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### **► To cite this version:**

Q. Laurent-Badr, C. Barbe, M. Brugel, V. Hautefeuille, J. Volet, et al.. Time intervals to diagnosis and chemotherapy do not influence survival outcome in patients with advanced pancreatic adenocarcinoma.. Digestive and Liver Disease, 2020, 52, pp.658 - 667. <10.1016/j.dld.2020.03.014>. <hal-03490942>

**HAL Id: hal-03490942**

**<https://hal.science/hal-03490942v1>**

Submitted on 22 Aug 2022

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**Time intervals to diagnosis and chemotherapy do not influence survival outcome in patients with advanced pancreatic adenocarcinoma.**

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**Electronic word count:** 3491 (excluding abstract, references and figures legends)

**Short running head:** Time intervals and prognosis of advanced pancreatic adenocarcinoma

**Sources of support:** none

**Conflict of interest disclosure:** all authors have no conflict of interest to declare.

**Abbreviations list:**

OS: Overall survival

PDAC: Pancreatic Ductal Adenocarcinoma

CHU: University Hospital Center

BMI: Body Mass Index

CA 19.9: Carbohydrate antigen 19-9

WHO PS: WHO Performance Status

HR: Hazard ratio

## ABSTRACT

**Background:** The effect of treatment delay on survival in pancreatic ductal adenocarcinoma (PDAC) remains unclear.

**Aims:** This study aimed to assess the prognostic impact of time to diagnosis and chemotherapy in advanced PDAC and factors influencing the time intervals.

**Methods:** advanced PDAC patients receiving chemotherapy in five centers in the decade 2007-2016 were included. Key time points during care pathway from clinical presentation to beginning of chemotherapy were retrospectively collected. Multivariate Cox proportional hazard model was performed.

**Results:** A total of 409 patients were included (mean age  $66.1 \pm 10.3$  years; 250 metastatic (61%); 139 received FOLFIRINOX chemotherapy (34%). The median overall survival (OS) was 7.2 months. The median times from first symptoms and from first specialist visit to the beginning of chemotherapy were respectively 100 days and 47 days. None of time intervals was significantly associated with OS. Significant prognostic factors were FOLFIRINOX chemotherapy (HR 0.6 [0.5-0.8];  $P < 0.001$ ), metastasis (HR 1.6 [1.3-2.0];  $P = 0.001$ ), WHO PS  $\geq 2$  (HR 1.6 [1.2-2.1];  $P < 0.001$ ) and acute pancreatitis as first symptom (HR 2.9 [1.7-4.9];  $P < 0.001$ ). Jaundice shortened time to diagnosis ( $P < 0.001$ ). Acute pancreatitis ( $P < 0.001$ ) and diabetes ( $P = 0.01$ ) increased time to treatment.

**Conclusion:** Wait times from clinical presentation to beginning of chemotherapy do not influence survival in advanced PDAC.

**Key words:** pancreatic cancer, chemotherapy, survival, time intervals, time to diagnosis, time to treatment

## INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the 10<sup>th</sup> most frequent cancer in frequency and the 5<sup>th</sup> cause of cancer-related death in developed countries [1]. The incidence of pancreatic cancer has increased in the last 30 years with a yearly growth between 2.7% and 3.8%. A total of 128 000 patients died from this disease in Europe in 2018 [2] and it is expected to become the 2<sup>nd</sup> cause of cancer-related death in the next years [1,3–5].

The prognosis of this disease remains extremely poor, with a 5-year survival rate ~7% all stages taken together, despite the recent improvement in chemotherapy [6–8] and supportive care [9]. Late diagnosis is often made due to the non-specific presenting symptoms of the disease and the lack of efficient screening strategies.

Although it is widely held that the diagnosis and treatment time interval can affect the prognosis of cancers, results from multiple, independent studies remain contradictory. A recent systematic review support the conclusion that shorter diagnostic and treatment time intervals yield improved outcomes for breast, colorectal, testicles and melanoma cancer [10]. Because of the biological behavior of the PDAC, how early or how late diagnosis takes place may affect the patient survival [11]. Surgical resection remains the strongest prognostic factor with a 5-year survival rate that can reach 20% in case of complete resection [11–15]. Nonetheless, several studies were conducted in PDAC patients and failed to demonstrate that a shorter time between the onset of the symptoms and the beginning of treatment improves the outcome [16–21].

Most of these studies established a relationship between time to surgery and outcome in resectable PDAC but only a few studies focused on time intervals in advanced PDAC [22]. It was suggested that the centralised care of advanced PDAC in tertiary centers might be more efficient in terms of promptness, safety and higher use of chemotherapy, and presents a modest survival benefit [22,23]. Moreover, disparities of the overall survival (OS) could be

explained by an unequal access to healthcare [24]. In the French clinical guidelines, there are no recommendations concerning the treatment delay [5].

The aim of the present study is to assess the relationship between time intervals to diagnosis and treatment (beginning of chemotherapy) and OS in advanced PDAC. Secondary objective is to investigate about the factors influencing diagnosis and chemotherapy delays.

## **MATERIAL AND METHODS**

### **Design**

This retrospective study included patients from five centers located in France (two University Hospital Centers [Reims and Amiens], one primary Hospital Center [Châlons-en-Champagne], one private care center [Reims] and one Cancer Institute [Reims]).

### **Ethics**

Patient records were anonymised prior to analysis. The database was built in accordance with the protocol MR004 from the *Commission Nationale de l'Informatique et des Libertés* (n°2206749, 13/09/2018), and followed the French authorities' requirements.

### **Patients**

All patients with pathologically proven, advanced (unresectable locally advanced or metastatic disease) PDAC receiving at least one cycle in first-line of palliative chemotherapy between January 2007 and June 2016 were included. Exclusion criteria were respectively: age < 18 years, metachronous metastasis (after primitive tumour resection), any medical history involving other types of cancer in the last five years.

The clinical characteristics, tumour features and treatments were obtained from medical records: age, gender, body mass index (BMI), distance (kilometers) between patients' place of

residence and cancer care center, serum Carbohydrate antigen 19-9 (Ca19.9) level (U/mL), smoking and alcohol usage, diabetes mellitus, analgesics use, WHO performance status (PS), type of first symptoms, tumour size in millimeter, presence of metastasis, the type of chemotherapy regimen, the date of death.

Smoking history was divided in three groups: non-smokers, current smoker, ex-smokers. The existence of diabetes mellitus and its characteristics were noted: recent <2 years or established  $\geq 2$  years; treatment by metformin or insulinotherapy.

The method used for radiological or histological diagnosis and the need for biliary drainage or surgical intervention (for jaundice or digestive tract obstruction) performed before the beginning of chemotherapy were also collected, as well as hospitalisations at moment of the diagnosis.

