Surgical and oncological outcomes after neoadjuvant FOLFIRINOX chemotherapy for (borderline) resectable and locally advanced pancreatic cancer: a pan-European cohort

E. van Veldhuisen[1*], S. Klompmaker[1*], Q.P. Janssen[2] <<participating surgeons>>>> M. Abu Hilal[3], C. Bassi[4], O.R. Busch[1], M. del Chiaro[5], J.W. Wilmink[6], I.Q. Molenaar[7], M. Lesurtel[8], T. Keck[9], J. Kleeff[10], R. Salvia[4], O. Strobel[10], B. Groot Koerkamp[2&], M.G. Besselink[1&] on behalf of the scientific committee of the European-African Hepato-Pancreato-Biliary Association

[1] Department of Surgery, Cancer Center Amsterdam, Academic Medical Center, University of Amsterdam, the Netherlands; [2] Department of Surgery, Erasmus Medical Center, Rotterdam, the Netherlands; [3] Department of Surgery, University Hospital Southampton NHS, United Kingdom; [4] Department of Surgery, GB Rossi Hospital, Verona, Italy; [5] Department of Surgery, Karolinska Institutet, Stockholm, Sweden; [6] Department of Medical Oncology, Academic Medical Center, Cancer Center Amsterdam, University of Amsterdam, the Netherlands; [7] Department of Surgery, University Medical Center Utrecht, Utrecht, the Netherlands; [8] Hôpital Universitaire Croix Rousse, Hospices Civils de Lyon, Lyon, France; [9] Department of Surgery, Universitaet zu Luebeck, Luebeck, Germany; [10] Department of Surgery, Universitätsklinikum Heidelberg, Heidelberg, Germany.[*] These authors share first authorship; [&] these authors share senior responsibility

Study coordinators:

Eran van Veldhuisen, BSc
PhD Student
+31 20 56 62 670 / e.vanveldhuisen@amc.nl

Sjors Klompmaker, MD
PhD Student
s.klompmaker@amc.nl

Corresponding author:

Marc G Besselink, MD MSc PhD
Hepato-Pancreato-Biliary surgeon
Department of Surgery, Cancer Center Amsterdam
Academic Medical Center, University of Amsterdam the Netherlands
+31-20-5669111 / m.g.besselink@amc.nl

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List of abbreviations

AE	Adverse event
AJCC	American Join Committee on Cancer
ASA	American Society of Anesthesiologists
BRPC	Borderline resectable pancreatic cancer
CA19-9	Carbohydrate antigen 19-9
CHA	Common hepatic artery
eCRF	Electronic case report form
DP	Distal pancreatectomy
E-AHPBA	European-African Hepato-Pancreato-Biliary-Association
FOLFIRINOX	5-Fluorouracil, oxaliplatin, irinotecan and folic acid
GDA	Gastroduodenal artery
ICU	Intensive care unit
IQR	Interquartile range
ISGPS	International Study Group on Pancreatic Surgery
LAPC	Locally advanced pancreatic cancer
NCCN	National Comprehensive Cancer Network
PD	Pancreatoduodenectomy
PDAC	Pancreatic ductal adenocarcinoma
RECIST	Response evaluation criteria in solid tumors
SD	Standard deviation
SMA	Superior mesenteric artery
SMV	Superior mesenteric vein

1. Protocol abstract

BACKGROUND: FOLFIRINOX chemotherapy is used increasingly as neoadjuvant treatment for patients with borderline resectable or locally advanced pancreatic cancer. Since randomized trials are lacking, current evidence is mostly based on data from single, high-volume expert centers with little variation in neoadjuvant and adjuvant FOLFIRINOX strategies (i.e. number of cycles pre/post-surgery). Consequently, assessment of the impact of FOLFIRINOX practice variation on surgical and oncological outcomes using international, multicenter data is currently impossible.

AIM: This pan-European study, initiated by the E-AHPBA, will assess the pan-European implementation, morbidity, mortality, and oncological outcomes of pancreatic cancer resection following neoadjuvant FOLFIRINOX chemotherapy.

METHODS: Retrospective multicenter study including all consecutive patients undergoing pancreatic resection (i.e. distal pancreatectomy, pancreatoduodenectomy) following at least 2 cycles of FOLFIRINOX between January 1st 2012 and December 31st 2016 (5 year period), in centers performing 20 or more PDs annually. In a secondary analysis, we will explore the possibility to propensity match patients with (borderline) resectable pancreatic cancer treated with neoadjuvant FOLFIRINOX to chemo-naive controls extracted from Dutch (DPCA) and German national audits.

