicopathological characteristics were presented based on treatment (radiotherapy vs. no radiotherapy) using descriptive statistics. Chi-square test was used to compare categorical variables and the Mann-Whitney U test for continuous variables. To minimize confounding

biases, propensity score matching was performed using 1:1 nearest neighbor matching. Propensity scores were calculated using a logistic regression model including known prognostic factors that may determine subsequent treatment; sex, age at diagnosis (≤70 vs. >70 years), performance score (WHO 0 vs. WHO 1), tumor size (0-20 vs. 21-40 vs. >40 mm), tumor location (head/uncinate vs. body/tail), baseline CA 19-9 (≤500 vs. >500 U/mL), and number of neoadjuvant (m)FOLFIRINOX cycles (1-4 vs. 5-8 vs. >8). Sampling without replacement was used and only patients with complete data on the matching factors were included. After matching, a standardized difference of <0.10 was considered an insignificant and acceptable imbalance.[21,22] The primary endpoint was OS for the matched cohort, assessed using Kaplan-Meier estimates. The difference in OS between the treatment groups was tested using the log-rank test. The treatment effect was estimated using a Cox proportional hazards model and expressed as a hazard ratio (HR) with corresponding 95% confidence interval (CI). Secondary endpoints included differences in pathological outcomes between the matched treatment groups.

A subgroup analysis separately evaluated patients from the matched cohort who did or did not undergo a resection, comparing the treatment groups. A second subgroup analysis compared patients receiving conventional radiotherapy and SBRT.

All tests were two-sided and a p-value <0.05 was considered statistically significant. Analyses were performed using R software, version 3.4.3. The MatchIt package was used to create the matched sample.

RESULTS

3.1 Patient and treatment characteristics

Between 2012 and 2020, 531 patients with BR PDAC who received at least one cycle of neoadjuvant (m)FOLFIRINOX as initial treatment were extracted from the total TAPS cohort of 1835 patients. Of those, 107 patients (20.2%) were excluded for reasons shown in Figure 1. Of the remaining 424 patients, 195 (46.0%) received neoadjuvant radiotherapy. Overall, patients received a median of six cycles (IQR 4-8) of neoadjuvant (m)FOLFIRINOX (Table 1).

3.2 Radiotherapy regimens

Of the 195 patients with BR PDAC who received neoadjuvant radiotherapy, 128 patients (65.6%) received conventional radiotherapy and 63 patients (32.3%) received SBRT. For four patients, radiotherapy treatment specifics were unknown. For the patients receiving conventional radiotherapy, concurrent chemotherapy was given as radiosensitizer in 115/128 patients (89.8%) (Supplementary Table 1).

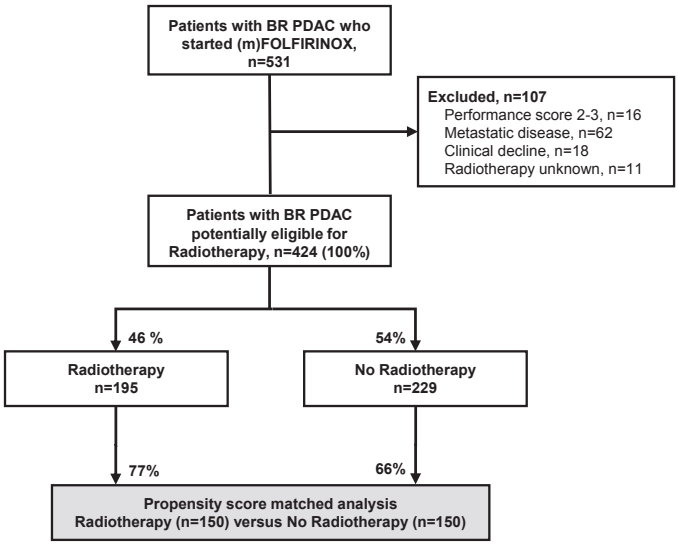

Figure 1. Flow diagram of patient enrollment

3.3 Propensity score matching

Baseline characteristics and treatment details before and after propensity score matching are summarized in Table 1. Before matching, patients in the radiotherapy group had worse performance scores ($p<0.001$) and received more neoadjuvant cycles of (m)FOLFIRINOX ($p=0.001$). With propensity score matching, 150 patients from the radiotherapy group (77%) were matched to 150 patients from the no radiotherapy group (66%). After matching, the absolute standardized differences for the unbalanced variables were low (range 1-5%), resulting in comparable patient, tumor, and treatment characteristics.

3.4 Survival analysis

After a median follow-up time of 36.5 months, 253/424 patients (59.7%) had died. The median OS in the unmatched cohort was 25.7 months (95% CI: 23.7-31.8) with radiotherapy versus 29.1 months (95% CI: 23.2-35.0) without radiotherapy (HR 0.99, 95% CI: 0.77-1.26, $p=0.91$) (Figure 2A). After matching, the median OS was 26.2 months (95% CI: 24.0-38.4) with radiotherapy versus 32.8 months (95% CI: 25.3-42.0) without radiotherapy (HR 1.06, 95% CI: 0.78-1.43, $p=0.71$) (Figure 2B). The 5-year OS was comparable (27 vs. 26%).

3.5 Surgical exploration and resection in the matched cohort

At multidisciplinary evaluation following completion of (m)FOLFIRINOX and radiotherapy in the radiotherapy group, 30 patients (20.0%) had developed locally unresectable disease, 19 patients (12.7%) with metastatic disease that became manifest at restaging following radiotherapy, and 2 patients (1.3%) had clinically declined precluding surgery. In the no radiotherapy group, 15 patients (10.0%) had developed locally unresectable disease after

Table 1. Baseline characteristics and treatment details, unmatched and matched cohort

	Unmatched cohort				Matched cohort			
	Overall n = 424	No radiotherapy n = 229	Radiotherapy n = 195	P-value	Overall n = 300	No radiotherapy n = 150	Radiotherapy n = 150	P-value
Female, n (%)	189 (44.6)	92 (40.2)	97 (49.7)	0.06	147 (49.0)	72 (48.0)	75 (50.0)	0.82
Age, years (median [IQR])	64 [57, 70]	64 [58, 69]	64 [57, 70]	0.85	64 [57, 70]	65 [58, 70]	64 [57, 70]	0.57
Performance status, n (%)				<0.001*				0.91
WHO 0	222 (52.4)	139 (60.7)	83 (42.6)		150 (50.0)	76 (50.7)	74 (49.3)	
WHO 1	202 (47.6)	90 (39.3)	112 (57.4)		150 (50.0)	74 (49.3)	76 (50.7)	
BMI, kg/m^2 (median [IQR])	26 [23, 29]	26 [23, 30]	26 [24, 29]	0.78	26 [24, 30]	26 [23, 30]	26 [24, 29]	0.77
Tumor location: Head/uncinate, n (%)	335 (79.0)	184 (80.3)	151 (77.4)	0.54	229 (76.3)	117 (78.0)	112 (74.7)	0.59
Tumor size on CT, mm (median [IQR])	34 [26, 41]	33 [26, 41]	34 [27, 43]	0.29	34 [27, 41]	34 [26, 41]	34 [27, 41]	0.58
Pre-treatment CA 19-9, U/mL (median [IQR])	196 [48, 653]	178 [42, 578]	232 [75, 706]	0.13	198 [46, 653]	157 [30, 582]	238 [73, 710]	0.14
Number of cycles, n (%)				0.001*				0.88
1-4 cycles	142 (33.5)	95 (41.5)	47 (24.1)		92 (30.7)	48 (32.0)	44 (29.3)	
5-8 cycles	230 (54.2)	109 (47.6)	121 (62.1)		172 (57.3)	84 (56.0)	88 (58.7)	
>8 cycles	52 (12.3)	25 (10.9)	27 (13.8)		36 (12.0)	18 (12.0)	18 (12.0)	

* = significant p-value <0.05. Abbreviations: BMI, body mass index; CA 19-9, carbohydrate antigen 19-9; CT, computed tomography; IQR, interquartile range; n, number; WHO, World Health Organization. Missing data: BMI (n=6), tumor size (n=12), CA 19-9 (n=31).

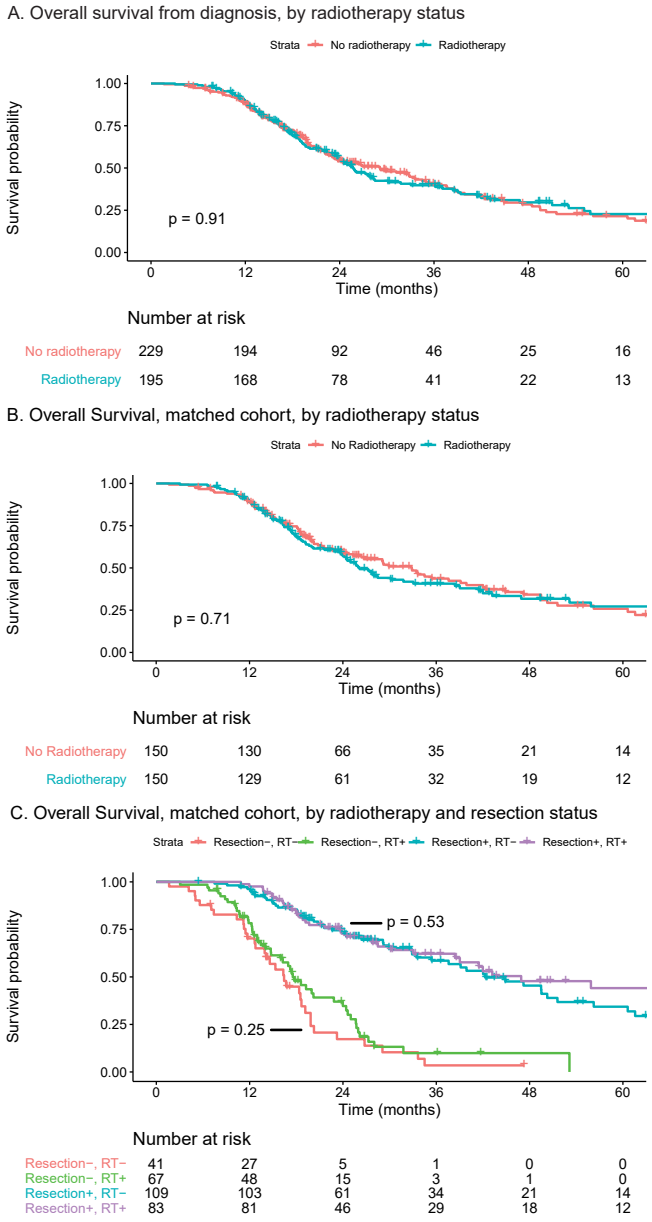

Figure 2. Overall survival from diagnosis for patients who did or did not receive neoadjuvant radiotherapy after (m)FOLFIRINOX, (A) in the unmatched cohort, (B) in the propensity score matched cohort, (C) in the propensity score matched cohort for patients who did or did not undergo a resection One-to-one matching based on sex, age at diagnosis (≤70 vs. >70 year), performance score (WHO 0 vs. WHO 1), tumor size (0-20 vs. 21-40 vs. >40 mm), tumor location (head/uncinate vs. body/tail), baseline CA 19-9 (≤500 vs. >500), and number of neoadjuvant cycles of (m)FOLFIRINOX (1-4 vs. 5-8 vs. >8). Abbreviations: CA, carcinogen antigen; RT, radiotherapy; WHO, World Health Organization.

completion of (m)FOLFIRINOX alone. As noted, patients with metastatic disease at restaging following (m)FOLFIRINOX were already excluded from the analyses.

Surgical exploration was recommended for the remaining 99 patients (66.0%) in the radiotherapy group and 135 patients (90.0%) in the no radiotherapy group (p<0.001). The median time from diagnosis to surgery was 229 days (IQR 189 – 268) in the radiotherapy group and 146 days (IQR 125 – 175) in the no radiotherapy group (p<0.001). In total, 83 patients (55.3%) underwent a resection in the radiotherapy group versus 109 patients (72.7%) in the no radiotherapy group (p=0.002). The resection rate of patients recommended for surgery was comparable (83.8% vs. 80.7%, p=0.54). A vascular resection was performed in 43 patients (51.8%) in the radiotherapy group versus 45 patients (42.1%) in the no radiotherapy group (p=0.23). Only one patient died within 30-days following resection, who was included in the no radiotherapy group. Adjuvant chemotherapy was started in 33 patients (39.8%) in the radiotherapy versus 85 patients (78.0%) in the no radiotherapy group (p<0.001). Palliative treatment was started in a comparable number of patients (52.0% vs. 51.3%, p=0.62).

Figure 2 shows the OS curves for both treatment groups, separately for the resection and non-resection cohort. For patients who underwent a resection, the median OS was 46.9 months (95% CI: 38.4-83.9) with radiotherapy versus 42.3 months (95% CI: 35.4-56.2) without radiotherapy (HR 0.87, 95% CI: 0.58-1.32, p=0.53). With resection, the 5-year OS was 44% (95% CI: 32-61%) with radiotherapy versus 34% (95% CI: 24-49%) without radiotherapy. For patients who did not undergo a resection, the median OS was 17.5 months (95% CI: 16.0-24.4) with radiotherapy versus 16.4 months (95% CI: 13.9-19.8) without radiotherapy (HR 0.77, 95% CI: 0.49-1.20, p=0.25). Without resection, the 5-year OS was 10% (95% CI: 4-26%) with radiotherapy versus 3% (95% CI: 1-24%) without radiotherapy.

