

# Locally Advanced or Metastatic Pancreatic Adenocarcinoma: Easily Available Factors of Predictive Prolonged Survival Under Gemcitabine

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**Abstract.** *Background: Prognosis of patients with locally advanced or metastatic pancreatic adenocarcinoma is poor. In this study, we assessed the predictive value of easily available baseline factors for prolonged survival. Patients and Methods: We conducted a retrospective study on patients who received gemcitabine between 1999 and 2010 for locally advanced or metastatic pancreatic adenocarcinoma. The primary end-point was the 12-month survival rate. Results: We included 195 patients. The median age was 62.9 years; the performance status was 0-1 in 80 and 2-3 in 92 patients. The median number of metastatic sites was one. A total of 73 patients (37.4%) were alive 12 months after beginning chemotherapy. In multivariate analysis, no liver metastasis, CA19-9 level <250 IU/ml and localized or locally advanced cancer at diagnosis were good prognostic factors. According to a clinical score based on these features, overall survival was 7.7, 13.5, 19.7 and 21.0 months, respectively ( $p < 0.001$ ). Conclusion: We identified easily available prognostic factors for prolonged survival in patients treated with gemcitabine.*

Pancreatic adenocarcinoma (PA) is the fourth cause of cancer-related deaths (1). Surgical resection represents the only hope for cure but only 10-20% of patients present with a surgically-resectable tumour.

For advanced and metastatic PA, systemic chemotherapy with single-agent nucleoside analogue gemcitabine is currently recommended as a standard in first-line treatment,

with a significantly improved quality of life, and a median overall survival (OS) of 6-9 months (2). Although the absolute survival benefit remains poor and controversial, some patients (18%) survive more than 12 months (2). Gemcitabine chemotherapy has represented the single standard therapy for PA for more than a decade. Recently, a randomized trial compared gemcitabine and 5-fluorouracil/leucovorin/irinotecan/oxaliplatin combination (FOLFIRINOX) in front-line treatment of 342 patients with locally advanced or metastatic PA (3). The FOLFIRINOX regimen was superior to gemcitabine in terms of OS (11.1 vs. 6.8 months), progression-free survival (PFS) (6.4 vs. 3.3 months), and objective response rate (31.6 vs. 9.4%). Moreover, a recent update indicated that FOLFIRINOX was also superior in terms of quality of life (4). FOLFIRINOX is now the standard therapy in FRANCE. Yet FOLFIRINOX use is restricted to selected patients with preserved Eastern Cooperative Oncology Group performance status of 0-1, and with normal bilirubinemia. The toxicity of FOLFIRINOX is significant, especially in regard to the cumulative oxaliplatin-related neurotoxicity. To avoid this toxicity, it would be useful to have easily available factors predictive of long survival with gemcitabine alone. The aim of the present study was to assess these potent predictive factors.

## Patients and Methods

*Patients.* We conducted a multicentric retrospective study between 1999 and 2010 at two centres in northern France before the advent of FOLFIRINOX (3). Inclusion criteria were: age >18 years; an histologically confirmed PA or a tumour radiologically suggestive of PA growing between two different computed tomographic (CT) scans or magnetic resonance imaging (MRI); locally advanced or metastatic tumor, and no previous chemotherapy.

Gemcitabine was administered at 1,000 mg/m<sup>2</sup> intravenously over 30 minutes weekly for 7 weeks followed by a 1-week break. Subsequent cycles consisted of weekly administrations 3 weeks out of 4. Radiological evaluations by CT scan or MRI were repeated every 2 months. Gemcitabine was stopped if the patient presented

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a limiting toxicity or a tumoural progression according to response evaluation criteria in solid tumor (RECIST) (5).

We assessed the prognostic value of the following features: demographical: age, gender; clinical: performance status, jaundice at diagnosis; tumoural: histology, intrapancreatic localisation, initial stage, differentiation, number of metastatic sites, metastasis localisation; and carcino antigen 19-9 (CA19-9) concentration. The primary end-point was 12-month OS.

*Statistical analyses.* OS was calculated from diagnosis of metastatic or locally advanced disease to death.

Univariate analysis was conducted on all variables with chi-square test. The continuous variables expressed as median (range) were tested as they were and then were separated into groups based on deciles. The prognostic factors significant at a level of 0.20 were included in a multivariate analysis conducted with logistic regression.

We then created a score based on prognostic factors, with one point given to each factor, and the statistical significance of this score was tested with chi-square test on 12-month OS rate and with Cox model on OS.

## Results

*Patients.* The study was performed on 195 consecutive patients. The median age was 62.9 years (range 28.6-84.4). The sex ratio (M/F) was 100/95. Eighty patients (41.0%) had an ECOG status of 0-1, and 92 (47.2%) of 2-3. The disease was revealed by jaundice in 72 (36.9%) patients. Tumour location was in the pancreatic head in the majority of cases [127 (65.1%)]. Adenocarcinoma was histologically confirmed in 154 cases (79.0%), and well-differentiated in 30 patients (15.4%). At diagnosis, only 33 patients (17.0%) had a localized tumor. At inclusion, the median number of metastatic sites was one, involving mainly the liver in 116 patients (59.5%) or the peritoneum in 45 patients (23.1%). The median CA19-9 concentration was 636 (range=1-372,000) IU/ml (Table I).

