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ORIGINAL ARTICLE

Characteristic and outcomes of patients with pathologic complete response after preoperative treatment in borderline and locally advanced pancreatic adenocarcinoma: An AGEO multicentric retrospective cohort

Hampig Kourie[a,b], Edouard Auclin[b,c,d], Antonio Sa Cunha[e], Sebastien Gaujoux[f], Mathieu Bruzzi[g], Alain Sauvanet[h], Nelson Lourenco[i], Isabelle Trouilloud[j], Samy Louafi[a,k], Ahmad El-Hajjar[a], Jean Christophe Vaillant[l], Denis Smith[m], Yann Touchefeu[n], Jean-Baptiste Bachet[o], Daniel Pietrasz[p], Julien Taieb[a,*]

[a] *Sorbonne Paris-Cité, Paris Descartes University, hepatogastroenterology and gastrointestinal oncology department, hôpital Européen Georges-Pompidou, 75015 Paris, France*
[b] *Unité de génétique médicale, faculté de médecine, université Saint Joseph de Beyrouth, Beyrouth, Lebanon*
[c] *Methodology and quality of life unit in oncology, university hospital of Besançon, Besançon, France*
[d] *Université Bourgogne Franche-Comté, Inserm, EFS BFC, UMR1098, interactions Hôte-Greffon-tumeur/ingenierie cellulaire et génique, 25000 Besançon, France*
[e] *Unité d'hospitalisation chirurgie hépatique, biliaire et pancréatique, centre hépato-biliaire, hôpital Paul-Brousse, faculté de médecine Paris-Sud, France*
[f] *Service de chirurgie digestive hépato-biliaire, pancréatique et endocrinienne, Hôpital Cochin, AP—HP, Paris, France*
[g] *Department of digestive and endocrine surgery, Saint-Louis hospital AP—HP, university Paris Diderot Sorbonne Paris Cite, Paris, France*
[h] *HPB surgery, Hopital Beaujon, AP—HP, university Paris VII, Clichy, France*
[i] *Versailles university, Boulogne-Billancourt, France*
[j] *Hôpital Saint-Antoine, 75012 Paris, France*

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* Corresponding author at: Department of hepatogastroenterology and gastrointestinal oncology, Sorbonne Paris CIté, Paris Descartes University, UMR, 1141, Georges-Pompidou European Hospital, 20, rue Leblanc, 75015 Paris, France.
E-mail address: jtaieb75@gmail.com (J. Taieb).

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[k] *CH de longjumeau, France*
[l] *AP—HP, Sorbonne Université, groupe hospitalier Pitié-Salpêtrère (AP—HP), Sorbonne Université, 75013 Paris, France*
[m] *Saint André Hospital, 1, rue Jean-Burguet, 33000 Bordeaux, France*
[n] *Institut des maladies de l'appareil digestif, gastrointestinal oncology unit, university hospital, 1, place Alexis-Ricordeau, 44093 Nantes Cedex 1, France*
[o] *Service d'hépato-gastro-entérologie, groupe hospitalier Pitié Salpêtrière, 75013 Paris, France*
[p] *Department of digestive and hepatobiliary surgery, Pitié-Salpêtrière hospital, Sorbonne University, UPMC University, 75013, Paris, France*