3.6 Pathological outcomes in the matched cohort

Patients in the radiotherapy group had a similar R0 resection rate (70.6% vs. 64.8%, p=0.53), more node-negative disease (ypN0: 57.3% vs. 37.6%, p=0.01), and more often had a major or complete pathologic response (24.7% vs. 8.3%, p=0.01) (Table 2).

3.7 Conventional radiotherapy versus SBRT

The median OS was 26.0 months (95% CI: 22.4-42.0) for the 63 patients receiving SBRT versus 25.7 months (95% CI: 22.5-38.4) for the 128 patients receiving conventional radiotherapy (HR 1.02, 95% CI: 0.69-1.52, p=0.92) (Figure 3).

DISCUSSION

This multicenter propensity score matched analysis of 300 patients with BR PDAC who received (m)FOLFIRINOX as initial treatment showed a median OS of 26.2 months with

Table 2. Pathological outcomes of patients who underwent a resection in the matched cohort

	Matched cohort `			
	Overall n = 192	No radiotherapy n = 109	Radiotherapy n = 83	P-value
Tumor size, mm (median [IQR])	25 [18, 33]	25 [20, 30]	25 [17, 36]	0.83
T stage [a], n (%)				0.13
ypT0	8 (4.2)	2 (1.8)	6 (7.3)	
ypT1-2	145 (75.9)	87 (79.8)	58 (70.7)	
ypT3-4	38 (19.9)	20 (18.3)	18 (22.0)	
N stage [a], n (%)				0.01*
ypN0	88 (46.1)	41 (37.6)	47 (57.3)	
ypN1	67 (35.1)	41 (37.6)	26 (31.7)	
ypN2	36 (18.8)	27 (24.8)	9 (11.0)	
Resection margin status [b], n (%)				0.53
R0	118 (67.0)	70 (64.8)	48 (70.6)	
R1	58 (33.0)	38 (35.2)	20 (29.4)	
Tumor differentiation, n (%)				0.01*
Well (G1)	5 (2.9)	5 (5.0)	0 (0.0)	
Moderate (G2)	125 (72.3)	77 (77.0)	48 (65.8)	
Poor (G3)	43 (24.9)	18 (18.0)	25 (34.2)	
Perineural invasion, n (%)	147 (77.4)	84 (77.8)	63 (76.8)	1
Lymphovascular invasion, n (%)	101 (53.4)	64 (59.3)	37 (45.7)	0.09
Pathologic response, n (%)				0.01*
<5% tumor viability	28 (15.8)	8 (8.3)	20 (24.7)	
≥5% tumor viability	149 (84.2)	88 (91.7)	61 (75.3)	

[a] 8th edition of American Joint Committee on Cancer Staging. [b] 1mm definition of Royal College of Pathologists.

* = significant p-value <0.05. Abbreviations: G, grade; IQR, interquartile range; n, number; yp, pathological outcome after neoadjuvant treatment. Missing data: tumor size (n=2), ypT (n=1), ypN (n=1), resection margin (n=16), tumor differentiation (n=19), perineural invasion (n=2), lymphovascular invasion (n=3), pathologic response (n=15)

radiotherapy compared with 32.8 months without radiotherapy (HR 1.06, 95% CI: 0.78-1.43, p=0.71). In addition, no difference in survival was found between the treatment groups when separately analyzing the resection and non-resection cohort. In those patients who underwent surgical resection, neoadjuvant radiotherapy was associated with more node-negative disease and better pathologic response. The OS of conventional and stereotactic body radiation approaches was similar.

To date, only one randomized phase II trial has been presented directly comparing neoadjuvant multi-agent chemotherapy with or without radiotherapy.[23,24] The ALLIANCE A021501 trial compared neoadjuvant mFOLFIRINOX (8 cycles) to mFOLFIRINOX (7 cycles) followed

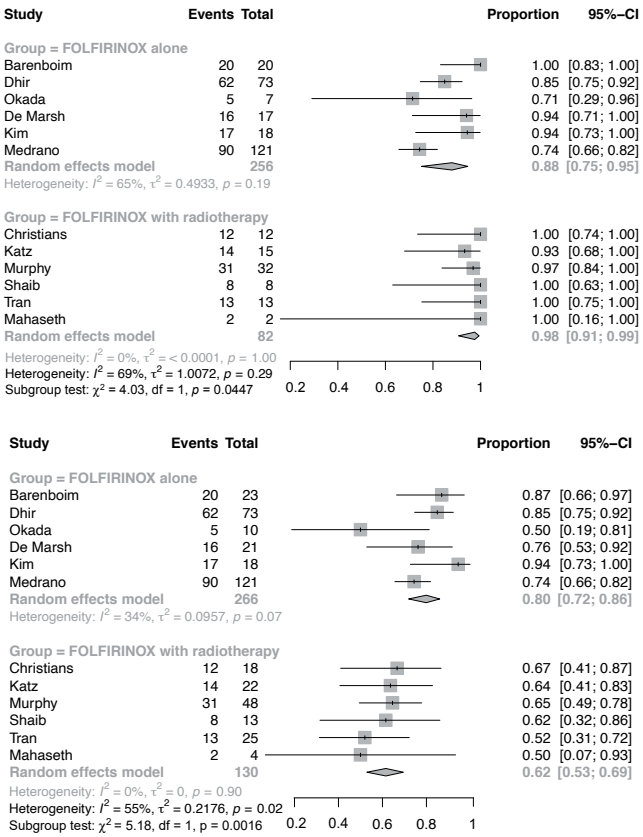

Figure 3. Overall survival from diagnosis for patients with BR PDAC who received neoadjuvant radiotherapy after (m)FOLFIRINOX, comparing stereotactic body radiation therapy (SBRT) with conventional radiotherapy (RT)

by SBRT (33-40 Gy in 5 fractions) or HIGRT (25 Gy in 5 fractions). After inclusion of 56 patients, the radiotherapy arm was closed due to futility regarding the R0 resection rate. At final analysis, OS in the radiotherapy arm (median OS: 17.1 months) was not better compared to historical data (18-23 months) and lower compared to mFOLFIRINOX without radiotherapy (31.0 months). Median OS without radiotherapy was similar between the ALLIANCE trial and the present study. In the ALLIANCE trial, SBRT rather than conventional RT was used, based on promising results in patients with LA PDAC.[25-27] In the present study, we found similar survival between SBRT and conventional radiotherapy for BR PDAC.

In a meta-analysis including 512 patients with BR or PR PDAC from 15 small single arm studies, neoadjuvant radiotherapy following (m)FOLFIRINOX was not associated with a difference in OS.[28] Retrospective series evaluating neoadjuvant chemotherapy regimens

other than (m)FOLFIRINOX [5-8] and the randomized LAP-07 trial for patients with locally advanced PDAC [29] also found no difference in OS with and without radiotherapy. Four studies found better survival with neoadjuvant radiotherapy following multi-agent chemotherapy regimens.[16,30-32] Three of these four studies, however, only included the selected subgroup of patients who underwent a resection, thereby introducing selection bias. In the no radiotherapy group, a patient who undergoes a resection might be diagnosed with liver metastases three months after surgery; in the radiotherapy group, the same patient would be diagnosed with liver metastases at restaging after radiotherapy and would therefore not end up in the resection cohort. We found that 12.7% of patients in the radiotherapy group had developed metastatic disease at restaging after radiotherapy, illustrating this selection bias in studies that only report the cohort who underwent a resection. These patients had an additional period for metastatic disease to become overt at restaging after radiotherapy. Consequently, a resection is avoided in the radiotherapy group in about 1 in 8 patients who would have developed early recurrent disease without a period of radiotherapy. In the present study, patients in the radiotherapy group also had higher risk of locally advanced (i.e., unresectable) disease at radiologic restaging (20.0% vs. 10.0%). Despite propensity matched analysis, patients in the radiotherapy group may have had more extensive vascular involvement at baseline within the spectrum of BR PDAC or less local response to (m) FOLFIRINOX (i.e., residual confounding).

In patients who underwent a resection in the matched cohort, radiotherapy was associated with a higher frequency of node-negative disease and major pathologic response, which is consistent with literature.[5-7,30,31,33] This may be explained by the locoregional effect of radiotherapy, although it may also be partly explained by selecting out patients with progressive disease during the prolonged treatment time for radiotherapy. No difference in R0 resection rate was found between the radiotherapy and no radiotherapy group. Other studies show conflicting data on this outcome.[6,7,24,28,30,31] Differences in the definition of R0 and pathology grossing techniques hamper the comparability of margin status across studies.[19,34,35] Of note, the conventional definition of an R0 resection based on 1 mm clearance may not be adequate following neoadjuvant therapy due to its cytoreductive effect, although consensus on the optimal assessment of margin status in this setting is lacking.[36] Since the main effect of radiotherapy seems to be improved locoregional control, future studies should try to identify those patients for whom survival is mainly defined by their local tumor.

Some surgeons have raised concerns that preoperative radiotherapy may increase postoperative complications. Two recent studies, however, have found no difference in postoperative complications between patients with and without preoperative radiotherapy. Moreover, the rate of postoperative pancreatic fistula was lower in patients who received preoperative radiotherapy.[37,38]

Currently, three randomized trials assess the role of neoadjuvant radiotherapy for BR PDAC. The 3-arm BRPCNCC-1 trial compares neoadjuvant gemcitabine plus nab-paclitaxel with or without SBRT to S1 plus nab-paclitaxel with SBRT in 150 patients.[39] The PANDAS-PRODIGE44 trial (NCT02676349) compares neoadjuvant mFOLFIRINOX with or without conventional chemoradiotherapy (50.4 Gy in 28 fractions) in 90 patients. Last, the PREOPANC-2 trial compares neoadjuvant FOLFIRINOX to neoadjuvant gemcitabine-based chemoradiotherapy in 368 patients with BR and PR PDAC.[40] It is unlikely, however, that these studies will completely resolve the debate on the added value of neoadjuvant radiotherapy for BR PDAC. Only a large randomized controlled trial (i.e. 500-1000 patients) directly comparing multi-agent systemic treatment with or without radiotherapy could definitively adjudicate whether the improved locoregional control of radiotherapy translates into a clinically relevant survival benefit.

Within the context of these data, routine use of radiotherapy for all BR PDAC patients may not be justified. Improved pathology outcomes in the radiotherapy group suggest that radiotherapy can benefit a subgroup of patients, but this subgroup remains to be identified. Selected radiotherapy prior to surgery may be indicated in patients with threatened margins or for vascular preservation to avoid the need for arterial resection.

The findings reported in this study should be interpreted with some limitations in mind. First, confounding by indication may have occurred, with more advanced tumors (within the definition of BR PDAC) in the radiotherapy group. On the other hand, guarantee-time bias was an advantage for the radiotherapy group.[41] These biases were addressed with propensity score matched analysis, but residual bias from unmeasured factors may still be present. Second, data on the exact extent of vascular involvement within the spectrum of BR PDAC and data on disease recurrence (i.e. locoregional or distant) were not available. Last, treatment protocols (e.g., selection for radiotherapy, type of radiotherapy, and subsequent adjuvant and palliative treatment) differed across centers and over time. However, a cohort in which similar patients received different treatments is a requirement for propensity score matching. Moreover, this reflects real-world protocol variations in experienced treatment centers. Strengths of this study include the large sample size, the uniform use of (m) FOLFIRINOX chemotherapy, and the inclusion of patients from experienced referral centers from two different countries.

In conclusion, neoadjuvant radiotherapy following (m)FOLFIRINOX for BR PDAC was not associated with improved OS despite some benefits in node-negative disease and pathologic response in those patients who underwent surgical resection. Routine use of neoadjuvant radiotherapy for all patients cannot be recommended based on these data. Future studies are needed to assess whether specific subgroups of patients with BR PDAC would benefit from neoadjuvant radiotherapy.

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SUPPLEMENTARY FILES

Supplementary Table 1. Radiotherapy treatment

	Overall n = 195 [a]	Conventional RT n = 128	SBRT n = 63
Radiotherapy dose in Gy (median [IQR])	40.0 [36.0, 50.4]	50.4 [36.0, 50.4]	36.0 [36.0, 40.0]
Number of fractions (median [IQR])	12.0 [5.0, 28.0]	25.0 [12.0, 28.0]	5.0 [3.0, 5.0]
Concurrent chemotherapy, n (%)			
Capecitabine	90 (47.1)	90 (70.3)	0
Gemcitabine	23 (12.0)	23 (18.0)	0
Other	2 (1.0)	2 (1.6)	0
Unknown	6 (3.1) [a]	2 (2.3)	0
No concurrent chemotherapy	74 (37.9)	11 (8.6)	63 (100.0)

[a] For four patients, radiotherapy treatment specifics were unknown, therefore these could not be categorized.

Abbreviations: Gy, Gray; IQR, interquartile range; n, number; RT, radiotherapy; SBRT, stereotactic body radiation therapy. Missing data: type (n=4), dose (n=8), fractions (n=8), concurrent chemotherapy (n=4).

CHAPTER 12

Real-world evidence of adjuvant gemcitabine plus capecitabine versus gemcitabine monotherapy for pancreatic ductal adenocarcinoma.

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ABSTRACT

Background

The added value of capecitabine to adjuvant gemcitabine monotherapy (GEM) in pancreatic ductal adenocarcinoma (PDAC) was shown by the ESPAC-4 trial. Real-world data on the effectiveness of gemcitabine plus capecitabine (GEMCAP), in patients inelegible for mFOLFIRINOX, are lacking. This study assessed whether adjuvant GEMCAP is superior to GEM in a nationwide cohort.