The date of death was obtained from medical records or by consulting the civil registry of deaths. Follow-up was conducted until May 2018.

### **Time intervals**

The critical key time points of the patient care pathway from the first symptom onset to first chemotherapy administration were collected, including dates of radiologic diagnosis, pathological diagnosis, first consultation with a specialist in the center and first administration of chemotherapy.

Time intervals were inspired by Neal et al.'s systematic review [10].

These different time intervals were referred:

- from the onset of the first symptoms to the imaging diagnosis
- from the onset of the first symptoms to the first visit with the specialist
- from the onset of the first symptoms to the pathological diagnosis
- from the onset of the first symptoms to the first chemotherapy administration

- from imaging diagnosis to the first chemotherapy administration
- from the first visit with the specialist to pathological diagnosis
- from the first visit with the specialist to the first chemotherapy administration
- from the pathological diagnosis to the first chemotherapy administration

Imaging diagnosis is often performed before the first visit with the specialist, but could also be performed thereafter. For this reason, only two interval times were chosen including the date of the imaging diagnosis (from first symptoms to imaging diagnosis, from imaging diagnosis to chemotherapy).

Definition of time intervals can be found in supplementary data (Figure F1).

### **Statistical analysis**

Qualitative variables were described as number and percentage where quantitative variables were as mean and standard deviation or median and range. OS was calculated from date of the first administration of chemotherapy to date of death or censoring. The survival curves were established using the Kaplan-Meier method. Variables associated with OS were identified by univariate analysis using Log rank tests and by multivariate analysis using a Cox proportional hazard model (factors significant at the 0.10 level in univariate analysis were included in a stepwise regression multivariate analysis with entry and removal limits set at 0.10). Factors associated with pre-hospital time interval (from first symptoms to first specialist visit) and time to treatment (first specialist visit to chemotherapy) were studied using univariate analyses (Student t tests, the Wilcoxon tests or Pearson's correlation coefficients as appropriate) and multivariate analyses (linear regressions using backward stepwise selection with an exit threshold of 0.10 and factors significant at  $P=0.10$  included).

We decided to perform a 15-day cut-off for the first visit to treatment time interval by analogy with the ongoing GERCOR Urgence Pancreas D16-1 study



(<https://clinicaltrials.gov/ct2/show/NCT02979483>) that is investigating the feasibility and the effect of a 14-day integrative supportive care program to chemotherapy treatment.

A P value < 0.05 was considered significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

### **Baseline and treatment characteristics of patients and time intervals (Table 1)**

Among the 439 patients eligible for the study, 409 (93.2%) were finally included (20 missing data and 10 changes in the of chemotherapy center). A flow chart is figuring in supplementary data (Figure F2). A total of 300 patients (73.3%) were treated in University Hospital Centers. Mean age was  $66.1 \pm 10.3$  years old. Most patients were male (58.7%) and had metastasis (61.1%). One hundred and thirty-nine patients (34%) were treated by FOLFIRINOX regimen (oxaliplatin, 85 mg per square meter; irinotecan, 180 mg per square meter; leucovorin, 400 mg per square meter; and fluorouracil, 400 mg per square meter given as a bolus followed by 2400 mg per square meter given a 46-hour continuous infusion, every 2 weeks) as first line chemotherapy treatment. The most common first symptoms were pain (n=237, 58.0%) and weight loss (n=229, 56.0%), then jaundice (n=121, 29.6%). Among the 140 patients with diabetes mellitus, 20.1% were established and 12.2% recent.

The median interval time from the first symptoms to the start of chemotherapy, from the first symptoms to the first outpatient visit with a specialist and from the first specialist visit to beginning of chemotherapy were respectively 100 days or 3.3 months (range: 0.8-48.4), 40 days or 1.3 months (range: 0.0-46.2) and 47 days or 1.6 months (range: 0.1-13.5).

Additional baseline characteristics can be found in supplementary data (Table S1).

### **Factors associated with overall survival (Table 2)**

### ***Overall survival***

The median OS was 7.2 months (range: 0.0-65.0) (Figure 1). At the end of the follow-up, all patients have died.

In univariate analysis, age  $\geq 66$  years old ( $P=0.04$ ), asthenia ( $P=0.002$ ) and acute pancreatitis ( $P<0.001$ ) as first symptoms, WHO PS  $\geq 2$  ( $P<0.001$ ), metastatic disease at diagnosis ( $P<0.001$ ), serum Ca 19.9 level ( $P=0.005$ ) were significantly associated with poorer OS while FOLFIRINOX chemotherapy ( $P<0.001$ ) was significantly associated with longer OS. Moreover, time interval between radiologic diagnosis and chemotherapy tended to be associated with OS ( $P=0.06$ ). Time interval between the first consultation and the first chemotherapy, considered as quantitative variable or as a dichotomized variable (less than 15 days *versus* 15 days or more), was not significantly associated with OS ( $P=0.74$  and  $P=0.53$  respectively).

In multivariate analysis, FOLFIRINOX chemotherapy as first-line (HR 0.6 [0.5-0.8];  $P<0.001$ ), acute pancreatitis as first symptom (HR 2.9 [95% CI: 1.7-4.9];  $P<0.001$ ), metastatic disease at diagnosis (HR 1.6 [95% CI: 1.3-2.0] and WHO PS  $\geq 2$  (HR 1.6 [95% CI: 1.2-2.1];  $P<0.001$ ) were independently associated with OS (Figure 2). Moreover, presence of asthenia as first symptom tended to be associated with poorer OS (HR 1.3 [CI 95%: 0.9-1.8;  $P=0.07$ ]). None of the time intervals was significantly associated with OS.

### ***Subgroup of patients treated with FOLFIRINOX regimen as first-line chemotherapy***

Among the 409 included patients, 139 (34.0%) were treated with FOLFIRINOX regimen as first-line chemotherapy. The median OS for this population was 10.1 months (range 0.1-65.0). In univariate analysis, only acute pancreatitis as first symptom ( $P<0.001$ ) was significantly associated with a poorer OS. None of the time intervals was significantly associated with OS (data not shown, available on supplementary data Table S2).

### ***Subgroup of patients treated with metastatic disease***

Among the 409 included patients, 249 (60.8%) were metastatic. The median OS for this population was 5.8 months [range 0.1-65.0] versus 10.0 [0.6-53.7] for non-metastatic patients. In univariate and multivariate analysis, acute pancreatitis ( $P=0.01$ ) and asthenia ( $P=0.01$ ) as first symptoms, CA 19.9 level (U/ml) ( $P=0.02$ ), and WHO PS 0 or 1 ( $P<0.001$ ) were significantly associated with a poorer OS. None of the time intervals were significantly associated with OS (data not shown, available on supplementary data Table S3).

