Outcomes of Patients with Initially Locally Advanced Pancreatic Adenocarcinoma who did not Benefit from Resection: A Prospective Cohort Study

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Abstract

Background: There is no consensus about the optimal treatment for patients with unresectable non-metastatic locally advanced pancreatic adenocarcinoma (LAPA) after induction chemotherapy. Accordingly, the current study aimed to evaluate the outcomes of patients with LAPA who did not benefit from resection considering the treatment strategy. **Methods:** Between 2010 and 2017, 234 patients underwent induction chemotherapy for non-metastatic LAPA that could not be treated with surgery. After oncologic restaging, continuous chemotherapy or chemoradiation (CRT) was decided for patients without metastatic disease. The Kaplan-Meier method was used to determine overall survival (OS), and the Wilcoxon test to compare survival curves. Multivariate analysis was performed using the stepwise logistic regression method. **Results:** FOLFIRINOX was the most common induction regimen (168 patients, 72%), with a median of 6 chemotherapy cycles and resulted in higher OS, compared to gemcitabine (19 vs. 16 months, $P = .03$); however, no difference was observed after adjusting for age (≤ 75 years) and performance status score (0–1). At restaging, 187 patients (80%) had non-metastatic disease: CRT was administered to 126 patients (67%) while chemotherapy was continued in 61 (33%). Patients who received CRT had comparable characteristics to those who continued with chemotherapy, with similar OS; they also had longer recurrence-free survival (median 13.3 vs. 9.6 months, $P < .01$) and contrastingly, more frequently metastatic disease (hazard ratio=2.9, $P < .01$). **Conclusions:** The median survival of patients who could not undergo surgery was 19 months. Hence, CRT should not be eliminated as a treatment option and may be useful as a part of optimized sequential chemotherapy to treat both local and metastatic disease.

Background

Patients diagnosed with non-metastatic locally advanced pancreatic adenocarcinoma (LAPA; comprising both borderline and unresectable tumours) at the time of initial staging receive induction chemotherapy. During the last decade, pancreatic surgeons have been able to perform complex resection/reconstructions in patients with LAPA owing to the benefits of the FOLFIRINOX regimen, which seems to increase the number of patients who finally underwent resection(1). We recently showed that patients with LAPA strongly benefit from resection after induction chemotherapy, even if complex venous resection/reconstruction is needed(2,3). However, most patients who received induction chemotherapy will not have the opportunity to undergo resection because of progressive disease at restaging, altered performance status, or contraindications during explorative laparotomy (i.e. affirmation of extra pancreatic disease or major vasculature invasion). In these patients, chemotherapy and chemoradiation (CRT) are the two commonly used treatments administered by oncologists, in combination with new drugs in the setting of prospective trials. To date, no consensual strategies have been defined in patients who cannot benefit from surgery. Patients with extra-pancreatic disease dissemination at restaging or after laparotomy continue with chemotherapy. However, there is no strong evidence about which treatment is optimal for patients with non-metastatic LAPA. Consequently, multidisciplinary physicians

have to choose between continuing with chemotherapy (if well tolerated) or CRT according to induction chemotherapy tolerance, patient status, and centre/oncologists preferences.

This study aimed to evaluate the outcomes, according to the treatment, in patients with LAPA who did not benefit from resection after induction chemotherapy.

Methods

Patient selection

Between January 1, 2010 and December 31, 2017, 342 patients were diagnosed with LAPA (according to the National Comprehensive Cancer Network guidelines(4)), and received induction chemotherapy at the Institut Paoli-Calmettes, Marseille, France. Among these patients, 234 could not benefit from resection and were included in the study; 108 patients underwent pancreatectomy and their outcomes will be separately reported. Patient data were prospectively entered into a clinical database, as approved by the Institutional Review Board and analysed retrospectively. The study participants provided informed consent, and the study protocol adhered to the tenets of the Declaration of Helsinki.