Methods

Patients treated with adjuvant GEMCAP or GEM after resection of PDAC without preoperative treatment were identified from the Netherlands Cancer Registry (2015-2019). The primary outcome was overall survival (OS), measured from start of chemotherapy. The treatment effect of GEMCAP vs. GEM was adjusted for sex, age, performance status, tumor size, lymph node involvement, resection margin, and tumor differentiation in a multivariable Cox regression analysis. Secondary outcome was the percentage of patients who completed the planned six adjuvant treatment cycles.

Results

Overall, 778 patients were included, of whom 21.1% received GEMCAP and 78.9% received GEM. The median OS was 31.4 months (95% CI 26.8-40.7) for GEMCAP and 22.1 months (95% CI 20.6-25.0) for GEM (HR 0.71, 95% CI 0.56-0.90; logrank p=0.004). After adjustment for prognostic factors, survival remained superior for patients treated with GEMCAP (HR:0.73, 95% CI 0.57-0.92, logrank p=0.009). Survival with GEMCAP was superior to GEM in most subgroups of prognostic factors. Adjuvant chemotherapy was completed in 69.5% of the patients treated with GEMCAP and 62.7% with GEM (p=0.11).

Conclusion

In this nationwide cohort of patients with PDAC, adjuvant GEMCAP was associated with superior survival as compared to GEM monotherapy and number of cycles was similar.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a common cause of cancer-related mortality among men and women worldwide, with a five-year overall survival (OS) of only 3%.[1, 2] At time of diagnosis, the majority of the patients present with locally advanced or metastatic disease.[3] Only one fifth of the patients is able to undergo resection.[2, 4] However, resection alone does not overcome the risk of local or distant recurrent disease in the majority of patients.[5]

A beneficial effect of adjuvant chemotherapy on the risk of recurrence and OS in PDAC was first shown by Oettle et al. in 2007.[6] Ever since, several randomized controlled trials have studied the efficacy of various adjuvant chemotherapeutics in patients with PDAC who underwent resection.[7-11] For many years, gemcitabine monotherapy (GEM) has been the preferred adjuvant treatment in Western countries.[12, 13] Based on promising results in the metastatic setting, the use of combination therapies has emerged.[14-17] In 2017, the ESPAC-4 trial compared adjuvant gemcitabine plus capecitabine (GEMCAP) with GEM alone.[10] The median OS for patients treated with GEMCAP was 28.0 months compared with 25.5 months for patients treated with GEM (hazard ratio (HR): 0.82, 95% CI 0.68-0.98, p=0.032) with an acceptable level of treatment-related adverse events. The secondary analysis and long-term results confirmed the survival benefit as well as the decreased risk of developing local recurrence with GEMCAP treatment.[18, 19] In 2018, Conroy et al. showed the longest estimated survival thus far, with a median OS of 54.4 months in patients receiving adjuvant modified FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) compared with 35.0 months with GEM (HR: 0.64, 95% CI 0.48-86, p=0.003).[11] This evident survival advantage came at the cost of increased chemotherapy-related adverse events in patients treated with modified FOLFIRINOX (mFOLFIRINOX). As a consequence, international guidelines recommend adjuvant mFOLFIRINOX only in patients with a good performance status.[12, 20-22] In patients with impaired performance status, both adjuvant GEM and GEMCAP can be offered as alternative treatment. In the Netherlands, GEM was approved as adjuvant therapy in 2008 and recommended in the national guideline published in 2011.[23, 24] In the 2019 guideline update, the option GEMCAP was added for patients unfit for mFOLFIRINOX. [20, 25]

Evidence on the added value of capecitabine to adjuvant GEM monotherapy in PDAC is limited to the ESPAC-4 trial. Since clinical trial results cannot always be reproduced in real-world setting, this study aimed to assess whether adjuvant GEMCAP is associated with superior overall survival compared to adjuvant GEM in a Dutch nationwide cohort.

METHODS

Data collection

This retrospective study used data from the nationwide Netherlands Cancer Registry (NCR). The NCR is a population-based registry including all patients with a newly diagnosed malignancy in the Netherlands since 1989, notified by the nationwide automated pathological archive (PALGA) and supplemented with the National Registry of Hospital Care (DHD-LBZ). Information on patient and tumor characteristics, treatment, and clinical outcomes are routinely extracted from the medical records using standardized definitions by trained administrators of the NCR. Patient characteristics included sex, age, performance status, and information on comorbidities according to the Charlson Comorbidity Index.[26] Tumor characteristics included the origin and morphology of the tumor classified according to the International Classification of Diseases for Oncology (ICD-O-3, pages 69-218), tumor size, number of positive lymph nodes, resection margin status (≥1mm as R0), tumor differentiation grade, TNM classification and corresponding disease stage.[27, 28] For this study, the TNM classification was converted to the 8th edition of the American Joint Committee on Cancer for all patients, using pathological tumor size and number of positive lymph nodes.[29] The definitions of pT1 and pT4 were identical between the 7th and 8th edition, and were therefore used for uniform staging. pT2 and pT3 definitions differed between both editions and thus staging of these tumors was based on tumor size according to the 8th edition. Treatment specifications included type and timing of surgery, number of cycles, and type of adjuvant treatment. Clinical outcomes included survival data, which was obtained by annual linkage with the nationwide Municipal Personal Records Database including the vital status of all Dutch inhabitants. Follow-up was completed until February 1st, 2021.[30]

Study population

For the current study, all patients aged ≥18 years with pancreatic ductal adenocarcinoma (ICD-O C25 excluding C25.4, see Supplementary Table 1 for morphology codes) diagnosed from 2015 to 2019 who underwent a resection were selected from the NCR. Additional inclusion criteria were treatment with adjuvant GEM monotherapy or adjuvant GEMCAP. All patients who received at least one cycle were included. Exclusion criteria were metastatic (stage IV) disease, a resection with macroscopic residual tumor (R2), neoadjuvant therapy, and adjuvant chemotherapy received outside of the Netherlands.

Treatment and outcome measures

The primary endpoint was OS, measured from start of chemotherapy until death from any cause. Patients alive at last follow-up were censored. Secondary endpoints included the annual number and proportion of patients receiving GEMCAP or GEM, the number of adjuvant chemotherapy cycles, the number of patients who switched to other adjuvant chemotherapy, and the percentage of patients who completed the planned six adjuvant treatment cycles.

Statistical analysis

Clinicopathologic characteristics were summarized for all patients and for GEMCAP and GEM separately. Data were presented as frequencies with proportions for categorical variables and median with interquartile range (IQR) for continuous variables. For categorical variables, the Chi-square test was used to compare the treatment groups as appropriate. For continuous variables, the Wilcoxon rank sum test was used. Median follow-up was calculated with the reverse Kaplan-Meier method. OS was estimated using the Kaplan-Meier method and difference in survival between the two treatment groups was analyzed using the log-rank test. In addition, univariable and multivariable Cox regression analyses were performed to assess the treatment effect expressed as HR with corresponding 95% CI, corrected for known and available prognostic factors (sex, age, WHO performance status, location, pathological tumor size, lymph nodes, resection margin, and tumor differentiation). Multiple imputation of missing data was performed using 25 imputed datasets with variable estimates obtained with the use of Rubin's rules. Imputation was performed for WHO performance status (n=279), tumor size (n=213), resection margin (n=20), and tumor differentiation (n=109). The proportional hazards assumption was assessed by visualization of Schoenfeld residuals and the log(-log(survival)) versus log of survival time graph. The proportional hazards assumption was not violated for any of the included variables. Results of the Cox regression analyses were presented as HR with 95% CI. Furthermore, the treatment effect of GEMCAP vs. GEM was assessed in prespecified subgroups using a Cox regression model with subgroups based on sex, age, WHO performance status, comorbidities, tumor location, stage, pathological tumor size, lymph nodes, resection margin, and tumor differentiation. Interaction was tested by adding the interaction term in the model with the p-value of the interaction term as indicator of possible interaction. The Chi-square test was used to compare the proportion of patients who completed at least six cycles of adjuvant chemotherapy and the proportion of patients who received three or less cycles of adjuvant chemotherapy between the two treatment groups. All tests were two-sided and values < 0.05 were considered statistically significant. All analyses were performed using R software, version 3.4.3.

RESULTS

The NCR database contained data on 1,992 patients who underwent resection for PDAC in the period 2015 to 2019. After applying the prespecified eligibility criteria, 778 patients were included, of whom 164 (21.1%) received adjuvant GEMCAP and 614 (78.9%) received adjuvant GEM (Figure 1). Fifty-four percent of the patients were male, the median age was 67 years (IQR 59-72), and 60.7% of the patients had WHO performance status 0 (Table 1). Most patients were diagnosed at stage II (41.0%), followed by stage III (36.5%), and stage I (22.5%). No statistically significant differences in characteristics were seen between treatment groups. Median time (IQR) from resection to start of adjuvant chemotherapy was 54.0

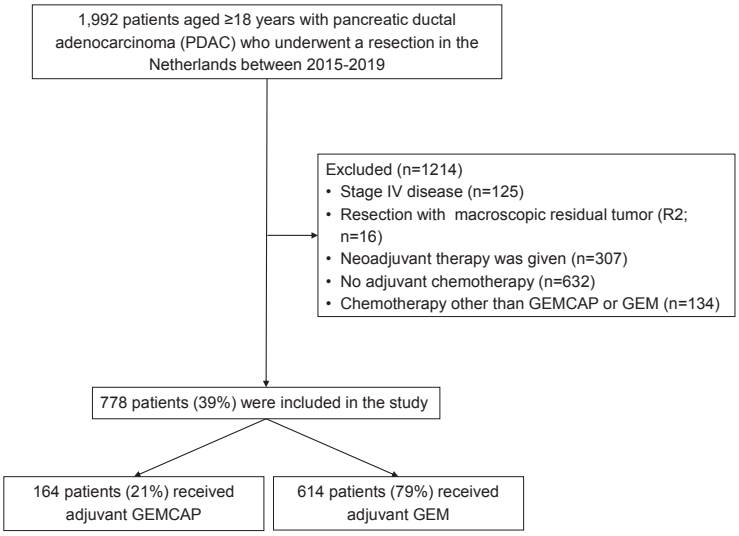

Figure 1. Selection of the study population
Abbreviations: GEM = gemcitabine monotherapy, GEMCAP = gemcitabine with capecitabine

days (42.0-71.0) for patients treated with GEMCAP and 52.0 days (42.2-64.0) for patients treated with GEM (p=0.332).

The number of patients receiving GEM decreased and the administration of GEMCAP increased from 2015 to 2018, although the absolute number of patients receiving GEMCAP decreased in 2019 (Figure 2).

Overall survival

The median follow-up time for patients alive at last follow-up was 33.5 months for patients treated with GEMCAP and 50.8 months for patients treated with GEM. Median OS for patients treated with GEMCAP was 31.4 months (95% CI 26.8-40.7) compared with 22.1 months (95% CI 20.6-25.0) for patients treated with GEM (unadjusted HR: 0.71, 95% CI 0.56-0.90, p=0.004; Figure 3).

Univariable analyses showed that besides treatment, the location of the primary tumor, tumor size, lymph node involvement, resection margin, and tumor differentiation were all associated with OS (Table 2). Independent predictors of survival were tumor size, lymph node involvement, resection margin, tumor differentiation, and treatment (GEM vs GEMCAP; HR: 0.73, 95% CI 0.58-0.93, p=0.010).

Table 1. Baseline characteristics

N	Overall 778	GEMCAP 164	GEM 614	P-value
Sex, n (%)				0.077
Male	420 (54.0)	78 (47.6)	342 (55.7)	
Female	358 (46.0)	86 (52.4)	272 (44.3)	
Age, years (median [IQR])	67.0 [59.0, 72.0]	66.0 [58.0, 71.0]	67.0 [60.0, 72.0]	0.118
WHO performance status, n (%)				0.455
WHO 0	303 (60.7)	62 (64.7)	241 (59.8)	
WHO 1	161 (32.3)	26 (27.1)	135 (33.5)	
WHO 2 - 3	35 (7.0)	8 (8.3)	27 (6.7)	
Concurrent conditions, n (%)				0.559
None	332 (48.2)	73 (50.7)	259 (47.5)	
Any	357 (51.8)	71 (49.3)	286 (52.5)	
Tumor location, n (%)				0.505
Other	148 (19.4)	34 (21.2)	114 (18.9)	
Head	615 (80.6)	126 (78.8)	489 (81.1)	
Type of resection, n (%)				0.452
Pancreatectomy	647 (84.6)	127 (83.6)	520 (84.8)	
Body / tail resection	110 (14.4)	22 (14.5)	88 (14.4)	
Total pancreatectomy	8 (1.0)	3 (2.0)	5 (0.8)	
Time to adjuvant chemo (days), (median [IQR])	52.0 [42.0, 64.8]	54.0 [42.0, 71.0]	52.0 [42.2, 64.0]	0.332
Pathological tumor stage*, n (%)				0.889
I	134 (22.5)	38 (23.9)	96 (22.0)	
II	244 (41.0)	64 (40.3)	180 (41.3)	
III	217 (36.5)	57 (35.8)	160 (36.7)	
Pathological tumor size, n (%)				0.156
<30 mm	245 (42.0)	75 (47.2)	170 (40.1)	
≥30 mm	338 (58.0)	84 (52.8)	254 (59.9)	
Lymph nodes, n (%)				0.912
Negative	199 (25.6)	43 (26.2)	156 (25.4)	
Positive	579 (74.4)	121 (73.8)	458 (74.6)	
Resection margin**, n (%)				0.054
R0	424 (55.9)	74 (48.7)	350 (57.8)	
R1	334 (44.1)	78 (51.3)	256 (42.2)	
Tumor differentiation, n (%)				0.086
Well	93 (13.9)	24 (16.9)	69 (13.1)	
Moderate	408 (61.0)	92 (64.8)	316 (60.0)	
Poor/Undifferentiated	168 (25.1)	26 (18.3)	142 (26.9)	

Abbreviations: GEM = gemcitabine, GEMCAP = gemcitabine with capecitabine, IQR = interquartile range, WHO = World Health Organization. * Tumor stage according to AJCC 8th edition. ** 1mm definition of Royal College of Pathologists. Percentage of missing data (overall/GEMCAP/GEM): sex (0%/0%/0%), age (0%/0%/0%), WHO performance status (36%/41%/34%), concurrent conditions (11%/24%/11%), location (2%/2%/2%), type of resection (2%/7%/0%), time to adjuvant chemo (0%/0%/0%), pathological tumor stage (24%/3%/29%), pathological tumor size (27%/1%/3%), lymph nodes (0%/0%/0%), resection margin (3%/7%/1%), tumor differentiation (14%/13%/14%).