### **Factors associated with time intervals**

The time intervals of patients treated in University Hospital Center (N=300) have been compared to the other centers. The time from the first visit to histological diagnosis is shortened in University Hospital Center ( $P=0.049$ ). Median time was 0.53 months (1.2-10.0) in University Hospital Center versus 0.3 months (1.6-6.5) in the other centers. There was no difference in the other considered time intervals.

### ***Factors influencing the pre-hospital time interval (first symptoms to first specialist visit)***

#### ***(Table 3):***

In univariate analysis, jaundice ( $P<0.001$ ), occlusion ( $P=0.001$ ) and acute pancreatitis ( $P=0.04$ ) as first symptoms, obesity ( $P<0.001$ ) and pancreatic head tumoral location ( $P=0.002$ ) were associated with shorter pre-hospital time interval while weight loss ( $P=0.009$ ), pruritus ( $P=0.02$ ) and diabetes mellitus ( $P=0.03$ ) as first symptoms, and tumour size ( $P=0.002$ ) were associated with increased pre-hospital time interval. Moreover, distance from home to hospital tended to be negatively associated with pre-hospital time interval ( $P=0.06$ ).

while pain as first symptom ( $P=0.10$ ) and presence of metastasis ( $P=0.07$ ) tended to be associated with longer pre-hospital time interval.

In multivariate analysis, jaundice as first symptom ( $P<0.001$ ) was associated with shorter pre-hospital time interval while pruritus ( $P<0.001$ ) and diabetes mellitus ( $P=0.009$ ) as first symptoms and tumour size ( $P=0.01$ ) were associated with increased pre-hospital time interval.

***Factors influencing the time to treatment (first specialist visit to chemotherapy) (Table 4)***

In univariate analysis, medical history of diabetes mellitus ( $P=0.009$ ), jaundice ( $P=0.001$ ) and acute pancreatitis ( $P=0.030$ ) as first symptoms, biliary drainage ( $P<0.001$ ), endoscopic ultrasound-guided biopsy ( $P=0.010$ ) and head pancreatic tumour location ( $P<0.001$ ) were associated with longer time between first specialist visit and chemotherapy while pain at first symptom ( $P<0.001$ ), tumour size ( $P<0.001$ ), percutaneous biopsy ( $P<0.001$ ) and presence of metastasis ( $P=0.02$ ) were associated with shorter time between first specialist visit and chemotherapy. Moreover, asthenia as first symptom tended to be associated with shorter time between first specialist visit and chemotherapy ( $P=0.07$ ).

In multivariate analysis, medical history of diabetes mellitus ( $P=0.01$ ) and acute pancreatitis as first symptom ( $P<0.001$ ) were associated with longer time between first visit and chemotherapy while percutaneous biopsy ( $P=0.02$ ) and tumour size ( $P=0.02$ ) were associated with shorter time between first visit and chemotherapy. Moreover, pain as first symptom ( $P=0.10$ ) tended to be associated with shorter time between first specialist visit and chemotherapy while head pancreatic tumoral location ( $P=0.09$ ) tended to be associated with longer time between first visit and chemotherapy.

## **DISCUSSION**

In the present study, time intervals to diagnosis and chemotherapy did not influence survival

outcome in advanced PDAC patients that were eligible to receive first-line chemotherapy treatment. It provides more evidence about the relationship between wait times from clinical presentation to the start of chemotherapy and prognosis in a non-selected population in real-life setting.

Prognosis of these patients with advanced PDAC was largely influenced by PS, metastatic stage and chemotherapies' efficiency. Our results concerning time intervals remained no significant in the good prognostic subgroup of patients treated with FOLFIRINOX regimen chemotherapy.

Our multicentric study with five different centers is one of the largest cohorts compared to previously published data. It included the era of new chemotherapy treatments as patients received FOLFIRINOX regimen and gemcitabine plus nab-paclitaxel as first-line chemotherapy. Besides, the OS of overall population and of FOLFIRINOX subgroup were consistent with previously pivotal randomized studies [6,7].

The time intervals studied in the literature widely varied. For this reason, we analysed many intervals and key time points of pathway care in order to complete the criteria of the Aarhus statement for studies about cancer diagnosis [25]. The design of our study was retrospective but only 30 patients (6.8%) were excluded due to missing data.

As common sense has it, rapid diagnosis and early treatment for cancer patients are desirable conditions. The impact of shorter time intervals has been already reported in many cancers [26]. Some cancers may progress even within the relatively short time frame of diagnostic intervals [27]. The systematic review performed in 2015 [10] is the most recent analysis of time to diagnosis-treatment and outcomes across all cancers.

Pancreatic cancers are very aggressive with fast-growing tumours [11]. There are several roadblocks to an early diagnosis and treatment. Symptoms may be insidious and nonspecific. The management of PDAC is complex [5]. Even if radiology can identify pancreatic

neoplasm, there are delays for arranging outpatient visit, treating the jaundice, obtaining the pathological diagnosis, implanting catheter device and starting the treatment in patients with preserved PS eligible for chemotherapy [21].

Most of the published studies did not specifically investigate interval times in patients with advanced PDAC; a majority of reports included patients in surgical curative setting. The Neal et al. systematic review included 207 studies which matched the quality criteria of the Weller consensus [10,25]. Only three studies about PDAC were relevant. Gobbi et al. showed in a 170-patient cohort with all-stages PDAC, that time intervals matter, with significant differences in survival when considering diagnosis was made before 4 weeks, *versus* between 4 and 16 weeks, and after 16 weeks [28]. The APACH Study (<https://clinicaltrials.gov/ct2/show/NCT01989624>) evaluated in particular the prognosis impact of time to treatment less than 2 weeks in primary hospital care centers. Another population study in 350 patients suggested that prognostic factors of survival were tumour resectability and the time from the beginning of symptoms to referral [16]. McLean et al. suggested no influence of treatment time intervals on survival in 355 patients with periampullary adenocarcinoma [20].

A most recent French population-based study found little evidence that timely care was associated with the survival of 298 treated PDAC patients [21]. However, this registry-based study included only 166 metastatic PDAC patients whose 106 were treated by chemotherapy. Gobbi et al. reported that pain and jaundice led to a shorter time to diagnosis and a better survival [28]. In line with our results, two studies suggested that patients with jaundice (and pruritus related) were more likely to have an earlier diagnosis but without impact on survival [17,21]. The shorter time to diagnosis could be due to more alarming symptom. The longer time to treatment, is likely due to the biliary drainage and the need to wait for several days/weeks to observe a sufficient decrease in bilirubin level in order to begin chemotherapy

treatment. In the present study, it is observed that distance from place to residence to cancer care center does not have any incidence on the care timeliness. The influence of distance to health care on cancer survival remains unclear [29,30]. In our study, acute pancreatitis as first symptom was a significant poorer prognostic factor and was also associated with increased time to chemotherapy. A large population-based cohort study recently confirmed the association between a diagnosis of acute pancreatitis and long-term risk of pancreatic cancer [31]. Similarly to our results, a Swedish population-based cohort study showed delay in the diagnosis of pre-existing pancreatic cancer if clinically presented as acute pancreatitis [32]. The proportion of diabetic patients in our population (34.5%) confirmed the association between established diabetes, even more recent diabetes and pancreatic cancer [33,34]. Medical history of diabetes mellitus was associated with increased time to diagnostic and chemotherapy. Thus, the simultaneous appearance of diabetes mellitus and digestive symptoms suggest a pancreatic cancer.