Invitations to participate will be distributed through the E-AHPBA network. Number of neoadjuvant and adjuvant cycles of FOLFIRINOX (or other concomitant chemotherapy) are recorded, as well as FOLFIRINOX regime changes over time.

Primary outcome is overall survival from time of diagnosis. Secondary outcomes include 90-day pancreas-specific complications (ISGPS definitions), major morbidity (Clavien-Dindo ≥ 3a), in-hospital and 90-day mortality, grade-B/C pancreatic fistula, length of hospital stay, resection margin (R0/R1/R2; and malignant lymph node ratio.

All data will be collected using predefined electronic case report forms (CASTOR EDC, Amsterdam). Analysis will include the impact of variations in use of FOLFIRINOX on outcomes (e.g. number of neoadjuvant and number of adjuvant cycles) and (if feasible) propensity score matching of patients with borderline resectable pancreatic cancer with patients from the Dutch and German audit undergoing upfront surgery (i.e. without neoadjuvant treatment).

LIMITATIONS: First, this study will not be able to provide detailed data on the chemotherapy-associated complications of FOLFIRINOX. Second, because only a limited number of BRPC patients

without neoadjuvant therapy are available in the DPCA data, results on the overall efficacy of neoadjuvant FOLFIRINOX therapy are limited. Third, the results will only be applicable to patients who have undergone resection in centers performing at least 20 PDs annually.

STRENGTHS: This could become one of the largest multicenter, international series of patients receiving pancreatic resection after FOLFIRINOX. It will provide an estimate of the implementation of FOLFIRINOX and the outcomes of surgery after FOLFIRINOX, as well as survival.

PLANNING: Study protocol completion by April 2018; Data collection in April-May-June 2018. Data-analysis during July-August and manuscript completion are expected at the end of 2018.

2. Introduction

Surgical resection, combined with systemic chemotherapy offers the best chance of long term survival in pancreatic ductal adenocarcinoma (PDAC).[1] However, only 10-20% of patients may present with primary resectable disease at diagnosis, many of whom will undergo a R1 resection.[2] The vast majority (50-60%) of patients present with metastatic disease, and the remaining 20-40% have extensive vascular tumor infiltration (i.e. locally advanced disease), rendering these patients unresectable.[2]

For patients with non-metastatic, locally advanced (LAPC) or borderline resectable pancreatic cancer (BRPC), FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan and folic acid) may lead to tumor down-staging and potentially a radical (R0) resection.[3, 4] When down-staging is achieved, radical resection rates can be as high as 92%.[5] However, only small- mono-center studies are currently available, with considerable heterogeneity in FOLFIRINOX administration (i.e. dose and number of cycles) and resectability criteria between studies, limiting the external validity.

This pan-European study will assess the oncologic efficacy, morbidity and mortality of pancreatoduodenectomy (PD) and distal pancreatectomy (DP) following neoadjuvant FOLFIRINOX chemotherapy among European centers performing at least 20 PDs annually.

3. Methods

This is a pan-European retrospective series within participating centers represented by members of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA).

3.1 Patients and Design

All consecutive patients undergoing resection for PDAC following a minimum of 2 cycles of FOLFIRINOX between January 1st 2012 and December 31st 2016 in European centers performing at least 20 PDs annually are eligible for inclusion. Patients are excluded in case of essential missing staging- or operative information (i.e. missing pre-chemotherapy CT-scan, operative reports, pathology reports etc.). Participating centers will receive a questionnaire about the centers' characteristics and policy to use FOLFIRINOX.

3.2 Definitions

Postoperative complications (morbidity) are scored and classified using the Clavien-Dindo classification of surgical complications.[6] Major complications are defined as Clavien-Dindo grade IIIa or higher. The definitions of the recommended International Study Group on Pancreatic Surgery (ISGPS) are used to score postoperative pancreatic fistula[7], delayed gastric emptying[8], chyle leak[9] and postpancreatectomy hemorrhage.[10] Ischemic morbidity is defined as an abdominal organ complication caused by surgery related ischemia. Resection margins, including transection and circumferential margins, are categorized according to the Royal College of Pathologists definition and classified into R0 (distance margin to tumor ≥ 1mm), R1 (distance margin to tumor < 1mm) and R2 (macroscopically positive margin).[11] Pre-operative resectability status is classified according to the National Comprehensive Cancer Networks (NCCN) Clinical Practice Guidelines for Pancreatic Adenocarcinoma and categorized in unresectable, borderline resectable and primary resectable respectively.[12] Staging of disease is performed according to the 8th version of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification.[13] Complications, re-admissions and mortality are all recorded up to 90-days postoperatively.