Initial staging and induction chemotherapy

All patients had histologically proven pancreatic adenocarcinoma before any treatment. Initial staging consisted of a physical examination, thoraco-abdominal computed tomography (CT), and CA 19-9 serum level determination. Until 2015, patients did not undergo routine liver magnetic resonance imaging (MRI); positron emission tomography (PET) was not performed routinely owing to the lack of evidence of its relevance in this setting. The chemotherapy regimen (i.e. FOLFIRINOX or gemcitabine) was selected according to the patients' age, performance status (PS) score, and decision of the multidisciplinary staff. The FOLFIRINOX regimen comprised a combination of oxaliplatin (85 mg/m²), irinotecan (180 mg/m²), leucovorin, and 5-fluorouracil (bolus and continuous infusion); the cycle was repeated every 2 weeks. If required, the administration of a 5-fluorouracil bolus was stopped and oxaliplatin/irinotecan doses were reduced. The gemcitabine regimen comprised a dose of 1000 mg/m² that was delivered weekly for 3 weeks over subsequent 4-week courses. One cycle corresponded to a 4-week period of treatment. Primary or secondary prophylaxis of neutropenia was initiated using the granulocyte colony-stimulating factor at the physician's discretion.

Treatment after restaging

All patients were restaged after 3 months of induction chemotherapy to identify patients with severe adverse events and/or disease progression, which helped determine whether patients should continue with the same regimen. After restaging, three strategies were debated among explorative laparotomy,

continuous chemotherapy with or without drug switching, or CRT. CRT comprised intensity-modulated fractionated radiotherapy combined with concurrent chemotherapy, with capecitabine (800 mg/m² twice daily, 5 days/week); the total dose of radiotherapy was 54 Gy in 30 fractions/6 weeks. The decision between CRT and continuous chemotherapy with or without drug switching in patients without evidence of extra-pancreatic disease was associated with the time at which the patients were included. Between 2010 and 2015, our strategy was to perform CRT after induction treatment for local treatment in patients without extrapancreatic extension and as part of reserve chemotherapy in case of metastatic progression; however, since 2016, according to the results of the LAP07 randomized trial(5), continuing with chemotherapy was the preferred strategy, with at least 8 cycles of chemotherapy being delivered along with a regimen change if the induction treatment was not well tolerated. The surgical decision for explorative laparotomy was made by the multidisciplinary staff. Resection was not performed in the following cases: a) metastatic spread discovered during explorative laparotomy (i.e., liver metastasis, carcinomatosis, and para-aortic lymph node invasion proven on frozen section(6,7)); b) superior mesenteric artery resection was needed; and c) venous reconstruction was not technically feasible.

Study parameters

The following variables were evaluated: age, sex, body mass index (BMI), CA 19-9 serum level (at diagnosis and after jaundice resolution), PS score (0, 1, 2, or 3), weight loss >5%, recent diabetes diagnosis (<1 year), tumour location (i.e. head, body, and tail), back pain, jaundice, arterial invasion at diagnosis, borderline or locally advanced tumours, induction regimen, and continuing with treatment after restaging. The Response Evaluation Criteria in Solid Tumours were not used in our series.

Statistical analysis

Data analyses were performed using GraphPad Prism software, version 6 (GraphPad Software Inc., La Jolla, CA, USA) and SPSS® version 24 (SPSS Inc., Chicago, IL, USA). Categorical factors were compared using the Fisher's exact test or chi-squared test, and continuous variables using the Student's t-test. The associations between the categorical factors and overall survival (OS) were assessed using the Kaplan-Meier method (based on the date of diagnosis and censoring date, January 1, 2019); in patients with rapid disease progression and early risk of death, we compared the survival curves using the Wilcoxon test. Multivariate analysis was performed using stepwise logistic regression. Statistical significance was set at $P < .05$.

Result

Induction treatment, restaging, and strategy after restaging

The patient characteristics are summarized in Table 1. FOLFIRINOX was the most commonly used induction regimen (168 patients, 72%), with a median number of 6 cycles of chemotherapy. Patients who received FOLFIRINOX were younger ($P<.01$) and had a better PS score ($P<.01$) compared to patients who received gemcitabine (Table 2). At restaging, 187 patients (80%) had non-metastatic LAPA whereas 47 (20%) showed metastatic disease progression. In patients with non-metastatic LAPA, 126 patients (67%) received CRT whereas 61 (33%) continued with chemotherapy. Metastatic disease progression was significantly more frequent among patients who received CRT (90 patients, 71%) than in those who continued with chemotherapy (26 patients, 43%; $P<.01$), with a comparable mean delay (12 vs. 10 months; $P=ns$).