Summary
Introduction: Following publication of improved patients' outcome using first line FOLFIRINOX for metastatic pancreatic adenocarcinoma, many physicians now prescribe it as neo-adjuvant or induction treatment for borderline and locally advanced pancreatic cancer. A pathologic complete response, rarely seen with previous preoperative regimens, is sometimes observed in these patients. The aim of this study was to assess long-term outcomes of patients presenting pathologic complete response after preoperative FOLFIRINOX usually followed by chemo-radiation therapy for non-metastatic pancreatic adenocarcinoma.
Material and methods: We retrospectively identified all resected patients with pancreatic cancer presenting pathologic complete response after FOLFIRINOX in 9 French centers from the AGEO group between November 2010 and May 2017.
Results: 29 patients were enrolled, 14 had borderline, 14 locally advanced and 1 oligo-metastatic pancreatic cancer. M/F ratio was 1.2 and the mean age was 57 years. All patients were treated with FOLFIRINOX ($n = 29$), de-escalated to gemcitabine ($n = 1$) and FOLFIRI ($n = 2$), and 24 (83 %) received radiation therapy after chemotherapy. Objective response rate to preoperative chemotherapy was 66% (RECIST V1.1). Only 8 patients received postoperative chemotherapy. After a median follow-up of 34 months from surgery, the median overall survival was not reached and the median disease free survival was 48 months. The 1-year and 2-year survival rates were 100% for OS and 96% and 72 % for DFS from surgery, 8 of the 9 observed recurrences were distant metastases.
Conclusions: The promising 1 and 2-year overall survival and disease free survival rates suggest that pathologic complete response is a major prognostic factor in resected pancreatic cancer following preoperative chemo-radiotherapy. A longer follow-up and prospective series are now necessary to confirm these encouraging results and to potentially validate pathologic complete response as a relevant surrogate marker of preoperative treatment efficacy.

Introduction

Recently, the natural history of metastatic pancreatic adenocarcinoma has changed after the introduction of FOLFIRINOX in our therapeutic armamentarium [1,2]. This new chemotherapeutical regimen allowed remarkable response rates and median overall survival reaching 12 months. This finding leads to largely adopt this triplet-chemotherapy in the setting of borderline and locally advanced pancreatic adenocarcinoma [3]. The main goal of this upfront aggressive therapy is to convert not easily or non-operable pancreatic adenocarcinoma to R0 surgery. In resected specimen pathologic complete response (pCR), rarely seen with previous preoperative regimens, has been observed in many centers. The pathologic complete response is defined as the complete eradication of cancer cells on the surgically resected material after chemotherapy ± radiation therapy.

Preoperative chemotherapy has been adopted in many gastro-intestinal cancers including esophageal, gastric and liver metastases from colorectal origin [4—7]. It offers numerous advantages including better tolerability and doses intensity than postoperative treatments, in vivo testing of drugs' efficacy and an evaluation of the pathologic response rate that recently led in other settings to an accelerated approval of drugs by the FDA [8]. Several studies have shown that patients who achieved pCR after preoperative treatment have generally a improved long-term outcome [4—7].

Consequently, increasing the rate of pCR became the endpoint of some neo-adjuvant trials, mainly in breast cancer with the expectation of translation into improved overall survival [9]. However pCR surrogacy remains controversial and pCR have been shown not to be a relevant surrogate marker of disease recurrence or long-term survival in other cancers such as rectal cancer [10,11].

Data evaluating pCR in pancreatic adenocarcinoma after preoperative chemotherapy remain very scarce, based only on retrospective studies [12]. The aim of this study was to assess long-term outcomes in patients achieving a pCR after preoperative FOLFIRINOX for an initially borderline or locally advanced pancreatic adenocarcinoma.

Material and methods

Study design and patients

This is an observational and retrospective study. All consecutive patients with PC presenting pCR after a FOLFIRINOX induction therapy in 9 French centers from the AGEO group between November 2010 and May 2017 were retrospectively included.

The FOLFIRINOX regimen was as follow oxaliplatin 85 mg/m^2, irinotecan of 180 mg/m^2 and standard 5-FU dose which is bolus 400 mg/m^2 infusion of 2,400 mg/m^2 over a 46-hours infusion every 2 weeks. The radiation therapy regimen varied according to the centers.

Borderline pancreatic cancer is defined as a tumor with abutment, encasement, or occlusion of superior mesenteric vein or portal vein, abutment of superior mesenteric artery (SMA) < 180°, and abutment or short segment encasement of common hepatic artery. Locally advanced pancreatic cancer is defined as a tumor with >180° abutment or encasement of the SMA, long segment common hepatic artery abutment, and encasement of the celiac axis as well as a nonreconstructible portal vein/superior mesenteric vein [13].

