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FOLFIRINOX-based neoadjuvant chemoradiotherapy for borderline and locally advanced pancreatic cancer: A pilot study from a tertiary centre

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ABSTRACT

Background: Neoadjuvant chemoradiotherapy, potentially relevant to increase resection rate in pancreatic cancer, is still debated.
Aims: To assess tolerance, resection rate and outcomes of patients with non-metastatic pancreatic ductal adenocarcinoma treated by concomitant chemoradiotherapy.
Methods: This monocentric study included all consecutive patients treated from 2010 to 2014 for non-metastatic pancreatic adenocarcinoma. Chemotherapy was followed by chemoradiotherapy in operable patients, surgical resectability being assessed by CT-scan.
Results: Seventy-nine patients were included: 41 patients had borderline and 38 locally advanced tumours. All patients were treated by chemotherapy (FOLFIRINOX), followed by chemoradiotherapy (median dose: 59 Gy, range 45–66 Gy) for 94% of patients. Thirty-seven patients (47%) could subsequently benefit from surgery with a complete R0 resection in 94% of cases, with a postoperative mortality of 5%. Median overall survival was 21.5 months (median follow-up: 48.8 months). Local control, overall and disease-free survival were significantly higher for patients who underwent resection compared to others, with 89.2% vs 59.5% ($p = 0.01$), 49.7 vs 17.4 months ($p < 0.01$) and 25.5 vs 9.2 months ($p < 0.01$), respectively.
Conclusion: Neoadjuvant treatment consisting of FOLFIRINOX chemotherapy followed by chemoradiotherapy is an efficient strategy for patients with borderline and locally advanced pancreatic cancer, resulting in a 43% rate of secondary complete surgical resection associated with high local control, overall and disease-free survival.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is associated with a poor prognosis since 5-year global survival rate is around 5% [1]. About 30–40% of patients have a locoregional non-metastatic disease at time of diagnosis, i.e. either resectable or unresectable tumours. Given that surgery with clear resection margins (i.e. R0 resection) is the only curative option [2], the question of resectability has been widely discussed in order to define criteria that could guide the treatment strategy. In 2017, the National Comprehensive Cancer Network (NCCN) updated their classification distinguishing locoregional disease in resectable cancers, borderline potentially resectable (BR) and unresectable locally advanced (LA) PDAC based on venous and/or arterial invasion status [3]. On the one hand, unresectable LA PDAC is treated by induction chemotherapy, possibly followed by chemoradiotherapy, resulting in secondary resection in about 20% of cases [4]. On the other hand, upfront surgery of BR

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cancers is associated with a high rate of microscopically incomplete resection (i.e. R1 resection) [5]. Therefore, for patients with BR or LA PDAC, there is a strong rationale for neoadjuvant therapy with the aim of converting unresectable tumours to resectable for LA PDACs and increasing the rate of R0 resections for BR cancers. Gillen's meta-analysis (111 studies, 4394 patients) showed that neoadjuvant chemoradiotherapy resulted in a secondary resection rate of 33.2% for LA initially unresectable cancers [4]. During the past couple of decades, the strategy in our institution was to treat LA PDAC by neoadjuvant chemotherapy followed by exclusive chemoradiotherapy but with systematic assessment by CT-scan at the end of treatment. Good responders were then considered for surgery. More recently, this regimen has been extended to BR tumours as a neoadjuvant strategy because of their high rate of R1 resections [7].

The aim of the study was to assess the secondary resection rate and the overall and disease-free survival of patients with BR or LA PDAC treated by concomitant chemoradiotherapy in a prospective observational cohort.

2. Methods and materials

This retrospective intent to treat analysis of a monocentric prospective observational cohort included all consecutive patients treated by FOLFIRINOX chemotherapy, followed by chemoradiotherapy or not, from January 2010 to December 2014 for BR and LA PDAC. The treatment strategy for every patient was decided on clinical data and CT-scan images by a multidisciplinary team (MDT: at least one oncologist, surgeon, radiologist, gastroenterologist and pathologist).The study was approved by the institutional review board and the need for written informed consent was waived.

2.1. Initial staging

All tumours were cytologically or histologically proven by echoendoscopic ultrasound-guided fine needle aspiration. Tumours were classified by the multidisciplinary team as LA or BR on CT-scan images, 1.25 mm slices, with arterial and portal contrast infusion. Knowing that the classification between LA and BR tumours could be a major bias in our analysis, all baseline CT-scans were reviewed retrospectively by a senior radiologist, and tumours reclassified with strict accordance to NCCN classification v2-2017 [3]. Post chemoradiotherapy staging was assessed by CT-scan and a liver MRI was done only in the case of suspicion of liver metastasis.