Survival

No patient was lost to follow-up (mean follow-up, 31 months). During the study period, 70% of patients ($n=163$) had metastatic progression, with the liver being the more frequent site of metastasis (88 patients, 54%) followed by carcinomatosis (45 patients, 28%). The median survival time of all patients was 18.7 months; the 1-, 3-, and 5-year OS were 80%, 7%, and 1%, respectively. At diagnosis, degraded PS, weight loss, and CA 19-9 level >500 U/mL were independent factors that poorly influenced OS (Table 3). At least 8 cycles of chemotherapy provide the optimal OS (19,6 vs. 18,4 months) without reaching the significance ($p=0,36$). On comparing induction chemotherapy regimens, FOLFIRINOX resulted in a higher OS than gemcitabine did (19 vs. 16 months, $P=.03$; Figure 1a); however, no difference was observed after adjusting for age (≤ 75 years) and PS score (0-1) (Figure 1b). At restaging, patients with non-metastatic disease ($n=187$) who received CRT or continued with chemotherapy had similar patient and tumour characteristics as well as CA 19-9 levels. Although patients who received CRT showed longer recurrence-free survival (median 13.3 vs. 9.6 months, $P<.01$; Figure 2a), they had metastatic disease more frequently (hazard ratio=2.9, 95% confidence interval [1.5–5.4] $P<.01$) and a trend of prolonged OS (median 20 vs. 18 months, $p=0.07$; Figure 2b) compared to those who continued with chemotherapy.

Discussions

The current study showed that the clinical status at diagnosis strongly influenced OS rather than the chemotherapy regimen itself, and that at restaging, patients without metastatic disease benefit from receiving CRT.

Patient characteristics and clinical status

Pancreatic adenocarcinoma often influences the patient's clinical status with weight loss and poor PS score. Our previous study recently showed the importance of these factors in patients with LAPA(8), and

our results indicated that nutrition and supportive care might help patients receive an optimal therapeutic strategy (i.e. induction treatment and resection). However, this finding needs to be further evaluated, as the patients' recovery course was not as desired considering that a poor clinical status might indicate aggressive tumour biology that cannot be treated with medical support.

At diagnosis, the CA 19-9 serum level and clinical status (PS score and weight loss) were independent factors of poor OS. A high initial CA 19-9 may indicate metastatic disease, with a reduced OS of 12 months(9). Instead of using the CA 19-9 level at diagnosis, the changes in the CA 19-9 level owing to induction chemotherapy might be a useful tool to decide between continuing with chemotherapy (indicated by an increased or still high CA 19-9 serum level) or CRT (indicated by a decrease in the CA 19-9 serum level)(10). Similarly, the neutrophil-to-lymphocyte ratio(11) and liquid biopsies(12–14), by evaluating circulating tumour cells or circulating tumour DNA, might be helpful to decide between local or systemic treatment at restaging in patients with no evidence of metastatic disease.

Induction treatment

CRT as induction treatment for patients with LAPA was changed to chemotherapy, because CRT could not be consistently used as a local treatment in a large proportion of patients with unknown metastatic disease(15,16). Thus, gemcitabine was the preferred induction treatment for patients with LAPA until 2010(17), which was the landmark treatment in the FOLFIRINOX era(18). Therefore, the current study focused on patients included in this later period, as we wanted to obtain a clear picture of the patient outcomes in the modern era. As FOLFIRINOX resulted in more patients being able to undergo resection(1), it also provided a survival advantage over the former gemcitabine regimen in our study. However, patients who received gemcitabine induction chemotherapy were older or had a weaker clinical status compared to patients who received the FOLFIRINOX regimen. Moreover, after adjusting for these factors, there was no survival advantage in patients who received the FOLFIRINOX regimen, possibly indicating that the clinical status was more important than the treatment regimen.