A total of 51 patients (26.1%) received second-line chemotherapy of capecitabine, leucovorin and fluorouracil (LV5FU2)-cisplatin, tomudex and oxaliplatin (TOMOX), gemcitabine and oxaliplatin (GEMOX), 5FU, irinotecan and oxaliplatin (FOLFIRINOX) or tomudex. Among the 57 patients with locally advanced cancer, four had surgery, two after chemotherapy, one after radiotherapy and one after radiochemotherapy; 11 patients received radiochemotherapy without surgery.

The median overall survival was 10.1 (0.8-116.3) months, with 73 patients (37.4%) alive 12 months after diagnosis.

*Factors predictive of prolonged survival >12 months.* Among the 16 assessed variables, eight were identified as having a good prognostic value on univariate analysis: jaundice ( $p=0.005$ ), locally advanced tumour at inclusion ( $p=0.030$ ), no synchronous metastasis at diagnosis ( $p<0.001$ ), bone metastasis ( $p=0.133$ ), no liver metastasis at diagnosis

Table I. Characteristics of patients at baseline.

Characteristic	Median (min-max)	Number (%)	Missing values
Age, years	62.9 (28.6-84.4)		0
Male gender		100 (53.5%)	0
Performance status			23 (11.8%)
0		16 (9.3%)	
1		64 (37.2%)	
2		66 (38.4%)	
3		26 (15.1%)	
Jaundice at diagnosis		72 (39.6%)	13 (6.7%)
CA19-9 (IU/ml)	636.3 (1-372000)		53 (27.2%)
Elevated CA19-9 (>5 IU/ml)		115 (76.2%)	44 (22.6%)
Tumour location			12 (6.2%)
Head		127 (69.8%)	
Body		29 (15.9%)	
Tail		26 (14.3%)	
Histological proof		154 (79.0%)	0
Differentiation			101 (51.8%)
Well		30 (31.9%)	
Moderate		55 (58.5%)	
Poor		7 (7.4%)	
Locally advanced disease		57 (29.2%)	0
Metastatic disease		105 (54.1%)	
Number of metastatic sites	1 (0-3)		8 (4.1%)
Liver metastasis		116 (59.5%)	0
Lung metastasis		18 (9.2%)	0
Peritoneal carcinomatosis		45 (23.1%)	0
Bone metastases		6 (3.1%)	0

CA19-9: Cancer antigen 19-9.

( $p<0.001$ ), CA19-9 <250 IU/ml ( $p=0.013$ ), histological proof ( $p=0.052$ ), and head location ( $p=0.149$ ) (Table II).

Among the eight variables included in multivariate analysis, three were identified as having good prognostic value: no liver metastasis at diagnosis ( $p=0.001$ ), CA19-9 <250 IU/ml ( $p=0.009$ ) and no synchronous metastasis at diagnosis ( $p=0.015$ ) (Table III).

We then created a clinical score ascribing one point for each good prognostic feature. This score of 0 to 3 points was tested for correlation to 12-month OS ( $p<0.001$ ) in chi-square test.

The OS according to clinical scores of 0, 1, 2 and 3 was 7.7, 13.5, 19.7 and 21.0 months, respectively ( $p<0.001$ ) (Figure 1). Two-thirds of patients with 3 points had an OS >12 months.

## Discussion

In this study on 195 patients with PA treated with gemcitabine alone, we constructed a prognostic score from easily available clinical and biological features. We showed

Table II. Univariate analysis of 12 months overall survival (OS) with chi-square test.

Factor	OS >12 months (N=73, 37.4%), n (%)	p-Value
Male	43 (38.4%)	0.595
Jaundice	35 (48.6%)	0.005
PS 0-1	35 (39.8%)	0.726
Locally advanced disease	28 (49.1%)	0.030
No synchronous metastasis	24 (22.8%)	<0.001
1 or 2 metastases	58 (34.5%)	0.345
No liver metastasis	31 (26.7%)	<0.001
Bone metastasis	4 (66.7%)	0.133
Lung metastasis	8 (44.4%)	0.519
Peritoneal carcinomatosis	14 (31.1%)	0.318
Histological proof	63 (40.9%)	0.052
Well-differentiated	16 (51.6%)	0.258
Location		0.149
Head	53 (41.7%)	
Body	7 (24.1%)	
Tail	8 (30.8%)	
Age >62.9 years	37 (35.2%)	0.546
CA19-9 <250 IU/ml	50 (32.2%)	0.013

PS: Performance status; CA19-9: cancer antigen 19-9.