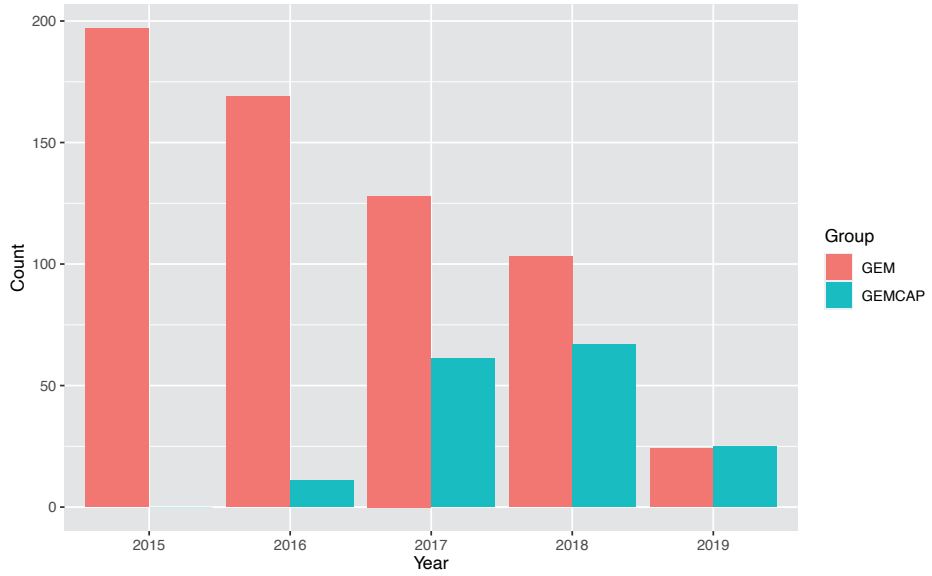

Figure 2. Number of patients receiving gemcitabine with capecitabine (GEMCAP) or gemcitabine monotherapy (GEM) over time

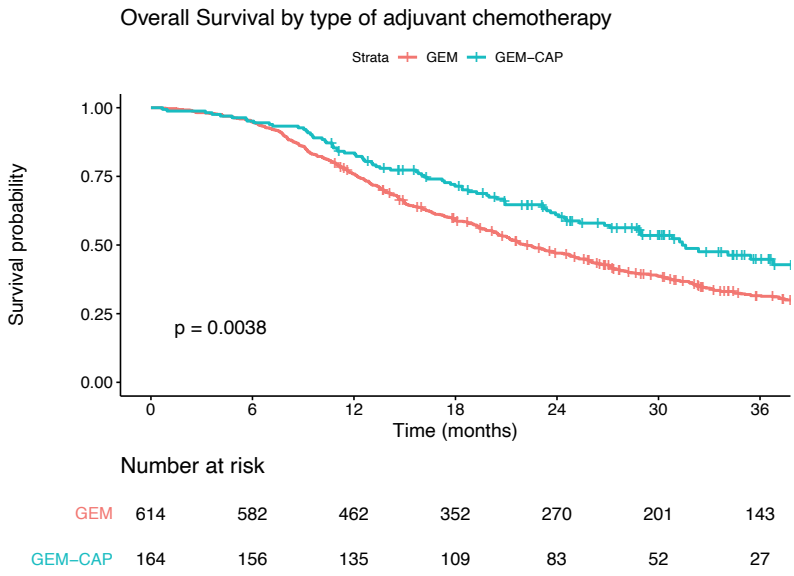

Figure 3. Overall Survival, by type of adjuvant chemotherapy
Hazard ratio for death: 0.71 (95% CI: 0.56 – 0.90), log-rank p=0.0038*
Abbreviations: GEM = gemcitabine monotherapy, GEMCAP = gemcitabine with capecitabine

Table 2. Univariable and Multivariable Cox Regression Analysis of Overall Survival

	Number of patients	Univariable analysis		Multivariable analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Treatment					
GEM	614	1 [Reference]	1	1 [Reference]	1
GEMCAP	164	0.71 (0.56 – 0.90)	0.004*	0.73 (0.58 – 0.93)	0.010*
Sex					
Male	420	1 [Reference]	1	1 [Reference]	1
Female	358	0.97 (0.82 – 1.16)	0.767	0.98 (0.82 – 1.17)	0.810
Age					
<65 years	310	1 [Reference]	1	1 [Reference]	1
≥65 years	468	0.96 (0.79 – 1.16)	0.656	0.94 (0.79 – 1.13)	0.538
Performance status					
WHO 0	303	1 [Reference]	1	1 [Reference]	1
WHO 1	161	1.18 (0.95 – 1.46)	0.179	1.08 (0.87 – 1.35)	0.486
WHO 2 - 3	35	0.93 (0.58 – 1.50)	0.934	0.93 (0.58 – 1.49)	0.754
Tumor location					
Other	148	1 [Reference]	1	1 [Reference]	1
Head	615	1.29 (1.03 – 1.62)	0.029*	1.25 (0.99 – 1.58)	0.062
Pathological tumor size					
<30 mm	245	1 [Reference]	1	1 [Reference]	1
≥30 mm	338	1.70 (1.39 – 2.09)	<0.001*	1.54 (1.26– 1.89)	<0.001*
Lymph nodes					
Negative	199	1 [Reference]	1	1 [Reference]	1
Positive	579	1.83 (1.48 – 2.27)	<0.001*	1.56 (1.25 – 1.94)	<0.001*
Resection margin					
R0	424	1 [Reference]	1	1 [Reference]	1
R1	334	1.44 (1.21 – 1.71)	<0.001*	1.38 (1.15 – 1.65)	<0.001*
Tumor differentiation					
Well	93	1 [Reference]	1	1 [Reference]	1
Moderate	408	1.57 (1.17 – 2.10)	0.003*	1.50 (1.11 – 2.03)	0.008*
Poor/ Undifferentiated	168	2.35 (1.72 – 3.21)	<0.001*	2.12 (1.54 – 2.93)	<0.001*

Abbreviations: CI = confidence interval, GEM = gemcitabine, GEMCAP = gemcitabine with capecitabine, HR = hazard ratio, WHO = World Health Organization, * p<0.05

Imputation of missing data: sex (0%), age (0%), WHO performance status (36%), location (2%), pathological tumor size (27%), lymph nodes (0%), resection margin (3%), tumor differentiation (14%)

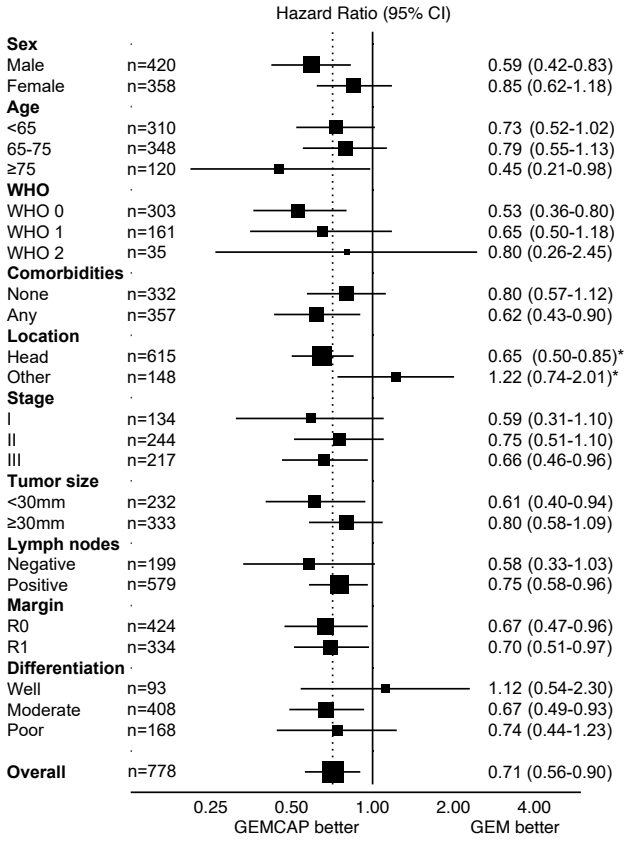

Figure 4. Forest plot of the treatment effect on overall survival in prespecified subgroups
* Significant interaction term of tumor location with adjuvant chemotherapy in unadjusted multivariable model including tumor location and adjuvant chemotherapy, p=0.02

Subgroup analyses demonstrated comparable or superior survival with adjuvant GEMCAP in almost all subgroups (Figure 4). A significant interaction was found between tumor location and treatment (p=0.02), with a significant benefit of GEMCAP in patients with a tumor located in the pancreatic head (HR: 0.65, 95% CI 0.50-0.85, p=0.002), but no significant benefit of GEMCAP in patients with a tumor located outside of the pancreatic head (HR: 1.22, 95% CI 0.74-2.01, p=0.44). The positive effect of GEMCAP on OS was found in both patients with a positive resection margin (HR: 0.70, 95% CI 0.51-0.97, p=0.034) and patients with a negative resection margin (HR: 0.67, 95% CI 0.47-0.96, p=0.029).

Table 3. Number of completed chemotherapy cycles in patients treated with gemcitabine with capecitabine (GEMCAP) or gemcitabine (GEM)*

Number of cycles (%)	Overall (n=778)	GEMCAP (n=164)	GEM (n=614)
>6	17 (2.2)	3 (1.8)	14 (2.3)
6	482 (62.0)	111 (67.7)	371 (60.4)
5	67 (8.6)	14 (8.5)	53 (8.6)
4	45 (5.8)	6 (3.7)	39 (6.4)
3	63 (8.1)	12 (7.3)	51 (8.3)
2	42 (5.4)	6 (3.7)	36 (5.9)
1	50 (6.4)	6 (3.7)	44 (7.2)
Unknown	12 (1.5)	6 (3.7)	6 (1.0)

* The proportion of patients who completed at least six chemotherapy cycles (p=0.11) and the proportion of patients who received three or less chemotherapy cycles (p=0.06) did not significantly differ between the two treatment groups.

Therapy

The proportion of patients completing six cycles of adjuvant chemotherapy was 69.5% in the GEMCAP group and 62.7% in the GEM group (p=0.11; Table 3). The proportion of patients receiving three or less cycles was 14.7% in the GEMCAP group and 21.4% in the GEM group (p=0.06).

Of the patients treated with GEMCAP, one patient switched to capecitabine monotherapy and five patients to gemcitabine monotherapy. Of the patients in the GEM group, one patient switched to GEMCAP, one patient to 5-FU and irinotecan, and four patients to capecitabine monotherapy as subsequent adjuvant therapy. One patient received tegafur/gimeracil/oteracil as third therapy after both gemcitabine and capecitabine monotherapy.

DISCUSSION

In this first nationwide study to compare adjuvant GEMCAP with adjuvant GEM in PDAC in daily clinical practice, adjuvant chemotherapy with GEMCAP was associated with a significantly prolonged OS compared with GEM monotherapy (median OS GEMCAP vs. GEM: 31.4 vs. 22.1 months; HR: 0.71, 95% CI 0.56-0.90, p=0.004). This survival benefit persisted after adjustment for known prognostic factors in a multivariable Cox regression analysis and was consistent across most subgroups. The number of completed chemotherapy cycles was similar in both treatment groups.

The survival benefit for patients treated with GEMCAP compared with GEM corresponds to the positive effect in the ESPAC-4 trial (median OS 28.0 vs. 25.5 months; HR: 0.82, 95% CI 0.68-0.98, p=0.032).[10] Our study thereby confirms the findings of the ESPAC-4 trial in an

unselected nationwide cohort. The superiority of GEMCAP on OS in our study appears to be even greater when compared with the ESPAC-4 study. However, differences in patient characteristics may explain the large difference to some extent. Both the present study and the ESPAC-4 trial excluded patients treated with neoadjuvant therapy and patients who underwent R2 resections. The ESPAC-4 trial also excluded patients with a poor performance status (WHO ≥2), while the present study included 7% of patients with WHO 2.[10] Several baseline characteristics in the ESPAC-4 trial were worse than in this nationwide cohort; for example, co-morbidity, R1 resection rate, and nodal disease. Nonetheless, these differences existed in both treatment groups, thus this cannot explain the larger treatment effect of GEMCAP found in the current study. A possible explanation for the larger survival benefit of GEMCAP compared with the ESPAC-4 trial is that our patients were not randomized, with subsequent risk of confounding by indication. Although our study showed no difference in baseline characteristics between GEMCAP and GEM and the benefit remained after adjustment for relevant prognostic factors, the possible influence of residual confounding increasing the effect cannot be completely ruled out. Of note, the proportion of patients with pancreatic cancer who are eligible for both surgery and adjuvant therapy is limited. The findings therefore apply to only this subset of patients. However, our patient selection is less restrictive than in clinical trials on adjuvant chemotherapy.