3.3 Primary and secondary endpoints

Primary endpoint is overall survival (stratified by resectability status at diagnosis). Secondary outcomes are R0 resection margin (microscopically radical resection margin, according to the Royal College of Pathologists definition)[5], malignant lymph node ratio, oncologic outcomes (i.e. progression-free survival, time to recurrence) and postoperative outcomes (such as length of hospital stay, post-operative events and 90-day mortality). Analysis will include practice variation (e.g. cycles, dose and type of (radio)chemotherapy neoadjuvant and adjuvant) and the impact of this variation on surgical and oncological outcome (e.g. differences in survival or surgical complication rate depending on number of cycles neoadjuvant and adjuvant) over time.

3.4 Data collection

Invitations are distributed via e-mail through the E-AHPBA network. After an initial participation survey (Google™ Survey) confirming the study requirements. This survey will also contain questions regarding local methods of data collection and follow-up (e.g. on how survival was determined, who was responsible for the data collection) and local policy regarding the use of FOLFIRINOX (Appendix 2). Each participating center will appoint one dedicated local study coordinator, responsible for all communication with the central study coordinators (EV and SK). Study coordinators will receive a link

to an on-line case report form (eCRF) environment (CASTOR EDC™). All variables collected are mentioned in Appendix 1.

3.5 Ethics

Approval for this study was obtained from the Academic Medical Center ethics review committee. All data will be collected anonymously and managed according to the ICH-GCP guidelines. Patients will automatically be given a study ID (site name_res_no). The local study coordinators are asked to store the study ID locally. In case additional data extraction is needed, participating centers may be asked to re-identify the patient based on the study ID.

3.6 Statistical analysis

Data will be analyzed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Orchard Road Armonk, New York, US) or STATA version 14.1 (StataCorp LP, College Station, Texas, US). Categorical data will be presented as proportion, continuous data will be presented as either mean and standard deviation or median and inter-quartile-range as appropriate. Student's t, Mann Whitney U, Chi-square, or Fisher's exact tests will be used as appropriate. Alpha <0.05 will be used to indicate statistical significance.

The primary analysis will consist of a Cox regression model, including center of treatment and all relevant patient characteristics (e.g. cycles of neoadjuvant chemotherapy, resectability status at diagnosis, age, adjuvant treatment etc.) as covariates, to determine the overall survival and to identify potential predictors for prolonged overall survival.

In a second analysis, we will explore the possibility to propensity match patients with (borderline) resectable pancreatic cancer treated with neoadjuvant FOLFIRINOX (1:1 with a caliper of 0.2) to chemo-naive controls extracted from Dutch (DPCA) and German (DGAV, StuDoQ|Pancreas) national registries. Propensity scores will be obtained from a logistic regression model including preoperative variables: year of surgery, sex, age, ECOG score, Charlson comorbidity index[14], and arterial-/venous involvement. Kaplan-Meier survival curves in this sub-cohort will be used to assess the effect of FOLFIRINOX neoadjuvant therapy on overall survival. It is currently unclear whether a sufficient amount of patients is available to match.

4. Authorship and publication policy

Authorship is based on the international ICMJE guidelines. Centers will be eligible for 1 authorship position when providing at least 10 patients, and 2 authorship positions when providing at least 20

cases. Centers providing fewer than 10 patients or not complying with the ICMJE guidelines will be listed as 'collaborator' in the manuscript and the accepting journal will also be asked to list the collaborators as such on PubMed. Each participating center may decide who will be listed as co-author(s) as long as this person fulfills the ICMJE guidelines.

The study coordinators (EV and SK) will be the (shared) first authors. The last authorship positions are reserved for the 2 principal investigators (BGK, MB), which are preceded by the working group members and chair of the E-AHPBA scientific committee responsible for the current project. All other authors will be listed in alphabetical order.

Any primary publication, presentation or abstract on collected data will be delegated to all authors. Each center remains the possessor of their own data and additional reports on data collected will only be conducted in case of written author permission. All participating authors can suggest alterations to the study design or additional analyses to be performed.