Data collection

Baseline demographic tumor characteristics and staging (borderline, locally advanced or oligo-metastatic), treatments (pre and postoperative, adjuvant), outcomes of administered treatments (response rate, disease-free survival and overall survival) and the characteristics of disease recurrence (location of relapses, number of sites involved) were retrieved from the database and the pathology reports of the different centers involved in the study.

Statistical analysis

The disease-free survival (DFS) and overall survival (OS) were the two main outcomes evaluated in this study. Mean (standard deviation, SD) values and proportions (percentage) were provided for the description of continuous and categorical variables, respectively. Means and proportions were compared using Student's *t*-test and chi^2-test (or Fisher's exact test, if appropriate), respectively. Disease-free survival was defined as the time elapsed from the surgery until disease recurrence or death (all causes), whichever occurred first. Overall survival (OS) was defined as the time elapsed from the date of the surgery until death (all causes). Surviving patients were censored at the last follow-up date. Survival curves were estimated using the Kaplan–Meier method. Median follow-up and the 95% CI were calculated with the reverse Kaplan–Meier method. *P*-value inferior to 0.05 was considered as statistically significant. Statistical analyses were made with RStudio software.

Table 1 Patients and tumor characteristics.

Characteristic	*n* = 29
Age-year: mean [range]	57.3 [35; 78]
Male sex — *n* (%)	16 (55.2)
Tumor (mm): mean [range]	34.6 [20; 70]
Extension of the disease — *n* (%)	
Borderline	14(48.3)
Locally advanced	14(48.3)
Oligo-metastatic	1(3.4)
Preoperative treatment	
Chemotherapy — *n* (%)	
FOLFIRINOX	29(100)
De-escalation to gemcitabine	1(3.4)
De-escalation to FOLFIRI	2(6.9)
Number of cycles of chemotherapy mean [range]	6.68 [4–16]
Radiation therapy	24(82.8)
Radiation therapy alone	2 (7%)
Chemo-radiotherapy	22 (75.9%)
Surgery	
Distal pancreatectomy	3 (10.3%)
Pancreaticoduodenectomy	26 (89.6%)
Number of resected lymph nodes mean [range]	19.75 [8–48]
Adjuvant chemotherapy — *n* (%)	8 (29.6%)
Type of adjuvant chemotherapy	
Gemcitabine	4 (50%)
FOLFIRI	2 (25%)
FOLFOX	1 (12.5%)
GEMOX	1 (12.5%)

Results

Patient characteristics and previous treatment

Twenty-nine patients were enrolled, 16 of them were men and the median age was 58 years. Fourteen had borderline, 14 locally advanced as defined by the International Hepato-Pancreatico-Biliary Association (IHPBA) [14] and 1 oligo-metastatic pancreatic cancer (one solitary liver metastasis); the median tumor size was 31.5 mm (27–40). Baseline characteristics are summarized in Table 1.

All patients (*n* = 29) were treated with preoperative FOLFIRINOX, de-escalated to gemcitabine (poor hematological tolerance, *n* = 1) and FOLFIRI (cumulative sensory neuropathy, *n* = 2). The mean number of cycles of preoperative FOLFIRINOX chemotherapy was 6.7 cycles (4-16). The only patient with oligo-metastatic pancreatic adenocarcinoma had undergone first a resection of the liver

Table 2 Patient's outcomes.

Outcome	
RECIST response to neo-adjuvant chemotherapy — *n* (%)	
Complete response	2(6.9)
Partial response	17(58.6)
Stable disease	8(27.6)
Not evaluated	2(6.9)
Median OS (m)	NR
Median DFS (m)	48 (31-NR)
1-year OS (%)	100%
2-year OS (%)	100%
1-year-DFS (%) from surgery	96%
2-year-DFS (%) from surgery	72%

OS: overall survival; DFS: disease free survival; m: month.

metastasis by surgery, then received chemotherapy followed by radiation therapy. Twenty-four (83%) patients received additional radiation therapy after chemotherapy, combined with capecitabine in 22 cases.