The median OS of patients treated with GEM in our study (22.1 months) and in the ESPAC-4 trial (25.5 months) was lower than the median OS with GEM found in both the PRODIGE 24 trial (35.5 months) and the APACT trial (36.2 months, abstract available only).[11] This might be attributed to the more stringent selection criteria in these randomized studies, including only patients with a good performance status (WHO score 0-1) and with a serum carbohydrate antigen (CA) 19-9 level below 180 U/mL (PRODIGE) or below 100 U/mL (APACT). No criteria on CA 19-9 level was used in either the ESPAC-4 trial and the current study. Another explanation could be a difference in receipt of palliative treatment in case of disease recurrence. This data is unknown for the current study. However, a previous Dutch nationwide study among PDAC patients who underwent resection showed that only 31% of the patients with symptomatic recurrence and 48% of the patients with asymptomatic recurrence received palliative treatment.[31] Due to these inequalities between randomized studies, it is difficult to make a direct comparison between the intervention arms of different randomized studies (e.g., GEMCAP, mFOLFIRINOX, and nab-paclitaxel plus gemcitabine). Randomized trials with direct comparisons are required to assess which of these contemporary multi-agent chemotherapy regimens shows the most favorable results.

We found that treatment with GEMCAP was associated with better OS than GEM alone, for patients with a positive and negative resection margin. This is in contrast with the ESPAC-4 trial, in which the survival benefit of GEMCAP was only demonstrated in patients with a negative resection margin.[10] Both international and national guidelines do not distinguish between patients with positive and patients with negative resection margins.[20, 21] Our study

confirms that the choice of therapy should not depend on resection margin status. Furthermore, GEMCAP seems to result in a larger survival benefit compared to GEM in patients with a better performance status compared to patients with a poorer performance status. However, only a limited number of patients with a poor performance status (WHO=2) were included in this study. The interpretation of the impact of performance status on the found survival benefit is therefore hampered.

The addition of capecitabine to gemcitabine does not seem to result in less cycles of gemcitabine. The proportion of patients receiving a minimum of six cycles was similar in the GEMCAP group (69%) compared with the GEM group (62%). Adverse events and dose intensities were not available for our study population, but the ESPAC-4 trial observed no differences in reported adverse events between both treatment groups (26% vs. 25%, $p>0.05$).[10] In addition, a randomized trial comparing GEMCAP to GEM in patients with locally advanced PDAC showed acceptable levels of toxicity for both treatment groups.[14]

The use of GEMCAP increased after the results of the ESPAC-4 trial were published in March 2017.[10] The use of GEM alone also decreased over time due to the introduction of adjuvant mFOLFIRINOX. Overall, the number of patients who received adjuvant chemotherapy declined due to the increased use of neoadjuvant strategies in more recent years. The Dutch nationwide PREOPANC-2 study comparing two neoadjuvant strategies for patients with resectable or borderline resectable PDAC was initiated in June 2018, with neoadjuvant treatment precluding eligibility for the current study.[32]

This is the first study comparing adjuvant GEMCAP with adjuvant GEM in resectable PDAC in daily clinical practice. However, some limitations of this study should be taken into account. First, the number of patients receiving GEMCAP was only 164 patients, resulting in wide confidence intervals. Second, data on recurrence, palliative treatment, quality of life, and adverse events were not available, thereby precluding additional comparisons such as disease-free survival and toxicity. As a result, we cannot conclude what the impact of both adjuvant chemotherapies is on disease-free survival, how palliative treatment might have affected the overall survival, and what the impact of possible side effects has been. Third, inherent to the retrospective study design, some data (e.g., tumor size and WHO performance status) were incomplete, which was addressed by multiple imputation in the multivariable Cox regression analysis. Fourth, although we adjusted for many variables, not all possible prognostic variables (e.g., CA 19-9 and smoking) were available, with subsequent risk of residual confounding.[33] Fifth, our study population differs from the current patient population as mFOLFIRINOX was introduced in 2019, which is currently considered the preferred adjuvant treatment for most eligible patients.[20, 21] Last, patients who received neoadjuvant therapy were excluded from our study, thereby limiting the generalizability to this specific population.

To conclude, this nationwide study demonstrated that the GEMCAP is associated with better OS as compared to gemcitabine monotherapy. The proportion of patients receiving the planned number of six chemotherapy cycles were similar in both treatment groups. Therefore, adjuvant gemcitabine plus capecitabine should be preferred over gemcitabine monotherapy in patients who are not eligible for mFOLFIRINOX.

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PART IV

SUMMARY, DISCUSSION, AND APPENDICES

CHAPTER 13

Summary, discussion, and future perspectives

SUMMARY

The prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) remains poor, with only minor improvements in overall survival (OS) shown over the last decade. Even patients with radiographically early-stage disease are at high risk of disease recurrence following curative-intent resection. Therefore, one of the most important challenges is to find more effective systemic treatment options and to identify which patients may benefit from additional local treatment including radiotherapy and surgery. Optimal treatment, however, first requires an optimal diagnostic workup. The purpose of this thesis was threefold. First, to evaluate the diagnostic workup of focal pancreatic lesions. Second, to investigate the outcomes of patients with localized PDAC, with a special focus on neoadjuvant treatment of borderline resectable and resectable PDAC. Finally, to assess the role of neoadjuvant radiotherapy and adjuvant systemic treatment other than (m)FOLFIRINOX.

PART I: DIAGNOSTIC WORKUP OF FOCAL PANCREATIC LESIONS

Part I of this thesis described the diagnostic workup of patients with a focal pancreatic lesion. The differentiation between low risk pre-malignant versus high risk pre-malignant or malignant lesions can be challenging, with concern about both surgical over- and under-treatment. Optimization of the diagnostic workup of focal pancreatic lesions is therefore essential. Often, noninvasive cross-sectional imaging is used as initial diagnostic procedure, which may be followed by endoscopic ultrasonography (EUS) with or without additional tissue acquisition (TA). In **Chapter 2,** the additional value of EUS after cross-sectional imaging was assessed in patients with focal pancreatic body or tail lesions, showing that a preoperative EUS was of additional diagnostic value in 48% of all patients who underwent a resection. This additional value of EUS was more profound in patients with a cystic lesion (54%) compared to patients with a solid lesion (44%). The additional value of EUS was mostly based on providing the correct diagnosis in case of discrepancy with cross-sectional imaging. No serious adverse events following EUS were reported. In **Chapter 3**, the sensitivity of the different diagnostic modalities (i.e., CT, MRI, and EUS) was compared in the same cohort of patients who underwent a resection of a focal pancreatic body or tail lesion as Chapter 2. Sensitivity was thereby defined as the probability to determine the correct postoperative diagnosis. CT was the most sensitive modality for solid lesions (sensitivity 75%), whilst EUS with tissue acquisition (TA) was the most sensitive diagnostic procedure for cystic lesions (sensitivity 75%). Moreover, EUS with TA increased sensitivity to 71% compared to 64% with EUS without TA.

The ability to obtain a tissue diagnosis is one of the key advantages of endoscopic procedures over cross-sectional imaging. **Chapter 4** evaluated the diagnostic performance of the different endoscopy-guided TA procedures performed prior to inclusion in the PREOPANC and PREOPANC-2 randomized controlled trials (RCTs), which both included a neoadjuvant treatment arm. In this first nationwide study including 617 patients with suspected PDAC,

EUS-guided TA showed the highest sensitivity for malignancy of 85% (including both suspicious for malignancy and malignant as positive). Thereby, the international reference standard of ≥85% (including only malignant as positive) was approximated.[1] In comparison, the sensitivity of malignancy was 52% for ERCP-guided brush cytology and 38% for periampullary biopsies. The rate of adequate sampling, defined as the proportion of all procedures yielding a specimen sufficient for cyto-and/or histopathological analysis, was high for all endoscopy-guided TA procedures, ranging 94-100%. The rate of false positive result for malignancy (i.e., TA was at least suspicious for malignancy, but resected specimen showed no cancer) was 2% and misdiagnosis of other periampullary cancers was 5%.

PART II: NEOADJUVANT TREATMENT OF PANCREATIC CANCER

For patients with borderline resectable and resectable PDAC, upfront surgery followed by adjuvant chemotherapy has long been the standard treatment. With this strategy, however, about 40-50% of patients never receive systemic treatment due to postoperative complications or clinical deterioration. Consequently, an increasing number of studies have focused on the role of upfront (i.e., neoadjuvant or perioperative) systemic treatment. In **Chapter 5,** we gave an overview of the current treatment strategies for patients with borderline resectable and resectable PDAC, discussed the rationale for neoadjuvant treatment, and outlined the challenges when comparing studies focused on neoadjuvant and adjuvant treatment. The most important advantages of a neoadjuvant treatment strategy include the early treatment of and increased number of patients who receive systemic treatment for occult metastatic disease. Furthermore, it might increase the margin negative (R0) resection rate due to reduction of the tumor volume. Last, the neoadjuvant treatment time provides a 'test-of-time', during which patients with a rapidly progressive tumor can be identified at restaging following neoadjuvant treatment, thereby preventing futile surgery.

Chapter 6 combined the evidence of seven RCTs comparing a neoadjuvant approach with upfront surgery including 938 patients with borderline resectable or resectable PDAC. This meta-analysis demonstrated an improved OS with neoadjuvant therapy (hazard ratio (HR): 0.66, 95% CI: 0.52-0.85, p=0.001), representing an increase in median OS from 19 to 29 months. However, this evidence mainly applied to patients with borderline resectable PDAC. In addition, most trials in this meta-analysis included different types of mostly single-agent neoadjuvant chemotherapy, whilst multi-agent chemotherapy regimens are preferred nowadays.

Chapter 7 assessed the survival and toxicity following neoadjuvant (m)FOLFIRINOX in a patient-level meta-analysis including 283 patients with borderline resectable PDAC from 20 studies. The pooled median OS was 22.2 months, with a median progression-free survival of 18.0 months. The rate of severe adverse events was high, but no deaths were attributed to (m)FOLFIRINOX. Neutropenia (17.5 per 100 patients), diarrhea (11.1 per 100 patients), and fatigue (10.8 per 100 patients) were most commonly reported.

Chapter 8 described outcomes after (m)FOLFIRINOX as initial treatment of 1,835 consecutive patients with localized PDAC treated in five referral centers from the United States and the Netherlands (2012-2019). This study was the initial study of the **Trans-Atlantic Pancreatic Surgery (TAPS) consortium**. The resection rate after initial (m)FOLFIRINOX was 18% for locally advanced, 53% for borderline resectable, and 71% for resectable PDAC. The median OS was 18.7 months (95% CI, 17.7-19.9) for locally advanced, 23.2 months (95% CI, 21.0-25.7) for borderline resectable, and 31.2 months (95% CI, 26.2-36.6) for resectable PDAC. Independent prognostic factors at baseline for poor OS were more advanced stage, worse performance status, baseline CA 19-9 >500 U/mL, and BMI ≤18.5 kg/m2.

In **Chapter 9**, the study protocol of the PREOPANC-2 trial was presented, comparing neoadjuvant FOLFIRINOX (8 cycles) to neoadjuvant gemcitabine-based chemoradiotherapy (3 cycles, 36 Gy in 15 fractions) followed by adjuvant gemcitabine (4 cycles) for patients with borderline resectable and resectable PDAC. This nationwide RCT completed accrual of 375 patients in January 2021, after a rapid accrual phase of 2.5 years. The results for the primary outcome of OS are expected by the end of 2022.

PART III: RADIOTHERAPY AND ADJUVANT TREATMENT OF PANCREATIC CANCER

Chapter 10 and **Chapter 11**, investigated the role of radiotherapy following neoadjuvant (m) FOLFIRINOX for patients with borderline resectable or resectable PDAC. First, in a meta-analysis presented in **Chapter 10**, 512 patients from 15 studies were included, showing a higher R0 resection rate for patients who received additional radiotherapy (98% vs. 88%, p=0.045). However, other outcomes including OS, resection rate, and other pathological outcomes (pathologic complete response, perineural invasion, positive lymph nodes) were comparable in patients with and without radiotherapy. In **Chapter 11,** the added value of radiotherapy following (m)FOLFIRINOX for borderline resectable PDAC was addressed in a propensity score matched analysis of 300 patients from the international TAPS consortium. Neoadjuvant radiotherapy following (m)FOLFIRINOX was associated with a comparable R0 resection rate (70.6% vs. 64.8%, p=0.51), more node-negative disease (57% vs. 38%, p=0.01), and more major pathologic response (25% vs. 8%, p=0.006) in patients who underwent a resection, yet again no difference in median OS could be demonstrated (26.2 vs. 32.8 months, p=0.71). Median OS after conventional and stereotactic body radiation approaches was similar (25.7 vs. 26.0 months, p=0.92).

Finally, **Chapter 12** focused on adjuvant chemotherapy in a nationwide cohort of 778 patients who underwent a resection for PDAC and received adjuvant gemcitabine monotherapy (n=164) or gemcitabine plus capecitabine (n=164). This study investigated the research question of the ESPAC-4 trial in a real-world setting.[2] It confirmed that adjuvant gemcitabine plus capecitabine was associated with superior OS compared to gemcitabine monotherapy (31.4 vs. 22.1 months, HR=0.71, p=0.004). This survival difference remained after adjustment for prognostic factors.

DISCUSSION AND FUTURE PERSPECTIVES

This closing chapter discusses the clinical implications from this thesis and sheds light on future perspectives.