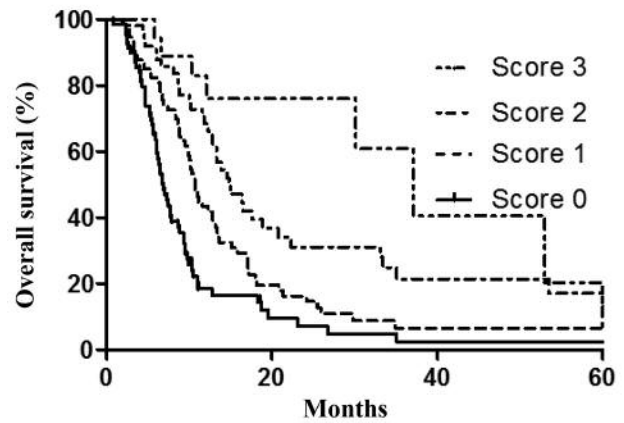
Table III. Multivariate analysis of odds of overall survival.

Factor	OR (95% CI)	p-Value
No liver metastasis	3.8 (1.7-8.6)	0.001
CA19-9 <250 IU/ml	2.9 (1.3-6.6)	0.009
No synchronous metastasis	2.7 (1.2-5.9)	0.015
Bone metastasis	0.2 (0.02-1.3)	0.083
Head location	0.4 (0.1-1.3)	0.225
Locally advanced	0.7 (0.3-2.2)	0.605
Jaundice	0.6 (0.3-1.3)	0.195
Histological proof	0.6 (0.2-2.0)	0.414

OR: Odds ratio; CA19-9: cancer antigen 19-9; CI: confidence interval.

that the absence of liver metastases, a CA19-9 concentration <250 IU/ml and the absence of synchronous metastasis at diagnosis were significantly associated with a prolonged OS (>12 months), with median OS of 21.0 months for patients with all three good prognosis factors.

The presence of synchronous metastases is an expected poor prognostic factor in several cancer types including of the pancreas (6-10). Liver metastasis is a known poor prognostic factor, and CA19-9 is described as poor prognostic factor in different studies, without a clear cut-off (6, 11, 12). Here we found that CA19-9 was a factor of poor prognosis when exceeding 250 IU/ml. In our study, the



No at risk	Time (months)						
	0	10	20	30	40	50	60
Score 0	69	16	4	2	1	1	1
Score 1	76	43	12	4	3	3	3
Score 2	50	36	14	10	6	6	4
Score 3	18	15	5	5	2	2	1

Figure 1. Overall survival according to the clinical score: 0, 1, 2 or 3 good prognostic factors between: no liver metastasis, CA 19-9 <250 and localized or locally advanced pancreatic cancer at diagnostic.

performance status (a subjective value) was not included, which means that all the relevant features used for our scorer here are objective. Our score is easily applicable in routine practice.

A limitation of this study is its retrospective nature. Moreover, we had much missing data, especially regarding CA19-9 concentration (22.6%). Our score needs to be confirmed in an independent cohort or by a prospective study.

In a recent study, a neutrophil/lymphocyte ratio of 2 or more was a prognostic factor for resectable pancreatic cancer (13). In another study, the lymphocyte/monocyte ratio was a good prognostic factor (13). Recently, several studies focused on the tumoural expression of the nucleoside transporter human equilibrative nucleoside transporter (hENT1) (10, 11, 14, 15). A high expression of hENT1 seems to be associated with a greater efficacy of gemcitabine. Yet the prognostic value of this remains controversial and has been mainly assessed in an adjuvant setting (16-18). The prognostic value of this expression seems to vary according to the antibody used. In a recent study, Svrcek *et al*. showed that murine antibody to hENT1 was predictive of OS in patients treated by gemcitabine, but rabbit antibody was not (19). Moreover, hENT1 expression is not currently routinely assessed.

Furthermore, recent studies showed several biomarkers in immunohistochemistry (20) or with polymerase chain reaction (PCR) analysis (21). However, such methods are not easily feasible in clinical practice.

The prognostic factors defined in the present study can be useful in selecting long surviving patients who will benefit more from gemcitabine and who can be spared from FOLFIRINOX toxicity. Indeed, FOLFIRINOX regimen is associated with several severe toxicities (grade 3-4) with 45.7% experiencing neutropenia, 23.6% fatigue, 14.5% vomiting, and 12.7% diarrhea in the study of Conroy *et al.* (3). Recently, new combination with gemcitabine and nab-paclitaxel led to longer OS than gemcitabine alone, with acceptable toxicities such as neuropathy (22). However, nab-paclitaxel is not available in many countries, such as France.

Nowadays, the aim of the clinician is to choose the best strategy to obtain long survival with acceptable toxicity. In long surviving patients, starting with a less toxic chemotherapy, such as gemcitabine, and switching to FOLFIRINOX at progression could be an effective strategy to achieve greater survival without toxicity.

Two studies are recruiting to test such different strategies. PRODIGE 35 aims to compare a standard 12 cycles of FOLFIRINOX followed by monitoring *versus* eight cycles of FOLFIRINOX followed by LV5FU2 *versus* alternate FOLFIRI for 2 months and gemcitabine for 2 months. PRODIGE 37 is evaluating another standard of gemcitabine plus nab-paclitaxel *versus* alternate FOLFIRI for 2 months and gemcitabine plus nab-paclitaxel for 2 months.

To conclude, the results of the present study suggest that using easily available prognostic factors could define patients who would have prolonged survival with gemcitabine alone, and whom could be spared from the higher toxicity of more aggressive regimens.

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