Continuing with chemotherapy or CRT at restaging

Data on the therapeutic strategies and their impact on survival are scarce in patients with unresectable LAPA. In the current study, patients who received CRT at restaging more often developed metastasis, reinforcing the concept that pancreatic cancer is a micrometastatic disease(5,16). Our findings are consistent with those of the LAP07 randomized trial that failed to demonstrate any benefit of CRT in patients with LAPA(5). Considering these points and the related adverse events, it remains unclear if CRT should not be performed for patients with LAPA who did not undergo resection.

Nevertheless, we should not be hasty to conclude that CRT is not beneficial, owing to many reasons. First, all cases of pancreatic adenocarcinoma show the expression of different genes(19). Thus, some patients

had a particular tumour biology that confers radiosensitivity. Accordingly, we adopted early neoadjuvant CRT for patients with resectable pancreatic cancer, but we abandoned this strategy owing to disappointing results on considering all treated patients.(20) However, we observed that some resected specimens had a complete histologic response, indicating radiosensitivity.(21,22) Second, in the current study, patients who received CRT had a prolonged recurrence-free survival time and a trend of prolonged OS. This indicates that CRT provided true local control(23), consistent with the loco-regional recurrence rate of 30% reported previously(10,19). This does not result in a significant OS improvement, as the micrometastatic part of the disease was probably insufficiently treated. Indeed, patients often receive only 4 to 6 cycles of induction chemotherapy before CRT, which therefore needs to be optimized. Third, continuing with chemotherapy results in a rapid increase in the incidence of adverse events, requiring dose reduction or chemotherapy interruption. Thus, CRT might be a therapeutic sequence that provides a systemic break in an occasionally prolonged therapeutic strategy.

Perspectives in patients with non-metastatic LAPA at restaging

In contrast to the treatment methods available for breast or colorectal cancers, oncologists who treat pancreatic cancer do not have many treatment options at disposal; accordingly, it is not sensible to exclude CRT as an option for patients with unresectable but non-metastatic LAPA at restaging. Therefore, we must focus on restaging to propose the appropriate treatment for each patient, which should include CT, liver MRI(24), explorative laparoscopy (with para-aortic lymph node picking if technically feasible), and CA 19-9 serum level measurements. After restaging, patients with no evidence of metastatic disease should have a discussion with multidisciplinary staff considering the following four aspects. First, physicians should consider the tumour evolution after induction treatment, as it makes sense to continue with chemotherapy in patients with an objective response. In this setting, ¹⁸F-fluorodeoxyglucose PET(25–27) imaging seemed to be helpful, but the utility has to be validated in large prospective cohorts. Second, the tolerance to induction chemotherapy should be kept in mind, as severe adverse events would require chemotherapy switching or interruption. Third, the number of cycles achieved: our results showed that patients might benefit from at least 8 cycles of chemotherapy before CRT, similar to the results of other studies(10). Finally, the level of CA 19-9 should be considered for the switch to CRT, as the current study showed that a CA 19-9 level >500 U/L was an independent predictive factor of survival, indicating persistent tumour activity. Thus, alternating between chemotherapy and CRT might help in treating both local and metastatic disease.

Study limitations

The present study has some limitations. Owing to the retrospective nature of the study, radiologic assessment of the objective response to induction treatment was not precisely noted. In addition, at the time of restaging, non-metastatic disease was affirmed by using mainly CT and eventually explorative

laparotomy. Indeed, any patients diagnosed with non-metastatic disease who received CRT probably had an unknown metastatic disease that negatively influenced the OS. Moreover, we did not take into account the toxicity of chemotherapy and objective measures of the quality of life. Nevertheless, the recent period of patient inclusion, the large sample size, and the homogeneity of the studied population are strengths that compensate for these limitations.

Conclusion

CRT resulted in better disease-free survival and a trend of improved OS over continued chemotherapy for patients with LAPA without any metastasis at restaging who did not benefit from surgery. Thus, CRT should not be completely discarded as a treatment option, as it might be useful when integrated as part of optimized sequential treatment to treat both local and metastatic disease. A low CA 19-9 level, a minimum of 8 cycles of chemotherapy, and controlled disease are factors that can indicate the switch to CRT.