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Appendix 1

Baseline and outcome variables

Table 1. Variables to identify

VARIABLE	FORMAT
Date of form completion	YYYY/MM/DD
Hospital	Drop-down
Case ID	Site name_FFX_no
Date of birth	YYYY/MM/DD
BASELINE – at time of surgery	
Age in years	YY
Sex	M/F
ECOG performance status	0-4
ASA score	1-4
Co-morbidity?	Y/N
If yes, please specify co-morbidity *	Cardiac/Vascular/Diabetes/Pulmonary/Neurological/Gastro-intestinal/Urogenital/Renal/Coagulopathic/Connective tissue disease/Immunologic/Oncologic/Other
Highest CA19-9 level prior to surgery	UI/L
Date measured	YYYY/MM/DD
Last CA 19-9 level prior to chemo	UI/L
Date measured	YYYY/MM/DD
Last CA 19-9 level before surgery (after neoadj ch)	UI/L
Date measured	YYYY/MM/DD
Malignant suspicion (preoperative)	Y/N
M1 disease (preoperative)	Y/N
Prior surgical exploration for pancreatic cancer	Y/N
Total number of neoadjuvant FOLFIRINOX cycles?	Count
Any dose reduction of FOLFIRINOX?	Free text
If yes, reason for dose reduction?	Free text
Any other chemotherapy?	Free text
If yes, what type and number of cycles?	Free text
Preoperative radiotherapy	Y/N
If yes, what type (i.e. pain relief, SBRT) and dose?	Free text/Gy
PRE-CHEMOTHERAPY IMAGING	
Type of imaging	CT/CT-A/MRI/EUS
Date of last imaging pre-chemotherapy	YYYY/MM/DD
Largest tumor size before chemotherapy	mm
Largest tumor size before surgery (after chemotherapy)	mm
Solid organ involvement on CT/MRI (other than pancreas)	Y/N
If yes, please specify the affected organs	Stomach/Colon/Mesocolon/Small intestine/Spleen/Adrenal gland/Kidney/Liver/Common bile duct/Other
TNM Stage on pre-operative CT/MRI	T 0-4 / N 0-1 / M 0-1/Other
Tumor location	Head/Uncinate process/Body/Tail/Other
Contact hepatic artery pre-chemotherapy	0/1-90/91-180/181-270/>270^{o}
Contact celiac trunk pre-chemotherapy	0/1-90/91-180/181-270/>270^{o}
Contact SMA pre-chemotherapy	0/1-90/91-180/181-270/>270^{o}
Contact portal vein pre-chemotherapy	0/1-90/91-180/181-270/>270^{o}

Contact superior mesenteric vein pre-chemotherapy	0/1-90/91-180/181-270/>270^{o}
PROCEDURE DETAILS	
Date of surgery	YYYY/MM/DD
Date of hospital discharge	YYYY/MM/DD
Type of resection	Pancreatoduodenectomy/Distal pancreatectomy/Total pancreatectomy/Other
Operative time (incision to closure)	Min.
Multivisceral resection	Y/N
Additional solid organs resected (other than pancreas)	Stomach/Colon/Mesocolon/Small intestine/Spleen/Adrenal gland/Kidney/Liver/Common bile duct/Other
Venous resection?	Y/N
If yes, please specify	Portal vein/SMV
Arterial resection?	Y/N
If yes, please specify	SMA/CHA/Proper hepatic artery/celiac trunk/GDA/Other
Surgical approach	Open/laparoscopic/robot-assisted/Other
PATHOLOGY	
Diagnosis	Drop-down
Largest tumor size	Mm
Closest distance (in mm) from tumor to margin	Mm
Overall resection margin (Royal College of Pathologists definition)	R0/R1/R2
Total number of harvested lymph nodes	Count
Number of malignant lymph nodes	Count
Vascular infiltration	Y/N
If yes, please specify vessel	Hepatic artery/Celiac trunk/SMA/Portal vein/SMV/Other
Perineural invasion	Y/N
Angio-lymphatic infiltration	Y/N
Solid organ involvement	Stomach/Colon/Mesocolon/Small intestine/Spleen/Adrenal
If yes, please specify the affected organs	gland/Kidney/Liver/Common bile duct/Other
Final T*N*M* Stage (AJCC)	T 0-4 /N 0-1 /M 0-1/Other
POSTOPERATIVE	
Any complication w/i 90-days	Y/N
Major complication (Clavien-Dindo ≥ 3a) w/i 90-days	Y/N
Ischemic abdominal morbidity?	Y/N
Specify organ	Free text
Liver ischemia?	Y/N
Pancreatic fistula w/i 90-days	Y/N
ISGPS fistula grade	B/C
(Re-)Intervention required	Y/N
Type of re-intervention	Free text
Date of last drain removal	YYYY/MM/DD
Delayed gastric emptying	Y/N
ISGPS grade	B/C
Post-pancreatectomy hemorrhage	Y/N
ISGPS-grade	B/C
Chyle leakage	Y/N
Non-pancreas specific complications	Surgical site infection/Septic shock/Myocardial infarction/Cardiac arrest/Pulmonary embolism/Stroke
Single organ failure?	Y/N