Our study has several limitations. Since the selection of the population was based on medical records and chemotherapy database register, only patients that received chemotherapy were included; patients that received supportive care only were not considered, thus creating a selection bias. These difficult-to treat patients could usually have a quickly evolving disease, and it would be interesting to investigate the care pathway in this specific subpopulation. Majority of patients undergoing palliative surgery had a bilio-digestive double bypass (N=32 (8%)) that is no more recommended nowadays in the guidelines [5]. Despite possible longer time intervals to chemotherapy in these patients, there was no difference in terms of OS in patients whose this surgery were performed versus the others. Moreover, the number of patients treated by palliative surgery was low and may lack of significance. Another limitation of our study was the lack of information about the dates of first visit with the general practitioner and catheter device implantation. In daily practice, the general

practitioner is often the first physician that the patient consults [35]. The point of view of patients and their general practitioner is also an important information. A qualitative analysis of the patient perspectives expressed in free-text comments identified factors that acted as either barriers or facilitators at different stages of the diagnostic process of breast, colorectal, lung and ovarian cancer [36].

In conclusion, our data confirm that wait times from clinical presentation to the start of chemotherapy do not influence outcome in patients with advanced PDAC eligible for chemotherapy. It can be suggested that the current time intervals are too long (both in University Hospital and other Centers) to see a difference for population study's patients. The current time intervals are comparable both for University Hospital and different Centers and therefore we need to implement palliative treatment instead of time to diagnosis and start of chemotherapy. Thus, chemotherapy should not be delayed and be systematically proposed although the diagnosis or the care pathway has been delayed. The ongoing GERCOR Urgence Pancreas D16-1 study (<https://clinicaltrials.gov/ct2/show/NCT02979483>) assess prospectively the feasibility and effects of an early 14-days integrative supportive care program, and times from the first medical appointment to the start of chemotherapy in patients with advanced PDAC. The aggressiveness of pancreatic cancer might not be only defined by its anatomical extent but also by biological markers. Thus, a better patient selection based on genomic analysis might be useful to have a greater impact on clinical outcomes than time to treatment [37].

## **Additional information**

### ***Availability of data and materials***



If you want to know more details about data and materials, please contact us by sending an email to: [qlaurent@chu-reims.fr](mailto:qlaurent@chu-reims.fr)

### ***Conflict of interest***

Q. Laurent-Badr: none

C. Barbe: none

M. Brugel : none

V. Hautefeuille : Novartis, Ipsen, Pfizer, AAA, Amgen, Servier, Merck, Sanofi. In relation to this study: none

J. Volet : in relation to this study: none

S. Grelet : none

E. Desot : none

D. Botsen : GlaxoSmithKline, Pierre Fabre, Chugai, Amgen, Novartis, Roche, Servier. In relation to this study: none

S. Deguelte : none

A. Pitta : none

N. Abdelli : Sanofi, Bayer, Roche. In relation to this study: none

M. Brasseur : Amgen, Bayer, Pierre Fabre, Roche. In relation to this study: none

L. De Mestier : Ipsen, Pfizer, Novartis. In relation to this study: none

C. Neuzillet : MSD, Astra Zeneca, BMS, Merck, Amgen, Roche, Servier, Novartis. In relation to this study: none

O. Bouche : Amgen, Roche, Merck, Servier, Pierre Fabre. In relation to this study: none

### ***Funding***

There was no funding for this study.

**Acknowledgements:** none.

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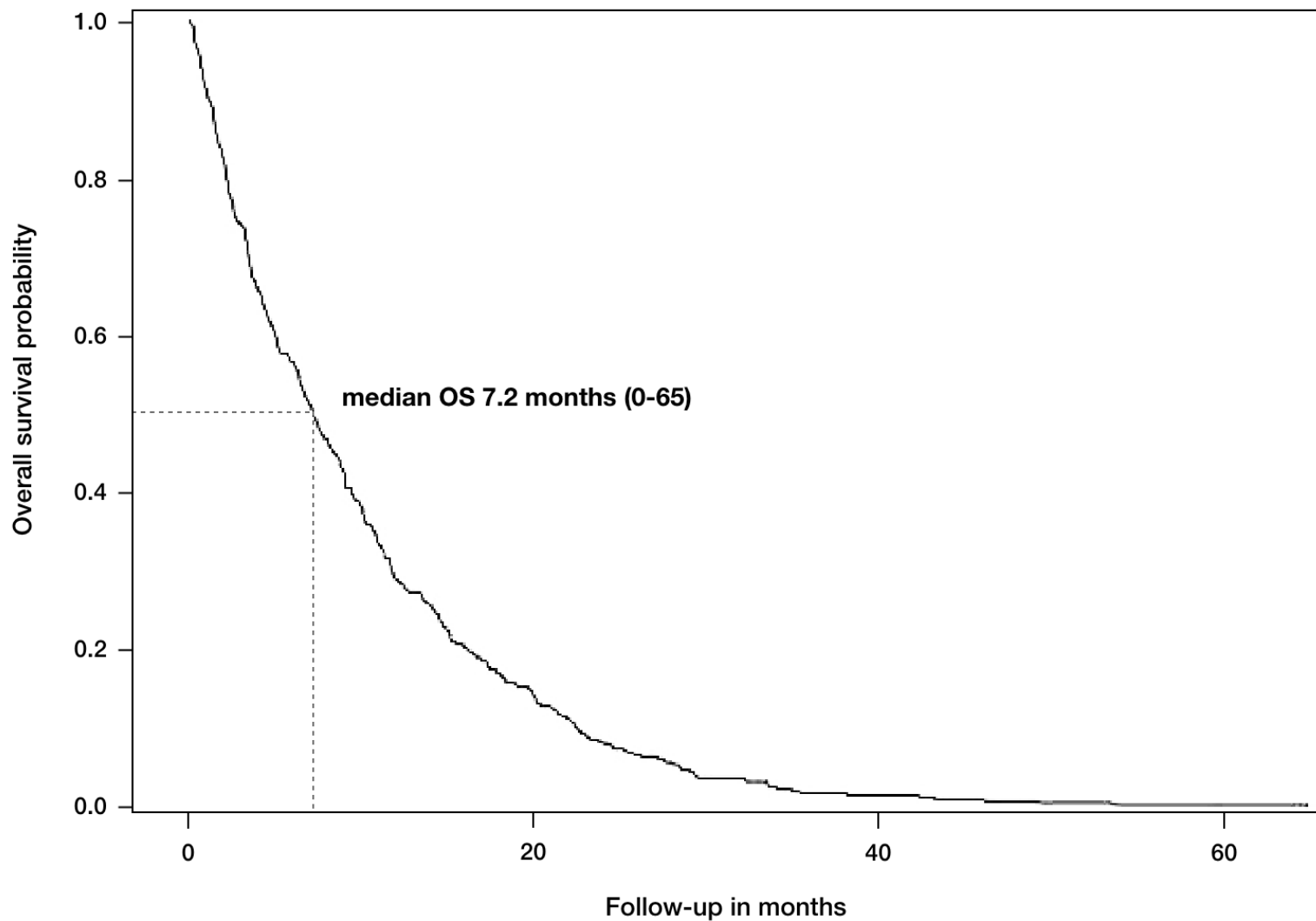
## **FIGURES LEGENDS**