List Of Abbreviations

BMI, body mass index

CRT, chemoradiation

CT, computed tomography

LAPA, locally advanced pancreatic adenocarcinoma

MRI, magnetic resonance imaging

OS, overall survival

PET, positron emission tomography

PS, performance status

Declarations

Ethics approval and consent to participate/for publication : The study participants provided informed consent, and the study protocol adhered to the tenets of the Declaration of Helsinki

Availability of data and materials : Patient data were prospectively entered into a clinical database, as approved by the Institutional Review Board and analysed retrospectively

Competing interests : The authors declare that they have no competing interests

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Tables

Table 1: Characteristics of patients with LAPA treated with induction chemotherapy (N=234)

Sex ratio (M/F)	2 (121/103)	
Mean age (range)	67 (29-89)	
Performance status* (%)		
	0-1	215 (92)
	2-3	19 (8)
Mean BMI* (range)	24 (14-42)	
Weight loss > 5%* (%)	160 (68)	
Diabetes (%)	15 (36)	
Back pain* (%)	152 (65)	
Jaundice (%)	136 (84)**	
CA 19-9 serum level* (UI) (range)	2292 (7-88300)	
Tumour location (%)		
	Head	161 (69)
	Body	57 (24)
	Tail	16 (7)
Tumour classification (%)		
	Borderline	158 (68)
	Locally advanced	76 (32)
Arterial invasion* (%)	93 (40)	
Induction regimen (%)		
	FOLFIRINOX	168 (72)
	Gemcitabine	66 (28)
Mean number of cycles before restaging (range)	6 (4-8)	
Explorative laparotomy (%)	45 (19)	
Treatment after restaging/laparotomy (%)		

FOLFIRINOX	78 (33)
Gemcitabine	30 (12)
Chemoradiation	126 (54)

LAPA: locally advanced pancreatic adenocarcinoma; BMI: body mass index

* at diagnosis; **calculated for patients with head LAPA

Table 2: Characteristics of patients with LAPA at initial staging and according to the delivered induction regimen (N=234)

	FOLFIRINOX (n=168)	Gemcitabine (n=66)	P-value
Mean age ($\pm$ SD)	64 ($\pm$ 9.55)	75 ($\pm$ 8.76)	<0.01
Performance status score 2-3 (%)	8 (5)	11 (17)	<0.01
Mean BMI ($\pm$ SD)	23.5 ($\pm$ 3.81)	23.5 ($\pm$ 4.41)	ns
Weight loss > 5%* (%)	110 (65)	50 (76)	ns
Diabetes (%)	10 (6)	5 (7.5)	ns
Back pain (%)	108 (64)	44 (67)	ns
CA 19-9 serum level* (UI) ($\pm$ SD)	3884 ($\pm$ 13137)	1743 ($\pm$ 4916)	ns
Tumour location (%)			ns
Head	117 (70)	44 (65)	
Body	40 (24)	17 (26)	
Tail	11 (6)	5 (9)	
Tumour classification (%)			ns
Borderline	116 (69)	42 (64)	
Locally advanced	52 (31)	24 (36)	
Arterial invasion (%)	68 (40.5)	25 (38)	ns

LAPA: locally advanced pancreatic adenocarcinoma; BMI: body mass index

Table 3: Univariate and multivariate analyses of factors influencing overall survival at diagnosis (N=234)

	<i>P</i> -value	Hazard Ratio	<i>P</i> -value
Performance status score ≥ 2	<0.01	1.92 [1.06; 3.46]	0.031
Borderline status at diagnosis	0.35		ns
Arterial invasion at diagnosis	0.48		ns
Back pain	0.041		ns
Weight loss	0.037	1.49 [1.02; 2.19]	0.041
CA 19-9 >500	0.087	1.79 [1.25; 2.57]	<0.01
Continuous chemotherapy	0.065		ns

Figures

Figure 1.

Figure 1

Overall survival of patients with LAPA who received FOLFIRINOX or gemcitabine as induction chemotherapy: a) overall survival of all patients, and b) overall survival of patients aged ≤ 75 years and performance status (PS) score of 0-1. LAPA, locally advanced pancreatic adenocarcinoma

Figure 2.

Figure 2

Survival of patients with non-metastatic LAPA at restaging (n=187) who received CRT or continued chemotherapy. LAPA, locally advanced pancreatic adenocarcinoma; CRT, chemoradiation