Diagnostic workup of focal pancreatic lesions

The diagnostic workup in patients with a focal pancreatic lesion continues to improve, with better protocols and techniques for both noninvasive and invasive procedures. Despite a thorough diagnostic workup, however, the differentiation between low- and high-risk pancreas lesions remains challenging. This was demonstrated by **Chapter 2** and **Chapter 3,** which concerned pancreatic body or tail lesions. These lesions are often underexposed in literature, and both chapters give a clear overview of the diagnostic value and accuracy of different modalities in this specific subgroup of patients. **Chapter 2** underlined that, even in patients for whom upfront surgery without a preoperative tissue diagnosis has been a commonly accepted approach, EUS has significant clinical value for both cystic (54%) and solid (44%) lesions. With the upcoming use of a neoadjuvant approach for PDAC, the value of EUS-guided TA is expected to even further increase. In addition, EUS-guided TA confirming a low grade small non-functional pancreatic neuroendocrine tumor (pNET) or mucinous neoplasm may safely allow active surveillance. **Chapter 3** showed a relatively modest accuracy for the different diagnostic modalities (75% at highest) in diagnosing solid and cystic pancreatic lesions. This may be partly due to the fact that diagnostically challenging lesions, including mucinous cystic neoplasm (MCN) and solitary pseudopapillary neoplasm (SPN), mainly occur in the pancreatic body and tail. The difficulty of correctly differentiating focal pancreatic lesions was also demonstrated by the finding of surgical overtreatment (i.e. resection of a benign or low-grade premalignant tumor) in 33% of cystic and 10% of solid lesions **(Chapter 2)**. Although no other study has specifically focused on pancreatic body and tail lesions, the substantial risk of surgical overtreatment has been confirmed in other studies, especially for pancreatic cystic lesions.[3,4] On the other hand, the risk of surgical overtreatment should be weighed against the risk of delayed treatment of cancer or lesions with high-grade dysplasia. Other factors to consider are the burden and costs of repeated follow-up with ongoing uncertainty and decreased quality of life. Uniform clinical practice guidelines are required to weigh all these factors and assist in the diagnosis, treatment, and follow-up of all types of pancreatic lesions.[5] Increased knowledge about the risk of malignant transformation of premalignant and progression of indolent pancreatic lesions (e.g., small pancreatic NETs) may further improve guidelines. Ongoing prospective studies evaluating this risk include the PACYFIC study (www.pacyfic.net) for asymptomatic pancreatic cystic neoplasms and the PANDORA study for small non-functional pNETs (Trial NL9584).[6,7]

In patients with suspected PDAC, another challenge lies within optimizing the logistics of the diagnostic workup. This is especially profound in patients who present with obstructive

jaundice, requiring both TA confirming PDAC and biliary drainage. Ideally, it would only require one procedure combining stent placement with TA, which would inherently be an ERCP. In reality, however, the sensitivity for malignancy of ERCP-guided brush for suspected PDAC is only 50%. An EUS-guided TA procedure is therefore often required, which has a clearly higher sensitivity for malignancy of ≥85% **(Chapter 4).** The debate on the sequence of these procedures is ongoing, especially in view of the yield of EUS-guided TA in the presence of biliary stents. Studies reporting this association for lesions in the head of the pancreas have been conflicting.[8-13] Some studies advocate either combined procedures or that EUS-guided TA should precede ERCP, especially in patients with small tumors, based on the finding of lower sensitivity and accuracy of EUS-guided TA following biliary stenting.[8-10] In contrast, other studies concluded that the diagnostic yield of EUS-guided TA was not adversely affected by biliary stenting.[11-13] Larger prospective and randomized studies are needed to clarify this ongoing debate. An efficient and patient-friendly option would be to combine the procedures. Some centers in the Netherlands have already created an infrastructure to efficiently plan combined procedures for patients presenting with obstructive jaundice. For many centers, however, it may be logistically challenging to plan a combined procedure due to the necessary presence of a specialized team including a gastroenterologist capable of performing both procedures, an anesthesiologist, and endoscopy assistants. In daily practice, patients with obstructive tumors are therefore often first planned to undergo an ERCP to alleviate symptomatic jaundice. In that case, it should be advised await the pathology report prior to performing an additional EUS procedure, since this may prevent the need for an additional endoscopy-guided TA procedure in approximately half of the patients **(Chapter 4)**. The additional EUS-guided TA procedure may already be planned, but would only be required in case of an uncertain or negative result, which is a clear benefit of this two-step approach. A potential drawback to consider is that brush cytology often contains insufficient diagnostic material for further analyses. This may become more essential in the following decades, partly depending on the further development of new analytic methods such as next generation sequencing (NGS) and the use of tumor-derived organoids as a tool to predict treatment response.[14] The use of organoid profiling is still under research, but may play a role in the road towards more personalized treatment in the future. The need for histology over cytology would influence the sequence of the diagnostic workup, further advocating a combined procedure of EUS and ERCP since both procedures would then be required for all patients.

Other strategies to enhance the diagnostic workup are the use of pathological and radiological review in pancreas expertise centers and the formation of regional multidisciplinary interest groups **(Chapter 4)**.[15] In addition, based on recent studies, molecular analyses using next-generation sequencing of acquired tissue and cystic fluid may increase the level of certainty of a diagnosis and detect advanced neoplasia.[16,17] On the contrary, rapid on-site evaluation of EUS-guided TA does not seem to improve the accuracy and sensitivity for malignancy in experienced centers, as was demonstrated by two recent multicenter RCTs

(FNB with ROSE vs. FNA without ROSE: 96.4% vs. 97.4%, p=0.40; FNA with ROSE vs. FNB without ROSE 93.3% vs. 92.2%, p=0.72, respectively).[18,19]

As was shown in this first part of the discussion, correctly diagnosing premalignant and malignant pancreatic lesions remains challenging, emphasizing the need for improvement. Improving the logistics and accuracy of the diagnostic workup will lead to reduced costs and, most importantly, a lower patient burden.

Neoadjuvant versus adjuvant treatment

For patients with PDAC, a decision on the treatment strategy should be made based on factors including the disease stage, tumor markers, performance status, comorbidities, age, and patient preferences. Consensus has been reached that outcomes are best if patients with borderline resectable or resectable PDAC receive both surgery and systemic treatment, rather than surgery alone. The debate on the preferred treatment sequence for resectable PDAC is ongoing and seems to have led to a dichotomy in believers and non-believers in a neoadjuvant approach versus upfront surgery.

As was outlined in **Chapter 5**, a neoadjuvant approach overcomes the most important drawback of upfront surgery, by giving timely systemic treatment to the vast majority of patients diagnosed with borderline resectable and resectable PDAC. On the other hand, opponents of a neoadjuvant approach argue that disease progression or clinical deterioration may occur during neoadjuvant treatment, thereby precluding a resection. However, it seems likely that early disease progression reflects the aggressive tumor biology rather than a missed opportunity of resection **(Chapter 5)**.

As presented in this thesis, evidence that a neoadjuvant approach is superior to upfront surgery for patients with borderline resectable PDAC is convincing **(Chapter 5-8)** .[20-26] The meta-analysis described in **Chapter 6** is the best available evidence for the neoadjuvant approach. Nowadays, both the NCCN (www.nccn.org) and Dutch guideline (www.richtlijnendatabase.nl) indeed recommend a neoadjuvant approach for borderline resectable PDAC.

Although most theoretical advantages of a neoadjuvant approach also apply to patients with resectable PDAC, definitive evidence favoring either approach for this stage is lacking. In our meta-analysis of all RCTs comparing the two treatment strategies **(Chapter 6),** no statistically significant difference in OS was observed in the subgroup analysis of patients with resectable PDAC. In addition, a stratified subgroup analysis in the PREOPANC trial comparing neoadjuvant gemcitabine-based chemoradiotherapy (3 cycles) and adjuvant gemcitabine (4 cycles) to upfront surgery and adjuvant gemcitabine (6 cycles) showed no significant difference in survival between the treatment arms in patients with resectable PDAC (HR 0.79; 95% CI 0.54 to 1.16; p=0.23). The interaction test of hazard rates, however, showed no significant difference between patients with borderline resectable and

resectable PDAC (p=0.12), thus this difference should be interpreted with caution.[27,28] Given the clinical equipoise between neoadjuvant and adjuvant treatment for resectable PDAC, RCTs comparing a neoadjuvant approach to upfront surgery are needed. Currently ongoing RCTs in patients with resectable PDAC include the NorPACT-1 trial from Denmark,[29] the PANACHE01-PRODIGE48 trial from France,[30] and the ALLIANCE A021806 trial from the United States of America (NCT04340141). In addition, the successor of the PREOPANC-2 trial **(Chapter 9)**: the PREOPANC-3 trial, has recently started accrual (NCT04927780). This trial compares neoadjuvant mFOLFIRINOX (8 cycles) followed by adjuvant mFOLFIRINOX (4 cycles) to adjuvant mFOLFIRINOX (12 cycles).

Opponents of a neoadjuvant approach point out that the median OS of the RCT comparing adjuvant FOLFIRINOX with adjuvant gemcitabine found a median OS of 54 months for adjuvant FOLFIRINOX.[31] This is clearly favorably to the median OS of 18 months for patients in the neoadjuvant chemoradiotherapy arm of the PREOPANC trial.[27,28] Who would choose a neoadjuvant approach when comparing these results? Survival outcomes of RCTs including only adjuvant regimens, however, cannot be compared to neoadjuvant RCTs due to a large difference in patient population **(Chapter 5)**. In order to be eligible for a trial on adjuvant chemotherapy, patients need to overcome several hurdles. First, stent-related problems can lead to postponement and cancellation of surgery. Second, occult metastases (10%) or unexpected locally unresectable disease (10%) can be found during surgery, precluding a resection.[32] Third, approximately 5% of patients die of postoperative complications, and 40% of patients do not recover sufficiently and timely to start adjuvant chemotherapy.[33-35] Last, patients are ineligible for adjuvant RCTs if they have early recurrence or elevated carbohydrate antigen (CA) 19-9. As a consequence, up to 75% of patients diagnosed with borderline resectable or resectable PDAC will never become eligible for a trial on adjuvant chemotherapy. In contrast, patients included in a trial on neoadjuvant chemotherapy do not need to overcome all these hurdles. This dissimilarity in study populations hampers a direct comparison between studies in the neoadjuvant and adjuvant settings. This selection is most strikingly demonstrated by comparing the outcomes following the exact same adjuvant treatment between neoadjuvant and adjuvant trials: median OS for adjuvant gemcitabine was 14 months in the PREOPANC trial (neoadjuvant study) yet 35 months in the PRODIGE 24/CCTG PA.6 trial (adjuvant study).[27,31] Thus, only studies randomizing patients to neoadjuvant or adjuvant treatment and performing intention-to- treat analyses can determine which strategy should be preferred. In addition, in the near future, patients will undoubtedly no longer only be staged on radiological images, but biomarkers such as CA 9-9 and others will likely play an important role for the selection of the optimal treatment.

Which chemotherapy regimen

The choice of chemotherapy regimen still largely depends on the performance status of the patient. Contemporary multi-agent chemotherapy regimens are mainly indicated for patients with a good performance status due to the high toxicity levels associated with

these regimens. For those relatively fit patients, mFOLFIRINOX and gemcitabine with nab-paclitaxel are the most widely used regimens nowadays. In the Netherlands, (m)FOLFIRINOX is often preferred due to more convincing superiority to gemcitabine monotherapy compared to gemcitabine with nab-paclitaxel and the lower associated costs.[36,37] Phase 3 RCTs focusing on preoperative (m)FOLFIRINOX for localized PDAC are lacking. Therefore, two large patient-level meta-analyses on induction (m)FOLFIRINOX for locally advanced PDAC [38] and neoadjuvant (m)FOLFIRINOX for borderline resectable PDAC **(Chapter 7)** have been the best available evidence. Based on these meta-analyses, (m)FOLFIRINOX was included in international guidelines as one of the preferred treatments in both settings. More recently, the TAPS cohort is the largest cohort of consecutive patients with localized PDAC who received (m)FOLFIRINOX as initial treatment **(Chapter 8)**. The results of this study will improve shared decision making by patients and clinicians by providing realistic estimates of resection rates and survival in patients with localized PDAC who started (m)FOLFIRINOX treatment in PDAC referral centers.

Although (m)FOLFIRINOX seems promising, the lack of high-level evidence directly comparing neoadjuvant mFOLFIRINOX to gemcitabine with nab-paclitaxel preclude a final conclusion on which regimen is superior. Available evidence comparing these regimens has been inconsistent. A meta-analysis of eight retrospective studies suggested prolonged OS with (m)FOLFIRINOX compared to gemcitabine with nab-paclitaxel for localized PDAC (HR: 0.65, 95% CI: 0.55–0.77, $p<0.001$).[39] In contrast, the phase 2 SWOG S1505 comparing 12 weeks of perioperative treatment (6+6) with either mFOLFIRINOX or gemcitabine with nab-paclitaxel for resectable PDAC showed no difference in median OS (23.2 vs. 23.6 months).[40]

Other neoadjuvant chemotherapy regimens that have been studied include gemcitabine plus capecitabine and gemcitabine- or capecitabine-based chemoradiotherapy. The four-arm phase 2 ESPAC-5F trial compared upfront surgery to neoadjuvant FOLFIRINOX, gemcitabine plus capecitabine, or capecitabine-based chemoradiotherapy in patients with borderline resectable PDAC.[41] Among the neoadjuvant treatment regimens, FOLFIRINOX demonstrated the best survival at one year, but the small number of included patients (90 in total) preclude any strong conclusion. Last, the Dutch PREOPANC-2 trial described in **Chapter 9** compared neoadjuvant FOLFIRINOX to neoadjuvant gemcitabine plus radiotherapy followed by adjuvant gemcitabine, the latter being the winning arm of the PREOPANC trial. The PREOPANC-2 trial is the largest RCT for borderline resectable or resectable PDAC to date and this study will provide high-level evidence on the neoadjuvant treatment of choice for these patients.