Three (10%) patients had a distal pancreatectomy and 26 (90%) had a pancreaticoduodenectomy. By definition, all resection were R0, and the mean number of resected lymph nodes was 19.75 (8-48).

Eight (29.6%) patients received postoperative chemotherapy; 4 of them were treated with gemcitabine as single agent, 2 with FOLFIRI, 1 with FOLFOX and 1 with the GEMOX combination therapy.

Treatment outcomes

According to CT Scan evaluation, response to pre-operative chemotherapy (RECIST V1.1), was as follows: complete response (CR) 6.9%, partial response (PR), 58.6%, stable disease (SD) 27.6% and 6.9% were not evaluable using RECIST criteria. After a median follow-up of 34 months (12.5—41.7) from surgery the median overall survival (OS) was not reached. Median disease free survival was 48 (31-NR) months. The 1-year and 2-year OS rates were 100%. The 1-year and 2-year DFS rates were respectively 96%(88-100%) and and 72% (55—94%). All the results are summarized in the Table 2.

No difference was found in DFS or in OS when comparing the 8 patients that did receive postoperative chemotherapy to those who did not (Fig. 1). The patient with oligometastatic pancreatic adenocarcinoma did not receive any adjuvant treatment and did not present any relapse after 14 months of follow-up.

Recurrence

Nine (31%) out of 29 patients relapsed. Only 1 patient presented a local recurrence and 8 developed distant metastases, none in the liver. Sites of recurrence are summarized in Table 3. The median time from surgery to recurrence was 17 (10.7—33.2) months and the median time from chemotherapy to recurrence was 24 months (17—39).

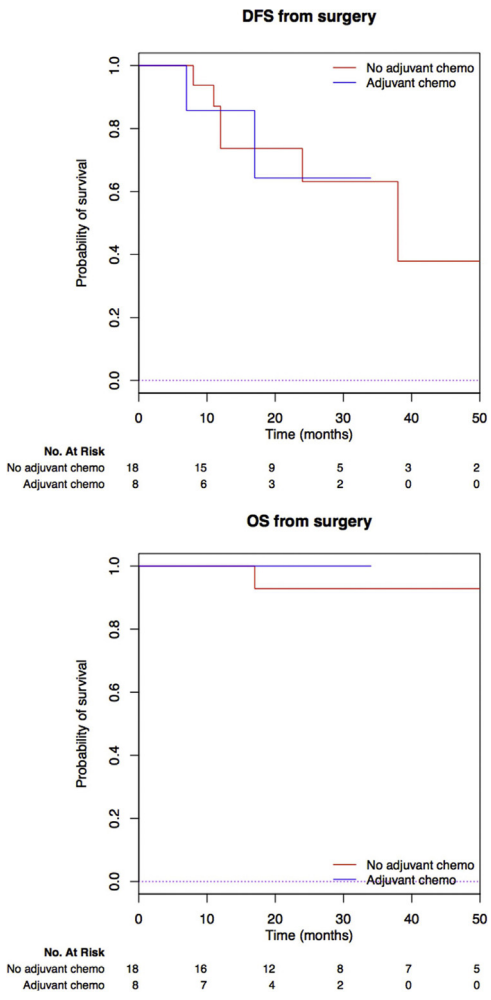

Figure 1 DFS and OS in patients with pancreatic adenocarcinoma from surgery, in patients who received adjuvant chemotherapy and who did not receive.

Table 3 Relapses characteristics.

Number of relapse — *n* (%)	9 (31%)
Distant relapse	8
Lung	4
Peritoneum and brain	1
Bladder	1
Lymph nodes	1
Peritoneum and local	1
Local relapse only	1

Discussion

The current work is, to our knowledge, the largest series ever reported on patients achieving pCR after an aggressive preoperative chemotherapy regimen followed by radiation therapy, based on the data of 9 French centers from the AGEO group. Furthermore, we examined in this specific population the roles of preoperative closure radiochemotherapy and adjuvant chemotherapy.