Multi organ failure?	Y/N
Re-intervention (related to index procedure)	Y/N
Type of re-intervention	Radiologic/Endoscopic/Surgical/Other
Reason for re-intervention	Free text
Intensive Care Unit admission (related to index procedure)	Y/N
Reason for ICU admission	Free text
Length of ICU admission	Days
POST-DISCHARGE	Y/N
Death w/i 90-days post op	Y/N
Date of death	YYYY/MM/DD
Readmission (related to index-procedure) w/i 90-days post op	Y/N
Reason for re-admission	Free text
Length of re-hospitalization	DD
Adjuvant chemotherapy	Y/N
Date of chemotherapy initiation	YYYY/MM
Type of chemotherapy	Free text
Number of courses	Free text
Adjuvant radiotherapy	Y/N
Date of radiotherapy initiation	YYYY/DD
Intensity of radiotherapy	Gy
Number of courses	Count
If both, chemo- and radiotherapy, please describe briefly sequence:	Free text
SURVIVAL	
Date of last follow up	YYYY/MM/DD
Occurrence of death	Y/N
Date of death	YYYY/MM/DD
Method of death determination	Based on in-hospital registry/ phone call or family follow-up/ national registry/ other

*dynamic structure depending on input

Appendix 2

Short survey per participating center

DATA COLLECTION QUESTIONS

1. Please provide the name and contact details of the study contact person at your institution:

   (Name, degree, position, official name of both department and hospital, email address, phone number, etc…)

2. Please confirm the person who is filling out this questionnaire is the same as the person mentioned in the previous question:

   (Yes/No)

3. Please state who was responsible for collecting the data in this study (e.g. medical students supervised by a surgeon; or a dedicated resident; or a PhD candidate).

   (Free text)

4. Please state how collection of preoperative, perioperative, and postoperative variables was performed:
   a. Prospectively maintained database;
   b. Retrospective medical record review of digital records;
   c. Retrospective medical record review of paper records;
   d. Other, please state…

5. Please state how overall survival was determined:
   a. Based on last hospital visit;
   b. Based on last hospital contact (phone or email);
   c. By actively contacting all patients (or family members/general practitioners) who underwent resection after FOLFIRINOX (phone or email);
   d. Review of a national mortality registry without cause of death information;
   e. Review of a national mortality registry with cause of death information;

SURGICAL EXPERTISE QUESTIONS

6. What is the total number of pancreatoduodenectomies (all indications) performed at your institution on average per year during the study period?

   (Number: 0-999)

7. What was the average yearly case volume of post-FOLFIRINOX resections at your institution between January 1st 2012 and December 31st 2016?

   (Number: 0-99)

8. Are resections after FOLFIRINOX, in your opinion/ experience, similar to conventional resections for pancreatic cancer?

   (Yes/No/NA)

9. If you answered the previous question with "No", please explain briefly why and which additional steps are performed during surgery in your institution.

   (Free text)

10. Which patients generally proceed to explorative laparotomy in your center?
    a. All patients with non-progressive disease following FOLFIRINOX;
    b. Patients with (borderline) resectable disease upon restaging;
    c. Only patients with regressive disease upon imaging;
    d. Patients with decreasing CA19-9 levels;
    e. Patients who undergo open local ablative therapy (i.e. IRE, RFA);
    f. Other, please state…

11. What criteria are used in your institution to classify borderline resectable/locally advanced disease?

    (Free text)

12. Did these criteria change between 2012 and 2017? If yes, how?
    (Free text)

STANDARD OF CARE QUESTIONS

13. Which patients were within the study period (2012-2016) generally treated with pre-operative FOLFIRINOX chemotherapy at your institution? (multiple answers possible)
    a. All patients with locally advanced pancreatic cancer;
    b. All patients with borderline resectable pancreatic cancer;
    c. All patients with primary resectable pancreatic cancer;
    d. Other, please state…

14. During the study period (2012-2016), in your institution, how many cycles of FOLFIRINOX were preferably administered to patients prior to surgery?
    (Number: 0-99)

15. Did these FOLFIRINOX regimens change during the study period?
    (Free text)

16. Is FOLFIRINOX generally administered at full dose, or are dose reductions also applied in your institution? If yes, what dose modifications?
    (Free text)

17. Is radiotherapy used in the setting of neoadjuvant treatment? If so, how?
    (Free text)

18. Currently, in your institution, what is the routine adjuvant approach after resection following neoadjuvant FOLFIRINOX (how many cycles of which chemotherapy regimen? Does this include additional radiotherapy?)
    (Free text)