**Figure 1. Kaplan Meier estimate of Overall Survival (OS) (date of the first administration of chemotherapy to date of death or censoring)**

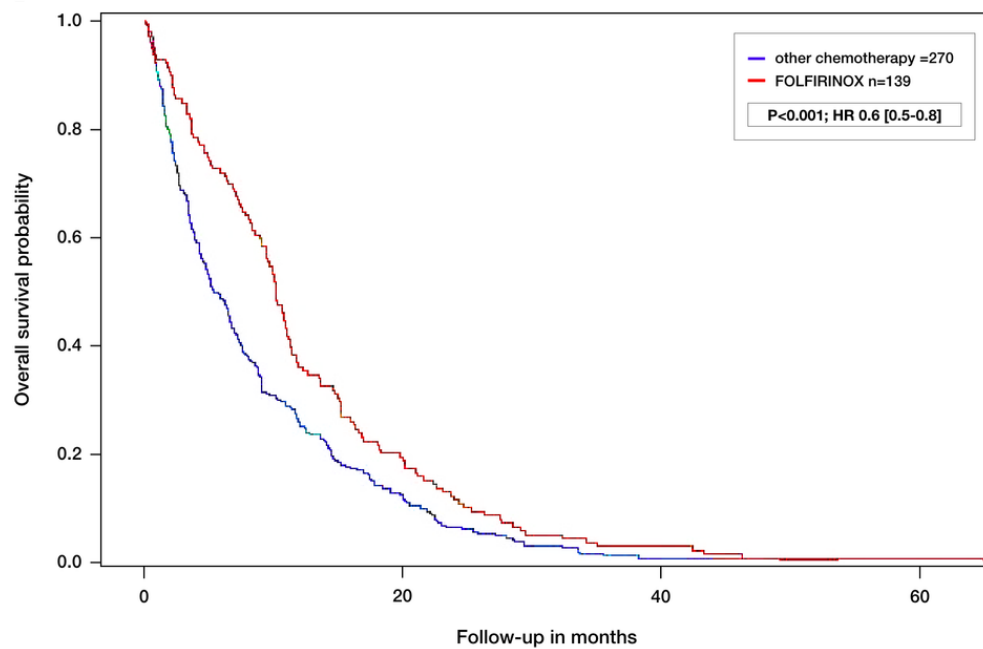
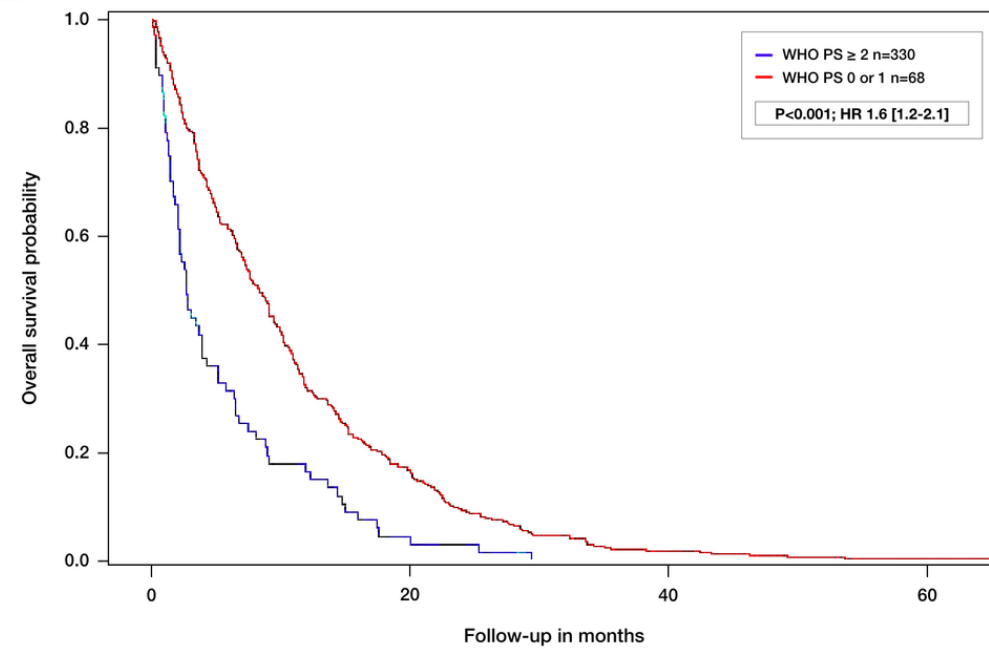
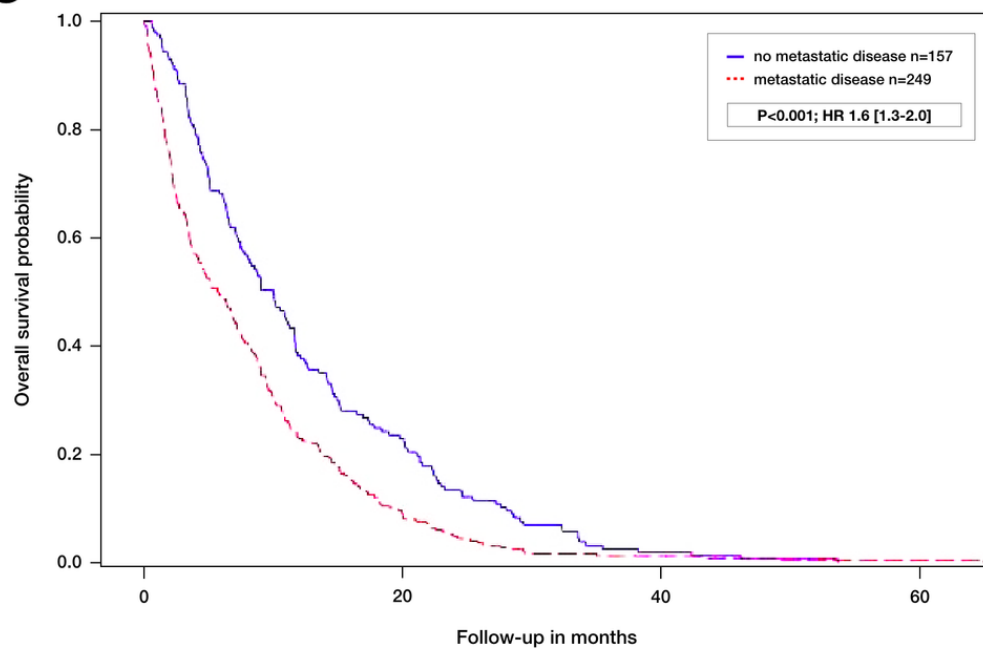
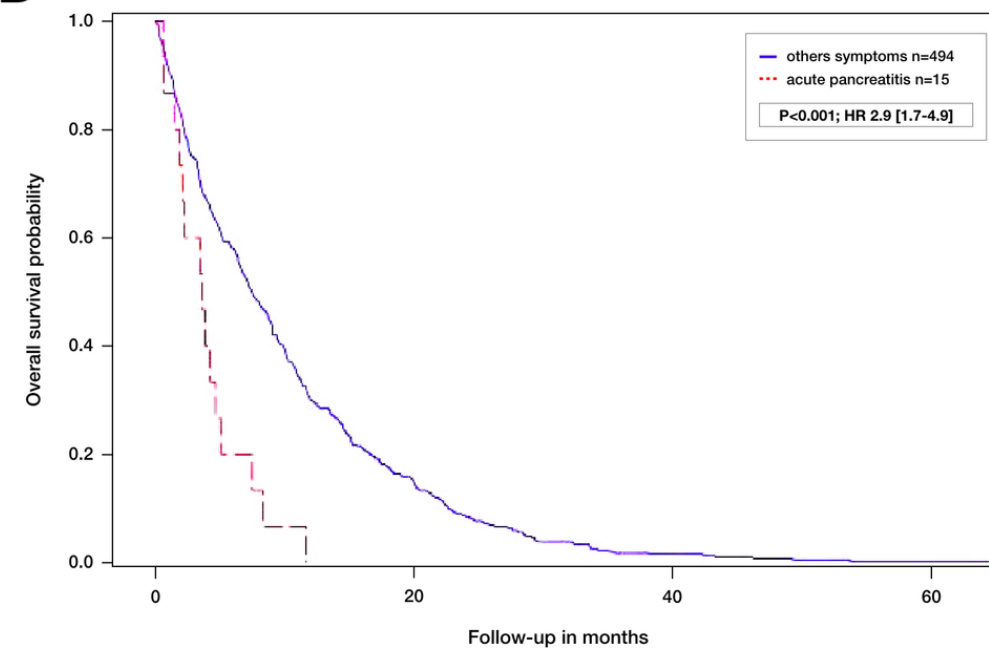
**Figure 2. Factors associated in univariate and multivariate analysis with Overall Survival (Kaplan Meier method); HR : Hazard Ratio**