In the adjuvant setting, several regimens showed superior OS compared to gemcitabine alone in large RCTs, although this was clearly most profound for adjuvant mFOLFIRINOX.[2,31,42] Based on these trials, both adjuvant gemcitabine plus capecitabine and gemcitabine plus nab-paclitaxel are included in guidelines as suitable options for patients who are not eligible

for mFOLFIRINOX. Due to the often stringent selection criteria used in RCTs, favorable results of RCTs may not be seen in daily clinical practice. For this reason, **Chapter 12** investigated outcomes following adjuvant gemcitabine plus capecitabine or gemcitabine monotherapy in a real-world setting outside of an RCT. This was the first population-based study that showed a significantly better OS with adjuvant gemcitabine plus capecitabine. The obtained results may help medical oncologists to select appropriate adjuvant chemotherapy in patients who may not tolerate mFOLFIRINOX.

Radiotherapy

The role of radiotherapy is one of the much debated issues in pancreatic cancer care. International NCCN guidelines include radiotherapy as optional treatment for selected patients with localized PDAC, without further specification of when this should be considered.[43] This is due to the lack of RCTs that have demonstrated a clear survival benefit of radiotherapy. The PREOPANC trial showed that neoadjuvant chemoradiotherapy was superior to adjuvant chemotherapy.[27,28] This study, however, could not distinguish between the benefit from the neoadjuvant approach and the benefit from the additional radiotherapy. The rationale behind neoadjuvant radiotherapy is that it may improve locoregional control by local ablation and by sterilizing positive resection margins and targeting regional lymph nodes. **Chapter 10** and **11** indeed showed that radiotherapy following (m)FOLFIRINOX was associated with improved R0 and node-negative resection rates, but a difference in OS could not be demonstrated. Therefore, routine use of radiotherapy cannot be recommended based on these data. As systemic therapies continue to improve, however, the effect of better locoregional control on survival may become more evident. Thus, radiotherapy remains of interest in future studies. Currently ongoing RCTs assessing the role of neoadjuvant radiotherapy for borderline resectable or resectable PDAC include the three-arm BRPCNCC-1 trial (NCT03777462), the PANDAS-PRODIGE44 trial (NCT02676349), the PREOPANC-2 trial **(Chapter 9)**, the MASTERPLAN study (NCT04089150), and the SOFT study (NCT03704662).

RCTs specifically investigating the additional value of radiotherapy for localized PDAC should randomize patients after completion of systemic treatment. This study design will minimize the noise of dropouts due to progressive disease during systemic treatment. A staging laparoscopy prior to start of initial treatment should be considered for adequate staging, since patients with occult metastatic disease are unlikely to benefit from local therapies.

Evidence on the efficacy of stereotactic body radiation therapy (SBRT) compared with conventional radiotherapy has been conflicting. To date, no prospective trial has directly compared these radiotherapy strategies. The propensity-score matched analysis of patients with borderline resectable PDAC in **Chapter 11** showed no difference between these strategies, whilst a large retrospective study found superior OS with SBRT in patients with resectable PDAC compared with conventional radiotherapy (median OS: 29 vs. 16 months,

p=0.002).[44] In the phase 2 Alliance A021501 trial, neoadjuvant mFOLFIRINOX followed by SBRT showed disappointing results, with no difference in OS compared to historical data and clearly lower OS than mFOLFIRINOX without SBRT (median OS: 17 vs. 31 months).[45] In contrast, its predecessor study (Alliance A021101) evaluating neoadjuvant mFOLFIRINOX followed by conventional radiotherapy showed more favorable outcomes (median OS: 21.7 months, 93% R0 resection, 47% major pathologic response).[46] A possible explanation for the disappointing results of SBRT in the Alliance A021501 trial is that the introduction of SBRT may have been prematurely applied, with insufficient experience using this approach.[47] Due to its high local ablative nature, SBRT may especially be of value in patients for whom the preferred locoregional treatment, a surgical resection, is not possible. Additionally, the concern of under coverage of high-risk vascular targets using SBRT, potentially contributing to local recurrences, does not apply to locally unresectable tumors. Indeed, several studies found promising results of SBRT in patients with locally advanced PDAC.[48-50] However, before definitively closing the door on SBRT for borderline resectable and resectable PDAC, the results of the previously mentioned MASTERPLAN study (NCT04089150) and SOFT study (NCT03704662) should be awaited, both directly comparing SBRT to conventional radiotherapy.

Another potential effect of radiotherapy may be the induction of an antitumor immune response, especially when combined with immunotherapy.[51-53] The use of immunotherapy in combination with radiotherapy is still in development but these investigations may provide a step towards a better understanding of the immune suppressive tumor microenvironment of PDAC and subsequent treatment targets (Trial NL7578).[54]

Adjuvant treatment following neoadjuvant treatment

Current guidelines recommend a total systemic treatment duration of at least 6 months for patients with localized PDAC, without specifying the perioperative distribution of systemic treatment.[43] Some clinicians recommend total neoadjuvant therapy whilst others advocate for a perioperative treatment approach. Published studies on this topic have shown conflicting results. A large retrospective cohort study including 1,357 patients showed no difference in OS between patients who did and did not receive adjuvant chemotherapy following neoadjuvant treatment and resection.[55] In contrast, other studies did demonstrate a survival benefit of adjuvant chemotherapy after neoadjuvant treatment and resection, irrespective of margin and nodal status.[56,57] Last, some studies suggested that adjuvant treatment only benefits the subgroup of patients with pathology-proven node-positive disease[58] or without clear CA 19-9 response following neoadjuvant treatment,[59] respectively. These opposing results may be partly explained by differences in type and duration of the neoadjuvant treatment. RCTs should be conducted to assess the role of adjuvant following neoadjuvant treatment, with stratification based on tumor marker response and nodal status. Finally, future studies should assess whether a switch to a different adjuvant systemic chemotherapy regimen based on the pathologic response could improve OS.

National and international collaborations

Slow accrual is a common pitfall in pancreatic cancer trials. This may result in hampered external validity, outdated results, and even early termination of trials which was the case in four RCTs over the past decade.[21,60-62] In contrast, both the PREOPANC and PREOPANC-2 trial both showed a high monthly accrual rate. This success largely depends on to the continuous effort and dedication of the local research teams including treating physicians, nurses, supporting professionals, and PhD candidates. Additionally, it underlines the effectiveness of national collaborations such as the Dutch Pancreatic Cancer Group (DPCG), which was initiated in 2011 and has since been one of the front leading collaborations in pancreatic cancer research worldwide. The DPCG consists of a multidisciplinary group of experts in the field of hepato-pancreato-biliary diseases, including surgeons, medical oncologists, gastroenterologists, radiation oncologists, pathologists, radiologists, and supporting professionals. This collaboration has been a successful platform for large multicenter studies with nationwide coverage, including but not limited to the PREOPANC trials. The benefits of the DPCG collaboration go beyond the conduct of RCTs. In addition, many multicenter retrospective cohort studies are performed **(Chapter 2** and **3)**, knowledge is shared through regular educational meetings, multidisciplinary discussions are promoted, patient organizations are actively involved, and initiatives to improve best-practices have been implemented throughout the country.[63]

Population-based registries are another important asset in improving pancreatic cancer research and care. In the Netherlands, important registries include the Netherlands Cancer Registry (NCR), the Dutch Pathology Registry (PALGA), the surgical registry (Dutch Pancreatic Cancer Audit (DPCA)), and the PACAP-PROMs for patient reported outcome measures. Within this thesis, we were able to use both the PALGA registry **(Chapter 4)** and the NCR **(Chapter 12)**.

Besides national collaborations, initiatives of international collaborations should be promoted. Advantages of international collaborations include the ability to share knowledge, better define standard treatment, create uniform definitions of outcome measures, compare practice variations and outcomes, and to better understand the influence of confounding factors. The multicenter TAPS consortium was used for **Chapter 8** and **11** and will form the basis of many future research projects. Legal issues have significantly slowed down our research collaboration and may deter others from collaborating. In order to overcome these hurdles and stimulate future international research collaborations, privacy legislation experts should investigate new legislation for international scientific research with patient data.

Personalized treatment and Quality of Life

Toxicity of contemporary multi-agent regimens remains a major concern in PDAC management. Unfortunately, not all patients benefit from these aggressive treatments, with the risk

of tumor progression during treatment while patients experience severe side-effects. Ideally, one would be able to predict the treatment response based on easily accessible biomarkers, such as circulating biomarkers using “liquid biopsies” or organoids for drug screening and next generation sequencing of tumor biopsies to find targetable drugs. This may enable more personalized cancer treatment. At present, no biomarker has been prospectively validated, nor is it used in daily clinical practice. However, several promising candidate biomarkers are being studied, including ctDNA, miRNA, and cytokines.[64-67] In the PREOPANC-2 trial **(Chapter 9)**, multiple blood samples before, during, and after treatment were successfully collected for almost 90% of patients. The collection of these samples within a large RCT forms a unique and valuable source for future research and may pave the path for further improvements in the management of patients with PDAC. In addition, the personal values of the individual patient should become more important in future practice. The concept of value-based healthcare has recently been implemented for breast cancer in the Erasmus MC Cancer Institute.[68] Future initiatives should aim to incorporate this patient-centered approach for patients with PDAC. The implementation of this new treatment concept will take time and requires an open mindset for treating clinicians. In the meantime, monitoring of the quality-of-life, tolerability of treatment, and other patient-reported outcome measures should be considered mandatory elements of good clinical practice. This has already been effectuated in the Netherlands, whereby all patients with newly diagnosed PDAC are contacted by a centrally coordinated team from within the DPCG to participate in prospective studies focused on quality-of-life. This centralized collection of patient reported outcomes is also used for RCTs such as the PREOPANC-2 trial, which assessed quality-of-life as one of the main endpoints. The outcomes of these studies should be further incorporated in the shared decision-making process by patients and clinicians.

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CHAPTER 14

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Patiënten die worden gediagnosticeerd met een pancreascarcinoom hebben vaak een slechte prognose en de overleving is de afgelopen 10 jaar slechts minimaal verbeterd. Zelfs patiënten met een vroeg stadium van de ziekte, bij wie een operatie nog mogelijk is, hebben een hoog risico op terugkeer van de tumor na een operatie. We staan voor de grote uitdaging om effectievere systemische behandelingsopties te ontdekken en te onderzoeken welke patiënten baat kunnen hebben bij een aanvullende lokale behandeling, waaronder bestraling en een operatie. Een optimale behandeling vereist echter eerst optimale diagnostiek. Het doel van dit proefschrift was drieledig. Ten eerste, om de diagnostiek van focale pancreaslaesies te evalueren. Ten tweede, om de uitkomsten van patiënten met gelokaliseerde pancreascarcinoom te onderzoeken, met een speciaal focus op de uitkomsten na neoadjuvante (preoperatieve) behandeling van patiënten met een resectabel of borderline resectabel pancreascarcinoom. Ten slotte, om de rol van neoadjuvante bestraling en adjuvante (postoperatieve) behandeling anders dan (m)FOLFIRINOX te beoordelen.

DEEL I: DIAGNOSTIEK VAN FOCALE PANCREASLAESIES

Deel I van dit proefschrift beschreef de diagnostiek van patiënten met een focale pancreaslaesie. Het onderscheid tussen premaligne laesies met een laag risico en premaligne of maligne laesies met een hoog risico kan complex zijn, met risico op zowel chirurgische over als onder behandeling. Het optimaliseren van de diagnostiek van focale pancreaslaesies is daarom essentieel. Vaak wordt in eerste instantie gekozen voor niet-invasieve beeldvorming zoals een CT- of MRI-scan, eventueel gevolgd door endoscopische echografie (EUS) met of zonder verkrijgen van weefsel (FNA/B). In **Hoofdstuk 2** werd de toegevoegde waarde van EUS na een CT- of MRI-scan onderzocht bij patiënten met een focale laesie in het lichaam of de staart van het pancreas. Uit dit onderzoek bleek dat een preoperatieve EUS van toegevoegde diagnostische waarde was bij 48% van alle patiënten die een resectie ondergingen. Deze toegevoegde waarde van EUS was groter bij patiënten met een cystische laesie (54%) dan bij patiënten met een solide laesie (44%). De toegevoegde waarde van EUS was vooral gebaseerd op het stellen van de juiste diagnose in geval de CT- of MRI-scan een andere waarschijnlijkheidsdiagnose gaf. Er werden geen ernstige bijwerkingen na EUS gemeld. In **Hoofdstuk 3** werd de sensitiviteit van de verschillende diagnostische onderzoeken (CT, MRI en EUS) vergeleken in hetzelfde cohort van patiënten die een resectie van een focale laesie in het lichaam of de staart van het pancreas ondergingen als Hoofdstuk 2. Sensitiviteit werd daarbij gedefinieerd als de gevoeligheid om de juiste postoperatieve diagnose te stellen. De CT-scan was het meest gevoelige onderzoek voor solide laesies (sensitiviteit 75%), terwijl EUS met verkrijgen van weefsel het meest gevoelige onderzoek was voor cystische laesies (sensitiviteit 75%). Bovendien verhoogde het verkrijgen van weefsel bij EUS de gevoeligheid tot 71% in vergelijking met 64% voor EUS zonder verkrijgen van weefsel.