Before the FOLFIRINOX era, only few case-series of pathologic complete response were reported in pancreatic adenocarcinoma following preoperative chemotherapy [15,16]. The percentage of pCR ranged between 2 and 4% according to the different case-series reported in the literature. Only two case-series reported more than 10 cases of pCR [17,18]. A case-series from MD Anderson (database from 1995 to 2010) reported 11 cases of pathologic complete response in pancreatic cancer after neo-adjuvant older chemotherapeutic regimens [15]. In this work, 5 patients received systemic chemotherapy with gemcitabine and cisplatin followed by gemcitabine-based chemoradiation, 3 patients received gemcitabine-based chemoradiation protocol and the remaining 3 patients received 5-fluorouracil-based chemoradiation. A second case-series from the same institution (database from 1990 to 2015) reported a pCR in 3.9% (23 patients) of 583 patients with preoperative chemotherapy or chemoradiation therapy with a median OS of 81 months [16].

Few case reports and one case-series from our group described this rare entity after treatment by FOLFIRINOX [13,19—22]. Our case-series showed pCR in 15% of patients after receiving pre-operative FOLFIRINOX followed by radiation therapy, however no further data on survival was reported on this subgroup with pCR in this article [13]. Another study from John Hopkins showed pCR in 10% (19 patients) of 177 patients with borderline or locally advanced pancreatic cancer following chemoradiation therapy, 58% of them having received FOLFIRINOX as chemotherapy. This study concluded that patients who had a pCR after neoadjuvant chemoradiation had a significantly prolonged survival (60 months) compared with those who had near complete response or a limited response [22].

Both borderline or locally advanced pancreatic cancer at diagnosis could present pCR after preoperative treatment; their distribution in our cohort was equal and their survivals were similar. This reflects the fact that patients presenting either locally advanced or borderline pancreatic cancer may both benefit from an intensive treatment, aiming to achieve complete pathologic response. It is noteworthy to mention that there is discordance between the radiologic and the pathologic responses observved in our study. Thus, some patients presenting a partial radiologic response presented a pathologic complete response. Consequently, surgery must be performed when feasible to assess pathological response in the absence of metastatic disease in pancreatic adenocarcinoma.

Our study showed better prognosis in patients presenting pCR after induction chemotherapy in pancreatic cancer as previously described by others [15,16,18]. Moreover, the percentage of patients presenting a pCR after FOLFIRINOX +/- chemoradiotherapy seems to be higher than before with gemcitabine based regimens +/- chemoradiotherapy. It is noteworthy to mention that a recent meta-analysis demonstrated that preoperative FOLFIRINOX was associated with improved survival in locally advance PC [23]. These results should be confirmed by prospective trials such as the ongoing NEOPAN PRODIGE trial (NCT02539537).

Interestingly, the wide majority (> 80%) of patients presenting pCR in our cohort received closure radiochemotherapy after FOLFIRINOX and before surgery. Another characteristic of our population is the absence of metastatic recurrence in the liver, which can be explained by different molecular landscape and reflected by better prognosis.

This study presents many limitations going from the retrospective assessment of the patients to the limited number of subjects (29 patients). Moreover, treatment heterogeneity with 3 patients experiencing treatment de-escalation, 8 patients only receiving adjuvant therapy and a large range concerning the number of preoperative chemotherapy cycles (4 to 16), are also important limitations. The absence of standardized preoperative FOLFIRINOX ± radiation therapy, the absence of data concerning radiation therapy regimens, the detailed surgical resection (vessel resection or not) and the lack of a centralized reviewing of CT-Scan before and after FOLFIRINOX ± radiation therapy are other limitations of this study.

Altogether, despite these limits, we found that patients with pancreatic adenocarcinoma presenting pCR after induction FOLFIRINOX+/- radiation therapy seem to have very good survival outcomes. These results have now to be confirmed in prospective series or randomized trials to validate pCR as a relevant surrogate marker of patients' survival.

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