**Figure F1 (Supplementary Data). Definition of time intervals**

**Figure F2 (Supplementary Data). Flow chart**





**A****B****C****D**

**Table 1. Baseline characteristics and time intervals**

Characteristics <sup>1</sup>	n = 409
Age <sup>2,3</sup> (years)	66.1 ± 10.3
Gender	
- Male	240 (58.7)
- Female	169 (41.3)
BMI (kg/m <sup>2</sup> ) <sup>2,4</sup>	24.4±4.5
Distance from place of residence to hospital (kilometer) <sup>2,3</sup>	49.8 ± 37.9
Smoking status <sup>5</sup>	
- Non smoker	278 (71.1)
- Ex-smoker	53 (13.5)
- Current smoker	60 (15.3)
Alcohol usage <sup>6</sup>	53 (13.3)
Diabetes <sup>7</sup>	140 (34.5)
First symptoms:	
- Jaundice	121 (29.6)
- Pain	237 (58)
- Acute pancreatitis	15 (3.7)
- Weight loss	229 (56)
- Asthenia	52 (12.7)
- Occlusion	26 (6.3)
- Pruritus	16 (3.9)
- Diabetes discovery	29 (7.1)
- Old diabetes with decompensation	22 (5.3)
- Diarrhea	12 (2.9)
- Others	21 (5.1)
Pain <sup>9</sup>	255 (63.7)
Use of analgesics <sup>10</sup>	124 (36.9)
Type of analgesics <sup>8</sup>	
- grade I	29 (24.6)
- grade II	56 (47.5)
- grade III	33 (28)
WHO PS <sup>11</sup>	
- 0	109 (27.4)
- 1	221 (55.5)
- 2	64 (16.1)
- 3	4 (1.0)
Hospitalised at diagnosis <sup>3</sup>	184 (45.1)
CA 19.9 level <sup>2, 12, 13</sup> (U/mL)	18373±82934
Tumour size <sup>2,14</sup> (millimeter)	39.6 (16.9)
Metastatic disease	250 (61.1)
Palliative surgery before chemotherapy	39 (9.5)
Type of palliative surgery <sup>3</sup>	

- Bilio-digestive double bypass	32 (82.0)
- Others	7 (18)
Duodenal prosthesis	4 (1.0)
Biliary drainage	156 (38.1)
First line Chemotherapy L1	
- FOLFIRINOX regimen	139 (34)
- Gemcitabine	211 (51.6)
- Gemcitabine-nab-paclitaxel	9 (2.2)
- FOLFOX	6 (1.4)
- Other	44 (10.8)
Time intervals <sup>15</sup> (months)	
- symptoms to 1 <sup>st</sup> visit	2.5±3.6; 1.3 [0-46.2]
- symptoms to pathological diagnosis	3.2±3.8; 2.1 [0-47.8]
- symptoms to treatment	4.5±3.9; 3.3 [0.8-48.4]
- first visit with specialist to pathological diagnosis	0.7±1.0; 0.4 [0-10.0]
- pathological diagnosis to treatment	1.3±1.2; 1.0 [0.1-13.5]
- first visit with specialist to treatment	1.9±1.5; 1.6 [0.1-13.5]
- symptoms to imaging diagnosis	2.6±4.2; 1.1 [0-46.8]
- imaging diagnosis to treatment	1.9±2.4; 1.6 [0-13.8]

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<sup>1</sup> Data are expressed as No (%) unless otherwise indicated; <sup>2</sup> Quantitative variables are reported as mean ± standard deviation; <sup>3</sup> 1 missing data; <sup>4</sup> 4 missing data; <sup>5</sup> 18 missing data; <sup>6</sup> 10 missing data; <sup>7</sup> 3 missing data; <sup>8</sup> 6 missing data; <sup>9</sup> 9 missing data; <sup>10</sup> 73 missing data; <sup>11</sup> 11 missing data; <sup>12</sup> 194 missing data; <sup>13</sup> median is 974 <sup>14</sup> 69 missing data; <sup>15</sup> data are presented as mean ± standard deviation; median [range].