De mogelijkheid om een weefseldiagnose te verkrijgen is een van de belangrijkste voordelen van endoscopische procedures ten opzichte van het maken van een CT- of MRI-scan. **Hoofdstuk 4** evalueerde de opbrengst van de verschillende endoscopische procedures voor het verkrijgen van weefsel die werden uitgevoerd voorafgaand aan deelname aan de PREOPANC en PREOPANC-2 gerandomiseerde studies (RCTs), die beide een neoadjuvante behandelarm hadden. In deze eerste landelijke studie met 617 patiënten met verdenking op een pancreascarcinoom, was de sensitiviteit voor het vinden van een maligniteit het hoogst bij EUS, met een sensitiviteit van 85% (waarbij weefsel wat op zijn minst verdacht was voor maligniteit als positief werd beschouwd). Daarbij werd de internationale referentiestandaard van ≥85% benaderd (waarbij alleen zeker maligne weefsel als positief wordt beschouwd).[1] De sensitiviteit voor het vinden van een maligniteit was 52% voor ERCP-geleide brush en 38% voor periampullaire biopsieën. De mate van adequate weefselafname, gedefinieerd als het percentage van alle procedures dat weefsel opleverde wat voldoende was voor cyto- en/of histopathologische analyse, was hoog voor alle endoscopische procedures, variërend van 94-100%. Het percentage fout-positieve resultaten voor maligniteit (d.w.z. het weefsel was op zijn minst verdacht voor maligniteit, maar het postoperatieve weefsel vertoonde geen kanker) was 2% en bij 5% bleek er sprake van een ander type kanker zoals van de distale galwegen of papil van Vater.

DEEL II: NEOADJUVANTE BEHANDELING VAN HET PANCREASCARCINOOM

Voor patiënten met een resectabel of borderline resectabel pancreascarcinoom is een operatie gevolgd door adjuvante chemotherapie al lange tijd de standaard behandeling. Met deze strategie krijgt echter ongeveer 40-50% van de patiënten nooit systemische behandeling vanwege postoperatieve complicaties of klinische verslechtering. Hierdoor zijn onderzoeken in toenemende mate gericht op de rol van systemische behandeling voorafgaand aan een eventuele operatie, wat ook wel neoadjuvante of perioperatieve behandeling wordt genoemd. In **Hoofdstuk 5** gaven we een overzicht van de huidige behandelstrategieën voor patiënten met een resectabel of borderline resectabel pancreascarcinoom, bespraken we de rationale van een neoadjuvante behandeling, en schetsten we de uitdagingen bij het vergelijken van studies gericht op neoadjuvante en adjuvante behandeling. De belangrijkste voordelen van een neoadjuvante behandeling zijn de vroege behandeling van eventuele occulte micrometastasen en de toename van het aantal patiënten dat überhaupt een systemische behandeling krijgt. Bovendien kan een neoadjuvante behandeling het percentage radicale (R0) resecties vergroten door de tumor te verkleinen. Ten slotte biedt de periode van neoadjuvante behandeling een zogenaamde ‘test-of-time’, waarin patiënten met een snel progressieve tumor kunnen worden geïdentificeerd bij het maken van een CT-scan na neoadjuvante behandeling. Hiermee kan zinloze chirurgie worden voorkomen.

Hoofdstuk 6 combineerde de resultaten van zeven RCTs waarin een neoadjuvante strategie werd vergeleken met de strategie van primair opereren. Hierbij werden in totaal 938 pati-

enten met een resectabel of borderline resectabel pancreascarcinoom onderzocht. Deze meta-analyse toonde een betere overleving met neoadjuvante behandeling (hazard ratio (HR): 0,66, 95% BI: 0,52-0,85, p=0,001), wat neerkomt op een toename van de mediane overleving van 19 naar 29 maanden. Dit bewijs was echter voornamelijk van toepassing op patiënten met een borderline resectabel pancreascarcinoom. Bovendien omvatten de meeste onderzoeken in deze meta-analyse verschillende soorten neoadjuvante chemotherapie, meestal met een enkel middel, terwijl chemotherapie behandelingen met meerdere middelen tegenwoordig de voorkeur hebben.

Hoofdstuk 7 onderzocht de uitkomsten na neoadjuvante (m)FOLFIRINOX in een meta-analyse op basis van individuele-patiëntdata van 283 patiënten met een borderline resectabel pancreascarcinoom uit 20 studies. De gepoolde mediane overleving was 22,2 maanden, en de mediane progressievrije overleving was 18,0 maanden. Het aantal ernstige bijwerkingen was hoog, maar er werden geen sterfgevallen toegeschreven aan (m)FOLFIRINOX. Neutropenie (17,5 per 100 patiënten), diarree (11,1 per 100 patiënten) en vermoeidheid (10,8 per 100 patiënten) werden het vaakst gemeld.

Hoofdstuk 8 onderzocht de uitkomsten van 1835 opeenvolgende patiënten met een pancreascarcinoom zonder uitzaaiingen. Deze patiënten werden allen behandeld met (m)FOLFIRINOX als initiële behandeling in vijf expertise centra uit de Verenigde Staten en Nederland (2012-2019). Dit onderzoek was het eerste onderzoek van het Trans-Atlantic Pancreatic Surgery (TAPS) consortium. Het resectiepercentage na (m)FOLFIRINOX was 18% voor lokaal gevorderde, 53% voor borderline resectabel en 71% voor resectabel pancreascarcinoom. De mediane overleving was 18.7 maanden (95%-BI, 17,7-19,9) voor lokaal gevorderd, 23,2 maanden (95%-BI, 21,0-25,7) voor borderline resectabel en 31,2 maanden (95%-BI, 26,2-36,6) voor resectabel pancreascarcinoom. Onafhankelijke prognostische factoren voor een slechte overleving waren: een verder gevorderd stadium, slechtere performance score, CA 19-9 >500 EH/ml en BMI ≤18,5 kg/m2.

In **Hoofdstuk 9** werd het onderzoeksprotocol van de PREOPANC-2 studie gepresenteerd, waarin neoadjuvante FOLFIRINOX (8 cycli) werd vergeleken met neoadjuvante chemoradiotherapie op basis van gemcitabine (3 cycli, 36 Gy in 15 fracties) gevolgd door adjuvante gemcitabine (4 cycli) voor patiënten met een resectabel of borderline resectabel pancreascarcinoom. Deze landelijke RCT heeft in januari 2021 alle 375 patiënten geïncludeerd, na een snelle inclusieperiode van 2,5 jaar. De resultaten voor de primaire uitkomst van overleving worden eind 2022 verwacht.

DEEL III: BESTRALING EN ADJUVANTE BEHANDELING VAN HET PANCREASCARCINOOM

Hoofdstuk 10 en **Hoofdstuk 11** onderzochten de rol van bestraling na neoadjuvante (m) FOLFIRINOX voor patiënten met een resectabel of borderline resectabel pancreascarci-

noom. In de meta-analyse gepresenteerd in **Hoofdstuk 10** werden 512 patiënten met resectabel en borderline resectabel pancreascarcinoom uit 15 studies geïncludeerd, die allen behandeld werden met (m)FOLFIRINOX met of zonder aanvullende bestraling. Deze studie liet een hoger radicaal (R0) resectiepercentage zien voor patiënten die aanvullende bestraling kregen (98% vs. 88%, p=0,045). Andere uitkomsten, waaronder overleving, het resectiepercentage en andere pathologische uitkomsten (pathologische complete respons, perineurale invasie, positieve lymfeklieren), waren echter vergelijkbaar bij patiënten met en zonder bestraling. In **Hoofdstuk 11** werd de toegevoegde waarde van bestraling na (m) FOLFIRINOX voor borderline resectabel pancreascarcinoom onderzocht in een propensity score matched analyse van 300 patiënten. Hiervoor werd gebruik gemaakt van patiënten uit het internationale TAPS consortium. Neoadjuvante bestraling na (m)FOLFIRINOX was geassocieerd met een vergelijkbaar radicaal (R0) resectiepercentage (70,6% vs. 64,8%, p=0,51), meer patiënten met enkel negatieve lymfeklieren (57% vs. 38%, p=0,01), en meer patiënten met een uitgebreide pathologische respons (25% vs. 8%, p=0,006) bij patiënten die een resectie ondergingen. Er kon echter geen verschil in mediane overleving worden aangetoond (26,2 vs. 32,8 maanden, p=0,71). De mediane overleving na conventionele en stereotactische bestraling was vergelijkbaar (25,7 vs. 26,0 maanden, p=0,92).

Ten slotte was **Hoofdstuk 12** gericht op adjuvante chemotherapie in een landelijk cohort van 778 patiënten die een resectie voor pancreascarcinoom ondergingen en adjuvante gemcitabine monotherapie (n=164) of gemcitabine met capecitabine (n=164) kregen. In deze studie werd de onderzoeksvraag van de ESPAC-4 studie beantwoord in een dagelijkse setting buiten een RCT.[2] De studie bevestigde dat adjuvante gemcitabine met capecitabine geassocieerd was met een betere overleving ten opzichte van gemcitabine monotherapie (31,4 vs. 22,1 maanden, HR=0,71, p=0,004). Dit overlevingsverschil bleef bestaan na correctie voor prognostische factoren.

APPENDICES

LIST OF PUBLICATIONS

This thesis

2022. **Janssen QP,** Quispel R, Besselink MG, Bonsing BA, Bruno MJ, Doukas M, Farina Sarasqueta A, Homs MYV, van Hooft JE, van Tienhoven G, van Velthuysen MF, Verheij J, Voermans RP, Wilmink JW, Groot Koerkamp B, van Eijck CHJ*, van Driel LMJW*, for the Dutch Pancreatic Cancer Group. Diagnostic performance of endoscopy-guided tissue acquisition for borderline resectable and resectable pancreatic ductal adenocarcinoma within the PREOPANC and PREOPANC-2 trials. *Submitted.*

2022. **Janssen QP,** van Dam JL, Doppenberg D, Prakash LR, van Eijck CHJ, Jarnagin WJ, O'Reilly EM, Paniccia A, Besselink MG, Katz MHG, Tzeng CW, Wei AC, Zureikat AH, Groot Koerkamp B, for the Trans-Atlantic Pancreatic Surgery (TAPS) Consortium. FOLFIRINOX as initial treatment for localized pancreatic adenocarcinoma: a retrospective analysis by the Trans-Atlantic Pancreatic Surgery (TAPS) Consortium. *J Natl Cancer Inst. 2022 Feb 14:djac018 online ahead of print*

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2019. Harms MH, **Janssen QP,** Adam R, *et al.,* for the European Liver and Intestine Transplant Association (ELITA). Trends in liver transplantation for primary biliary cholangitis in Europe over the past three decades. *Aliment Pharmacol Ther. 2019 Feb;49(3):285-295.*

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PhD period: 2017 – 2021
Promotores: Prof. dr. Casper H.J. van Eijck, Dr. Bas Groot Koerkamp
Copromotor: Dr. Lydi M.J.W. van Driel

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Courses		
Master Health Sciences (MSc): Clinical Epidemiology, NIHES	2018 – 2020	70.3
BROK (Basiscursus Regelgeving Klinisch Onderzoek), NFU	2018	1.0
Research Integrity, Erasmus MC	2018	0.3
Biomedical English writing course, Molmed	2019	2.0
Regression Techniques, EpidM	2020	5.0
Scientific presentations		
International Hepato-Pancreato-Biliary Association (IHPBA)	2018, 2020	4.0
ASCO Annual meeting	2018, 2021	3.0
European – African Hepato-Pancreato-Biliary Association (E-AHPBA)	2019	2.0
ACE Hepato-Pancreato-Biliary Diseases, Erasmus MC	2019	2.0
Wetenschapsdag Heelkunde Erasmus MC	2019	2.0
4e Multidisciplinair Gastro-Intestinaal Oncologie (5D) Congres	2020	2.0
Memorial Sloan Kettering Cancer Center (NY) Multidisciplinary Meeting	2020, 2021	2.0
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Living With Hope Research Foundation, research travel grant	2020	
Total		**98.6**

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ABOUT THE AUTHOR

Quisette Paulien (Kiki) Janssen was born in Rotterdam, The Netherlands, on the 4th of June, 1990. In 2008, she graduated from secondary school at the Montessori Lyceum in Rotterdam. After doing volunteer work in Borneo, Malaysia, and travelling through Australia and New Zealand, she moved to Amsterdam to study Psychobiology at the University of Amsterdam for one year, after which she commenced medical school at the Vrije Universiteit of Amsterdam. During her clinical rotations, she did an elective in radiology and a senior internship in gastroenterology and hepatology at the OLVG Hospital in Amsterdam. She performed an extended research rotation at the department of Hepatology of the Erasmus MC Rotterdam (supervisor prof. dr. H.J. Metselaar). After obtaining her cum laude medical degree in October of 2017, she started working on her PhD project conducting the research described in this thesis. She was supervised by prof. dr. C.H.J. van Eijck and dr. B. Groot Koerkamp from the department of Surgery, and dr. L.M.J.W. van Driel from the department of Gastroenterology and Hepatology, both at the Erasmus MC in Rotterdam. In addition, she performed part of her research as a research fellow at the Memorial Sloan Kettering Cancer Center in New York, under supervision of dr. A.C. Wei. During her PhD period, she obtained the Master of Health Sciences Degree, with the specialization of Clinical Epidemiology (NIHES, Erasmus University, Rotterdam). From August 2021 onwards, Kiki has been working as a resident in internal medicine at the Franciscus Gasthuis & Vlietland in Rotterdam.