BMI = body mass index, PS = performance status, CA 19.9 = Carbohydrate antigen 19.9

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**Table 2. Factors associated with Overall Survival at Univariate and Multivariate Analysis in 409 patients with advanced pancreatic ductal adenocarcinoma treated by chemotherapy**

Variables	Time survival (months) <sup>1</sup>	Univariate analysis		Multivariate analysis	
		HR [95% CI]	P	HR [95% CI]	P
Age profile above average (66 years old)			0.04		
– Yes	8.2 [0.1-65]	1.01 [1.0-1.1]			
– No	6.4 [0.2-53.7]				
Gender			0.132		
– Male	7.2 [0.1-49.3]	1.2 [1.0-1.4]			
– Female	7.4 [0.2-65.0]				
Distance from place of residence to hospital (kilometer)	-		0.40		
(BMI (kg/m <sup>2</sup> ))	-		0.16		
Alcohol usage			0.11		
– Yes	6.4 [0.2-42.4]	1.3 [0.9-1.7]			
– No	7.5 [0.1-65.0]				
Smoking (current &detoxed)			0.58		
– Yes	7.4 [0.1-42.4]	1.1 [0.8-1.4]			
– No	7.2 [0.1-65.0]				
Medical history of diabetes mellitus			0.90		
– Yes	7.9 [0.1-34.2]	1.0 [0.8-1.2]			
– No	7.1 [0.1-65.0]				
First symptoms:					
- Jaundice			0.675		
– Yes	7.6 [0.2-49.2]	0.9 [0.8-1.1]			
– No	7.0 [0.1-65.0]				
- Pain			0.217		
– Yes	7.9 [0.1-53.7]	0.8 [0.7-1.1]			
– No	6.6 [0.1-65.0]				
- Weight loss			0.90		
– Yes	6.7 [0.1-65.0]	1.0 [0.8-1.2]			
– No	7.8 [0.2-49.3]				
- Asthenia			0.002		0.07
– Yes	3.5 [0.1-42.4]	1.5 [1.1-2.1]		1.3 [0.9-1.8]	
– No	7.6 [0.1-56.0]			1	
- Diabetes mellitus			0.613		
– Yes	8.1 [1.0-26.2]	1.1 [0.8-1.6]			

– No	7.2 [0.1-65.0]			
- Acute pancreatitis			<0.001	<0.001
– Yes	3.6 [0.6-11.7]	2.5 [1.5-4.3]		2.9 [1.7-4.9]
– No	7.5 [0.1-65.0]			1
Analgesics use			0.369	
– grade I	4.2 [0.3-53.7]			
– grade II	7.3 [0.1-42.4]	0.8 [0.5-1.3]		
– grade III	8.8 [0.4-46.2]	0.7 [0.4-1.1]		
WHO PS			<0.001	<0.001
– 0 or 1	8.3 [0.1-65.0]	2.0 [1.5-2.6]		1
– ≥ 2	2.6 [0.1-29.4]			1.6 [1.2-2.1]
Hospitalised at diagnosis			0.25	
– Yes	6.5 [0.1-49.3]	1.1 [0.9-1.4]		
– No	8.1 [0.3-65.0]			
Ca 19.9 level			0.005	
Tumour size	-		0.116	
Metastatic disease			<0.001	0.001
– Yes	5.8 [0.1-65.0]			1.6 [1.3-2.0]
– No	10.0 [0.6-53.7]	0.6 [0.5-0.8]		1
Palliative surgery			0.26	
– Yes	7.1 [0.3-49.3]			
– No	7.2 [0.1-65.0]	1.2 [0.9-1.6]		
Biliary drainage			0.60	
– Yes	6.8 [0.1-49.7]			
– No	7.5 [0.1-65.0]	0.9 [0.8-1.2]		
First-line chemotherapy				<0.001
– FOLFIRINOX	10.1 [0.1-65.0]	1.4 [1.2-1.8]	<0.001	0.6 [0.5-0.8]
– Other	5.3 [0.1-53.7]			1
Time intervals				
- symptoms to first visit			0.85	
- symptoms to pathological diagnosis			0.71	
- symptoms to treatment			0.77	
- first visit with the specialist to pathological diagnosis			0.51	
- pathological diagnosis to treatment			0.85	
- first visit with specialist to treatment			0.74	
– < 15 days	7.6 [1.7-22.2]		0.53	
– > 15 days	7.2 [0.1-65.0]			
- symptoms to imaging diagnosis			0.57	

- imaging diagnosis to treatment

0.06

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<sup>1</sup> data are presented as median [range]; <sup>2</sup> factors included in multivariate analysis were: age greater than 66 years old, asthenia, pancreatitis, presence of metastasis, WHO PS (0 or 1 versus  $\geq 2$ ), FOLFIRINOX as first-line chemotherapy and time between imaging diagnosis and first chemotherapy. Serum Ca19.9 level was not included because of the number of missing data.

BMI = body mass index, PS = performance status, CA 19.9 = Carbohydrate antigen 19.9

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**Table 3: Factors influencing the time between first symptoms and first visit with specialist**

Variables	Time interval from first symptoms to first specialist visit (months) <sup>1</sup>	Univariate analysis		Multivariate analysis	
		Correlation coefficient (r)	P	$\beta \pm SE (\beta)$	P
Distance from place of residence to care center (kilometers)	-	-0.09	0.06		
Age	-	0.03	0.46		
BMI (kg/m <sup>2</sup> )		-0.09	0.07		
Obesity			<0.001		
- Yes	1.4±1.7; 0.9 [0-8.1]				
- No	2.6±3.7; 1.4 [0-46.2]				
Gender		-	0.13		
- Male	2.7±4.1, 1.6 [0-46.2]				
- Female	2.2±2.8, 1.0 [0-14.2]				
Alcohol use		-	0.65		
- Yes	2.5±3.7; 1.3 [0-46.2]				
- No	2.3±2.8; 1.2 [0-12.1]				
Tobacco use		-	0.81		
- Yes	2.1±2.3; 1.6 [0-8.4]				
- No	2.5±3.1; 1.3 [0-14.3]				
- Ancient	2.1±2.2; 1.3 [0-8.4]				
Diabetes mellitus		-	0.28		
- Yes	2.8±3.2; 1.6 [0-14.3]				
- No	2.3±3.8; 1.2 [0-46.2]				
First symptoms		-	<0.001		
Jaundice					<0.001
- Yes	1.4±2.7; 0.5 [0-14.3]			-1.6±0.4	
- No	3.0±3.8; 2.0 [0-46.2]			1	
Pruritus			0.02		<0.001
- Yes	4.1±11.6; 0.5 [0-46.2]			4.0±1.1	
- No	2.4±2.9; 1.4 [0-14.3]			1	
Diabetes mellitus			0.03		0.009
- Yes	4.2±4.3; 3.0 [0-14.3]			1.9±0.7	
- No	2.4±3.5; 1.2 [0-46.2]			1	
Pain			0.097		
- Yes	2.7±3.8; 1.9 [0-46.2]				

-	No	2.2±3.2; 0.8 [0-13.1]				
Weight loss				0.009		
-	Yes	2.9±3.0; 1.9 [0-14.2]				
-	No	1.9±4.2; 0.7 [0-46]				
Asthenia				0.83		
-	Yes	2.6±3.8; 1.9 [0-12.1]				
-	No	2.5±3.7; 1.3 [0-46.2]				
Occlusion				0.001		
-	Yes	1.5±2.8; [0-11.5]				
-	No	2.6±3.6; 1.4 [0-46]				
Acute pancreatitis				0.04		
-	Yes	1.5±2.2; 0.2 [0-6]				
-	No	2.5±3.6; 1.3 [0-46.2]				
Tumour size			0.17	0.002	0.03±0.01	0.01
Metastatic disease			-	0.07		
-	Yes	2.7±4.1; 1.6 [0-46.2]				
-	No	2.1±2.7; 1.0 [0-12.3]				
Pancreatic head tumoral location			-	0.002		
-	Yes	2.0±2.8; 0.8 [0-14.3]				
-	No	3.1±4.7; 2.0 [0-46.2]				

<sup>1</sup> data are presented as mean ± standard deviation; median [range]; <sup>2</sup> factors included in multivariate analysis were: jaundice, pain, weight loss, occlusion, pruritus, diabetes mellitus and acute pancreatitis as first symptoms, obesity, metastatic disease, pancreatic head tumoral location, tumour size

BMI = body mass index, PS = performance status



**Table 4: Factors influencing the time between the first visit with specialist and beginning of chemotherapy**

Variables	Time interval from first symptoms to first specialist visit (months) <sup>1</sup>	Univariate analysis		Multivariate analysis	
		Correlation coefficient (r)	P	$\beta \pm SE (\beta)$	P
Age	-	0.03	0.6		
BMI (kg/m <sup>2</sup> )		0.05	0.29		
Gender		-	0.4		
- Male	2.0±1.6; 1.5 [0.3-13.5]				
- Female	1.9±1.3; 1.6 [0.1-13.2]				
Alcohol use		-	0.11		
- Yes	2.4±2.2; 1.5 [0.5-13.5]				
- No	1.9±1.4; 1.6 [0.1-13.2]				
Tobacco use		-	0.9		
- Yes	2.1±1.6; 1.5 [0.1-7.8]				
- No	1.9±1.5; 1.6 [0.2-13.5]				
- Ancient	1.9±1.2, 1.5 [0.5-6.8]				
Medical history of diabetes mellitus		-	0.008	0.36±0.15	0.015
- Yes	2.2±1.6; 1.6 [0.5-13.2]				
- No	1.8±1.4; 1.4 [0.1-13.5]				
First symptoms					
Jaundice		-	0.001		
- Yes	2.4±2.0; 1.8 [0.2-13.5]				
- No	1.7±1.1; 1.4 [0.1-7.0]				
Pruritus			0.22		
- Yes	2.8±2.9; 2.0 [0.8-13.2]				
- No	1.9±1.4; 1.5 [0.1-13.5]				
Diabetes mellitus			0.9		
- Yes	2.0±2.3; 1.4 [0.6-13.2]				
- No	1.9±1.4; 1.6 [0.1-13.5]				
Pain			<0.001	-0.25±0.15	0.095
- Yes	1.6±1.1; 1.4 [0.2-7.0]				
- No	2.3±1.9; 1.8 [0.1-13.5]				
Weight loss			0.11		
- Yes	1.8±1.5; 1.5 [0.1-13.5]				
- No	2.1±1.5; 1.6 [0.3-11.9]				
Asthenia			0.07		

-	Yes	1.7±0.9; 1.6 [0.1-4.5]			
-	No	2.0±1.6; 1.5 [0.2-13.5]			
Occlusion			0.23		
-	Yes	1.6±1.2; 1.5 [0.4-6.8]			
-	No	2.0±1.5; 1.6 [0.1-13.5]			
Acute pancreatitis			0.03	1.29±0.36	<0.001
-	Yes	3.2±2.1; 2.9 [0.8-7.8]			
-	No	1.9±1.4; 1.5 [0.1-13.5]			
Tumour size			-0.18	<0.001	0.26±0.15
Metastatic disease			-	0.02	
-	Yes	1.8±1.5; 1.5 [0.1-13.5]			
-	No	2.1±1.5; 1.8 [0.2-11.9]			
Pancreatic head tumoral location			-	<0.001	-0.01±0.00
-	Yes	2.2±1.7; 1.7 [0.2-13.5]			
Hospitalisation at diagnosis			-	0.23	
-	Yes	2.0±1.6; 1.6 [0.3-13.2]			
-	No	1.8±1.4; 1.5 [0.1-13.5]			
Biliary drain			-	<0.001	
-	Yes	2.3±1.9; 1.8 [0.6-13.5]			
-	No	1.7±1.1; 1.4 [0.1-7.0]			
Endoscopic ultrasound-guided biopsy			-	0.01	
-	Yes	2.2±1.9; 1.6 [0.2-13.5]			
-	No	1.7±1.2; 1.5 [0.1-11.9]			
Percutaneous biopsy			-	<0.001	-0.35±0.15
-	Yes	1.6±1.2; 1.4 [0.1-11.9]			0.017
-	No	2.2±1.6; 1.7 [0.2-13.5]			

<sup>1</sup> data are presented as mean ± standard deviation; median [range]; <sup>2</sup> factors included in multivariate analysis were: diabetes mellitus, percutaneous biopsy, pancreatic head tumoral location, tumour size, pain and acute pancreatitis as first symptoms  
BMI = body mass index, PS = performance status