2.2. Treatment

The treatment strategy consisted of first-line chemotherapy followed, in the absence of progression, by conformational chemoradiotherapy. Chemotherapy consisted of 4–6 cycles of the FOLFIRINOX regimen (oxaliplatin, irinotecan, 5FU-folinic acid) as first choice [8]. Radiotherapy was a 3D conformal irradiation to the tumour volume, up to 59.4 Gy in 33 fractions over 6.5 weeks. Chemotherapy associated with radiotherapy consisted of a FOLFOX regimen (oxaliplatin, 5FU-folinic acid) as first choice, capecitabine (1600 mg/m^2 five days a week) or gemcitabine (600 mg/m^2/week) in the case of FOLFOX contra-indication. Reassessment was carried out by the multidisciplinary team at the end of first-line chemotherapy and 4–6 weeks after the end of chemoradiotherapy. This reassessment was based on clinical signs and performance status, CA 19-9 levels and CT-scan evaluation in order to decide on surgical resection or not. Surgery was indicated in the case of tumour response or stability, performance status 0 or 1 and decrease of vascular abutment, or even, in the case of persistent vascular abutment images if limited to less than 180° encasement. Adjuvant chemotherapy (gemcitabine) was proposed on MDT decision alone in the case of poor pathological features (R1 resection or major nodal involvement) and carried out depending on the patient's performance status.

2.3. Surgical procedures and pathological protocol

For resectable tumours, a classic Whipple procedure was carried out with an 'artery first' approach to determine resectability [9], with resection of the distal stomach without pylorus preservation, including removal of all lymph nodes as recommended by the International Study Group on Pancreatic Surgery (ISGPS) group [10]. For the left side pancreatic cancer, a radical antegrade modular pancreatosplenectomy was performed. If persistent vascular abutment to the portal vein was found, a wedge or segmental resection was included in the procedure, and the venous segment was clearly identified. For segmental resection shorter than 3 cm end to end, anastomosis without graft was performed. In the case of segmental resection longer than 3 cm a peritoneal graft was used. The surgeon carried out inking of the circumferential margins before sending on to the pathologist in order to assist subsequent localization of the portal vein, the superior mesenteric vein groove, the superior mesenteric artery and the posterior margins [11]. A macroscopic pathological procedure then followed a standardized protocol by serial slicing of the pancreatic head in a single axial plane, perpendicular to the longitudinal axis of the duodenum, to obtain slices covering the tumour and its ranges up to the inked margins [5]. R0 resection was defined as margin strictly superior to 0 mm. R1 resection presented tumour cells on the inked margin. Surgical morbidity was defined as significant surgical postoperative complications of Grade III, IV or V, as classified by Dindo et al. [12]. Grade III includes complications that required surgical, endoscopic or radiological intervention, with or without general anaesthesia. Grade IV includes life-threatening complications that require management in an intensive care unit. Grade V complications cause postoperative death.

2.4. Statistics

The assessed end points were acute toxicity, post-operative mortality and morbidity occurring within 30 days post-surgery, subsequent surgery rate (R0 or R1), local control rate, overall survival (OS) and progression free survival (PFS). The Kaplan–Meier method was used to estimate OS which was calculated from the date of diagnosis to the date of death or last follow-up. PFS was calculated from the date of diagnosis to the date of progression or the last follow-up.

Univariate and multivariate analyses of survival were done using a log-rank test and a stepwise Cox proportional hazards model, respectively. Univariate and multivariate analyses of the relationship between treatment factors (venous or arterial abutment, tumour size, CA19.9 level at initial staging, age, gender, tumour classification (LA vs BR)) and surgery were done using Chi-2 test or Fisher's exact and Whitney U test or parametric Student's test for qualitative and quantitative variables respectively. The results were considered significant when p-value < 0.05. Statistical analysis was carried out with R software, version 3.2.4. Analysis of the data was carried out in January 2016 so that a minimum 18 months follow-up was possible for all patients.

3. Results

3.1. Patients

Between 2010 and 2014, 79 patients (43 men, 36 women), with a median age of 60 years (range 35–76) were included (Table 1).

Table 1
Patients and tumor characteristics at initial staging.

Patient characteristics	N	%
Age		
<65	50	63.3
≥65	29	36.7
Gender		
Male	43	58.9
Female	36	45.5
Initial OMS status		
0	24	30.4
1	48	60.8
2	7	8.9
Initial CA 19-9(Ui/ml) (median/range)	175	0.9–11927
Tumor characteristics		
Borderline	41	51.9
Arterial contact	22	53.7[a]
Venous contact	40	97.6[a]
Locally advanced	38	48.1
Arterial contact	37	97.4[b]
Venous contact	32	84.2[b]

[a] Percentage among patients with borderline tumors.
[b] Percentage among patients with locally advanced tumors.

According to the NCCN v2-2017 classification, 41 and 38 patients respectively had baseline BR and LA unresectable tumours (Table 1).

3.2. Neoadjuvant treatment

All patients were treated by chemotherapy consisting of FOLFIRINOX (median number of cycles: 5 [1–13], resulting in Grade 3–4 toxicity for 4 patients (Grade 3 toxicities were asthenia, diarrhea and vomiting, whereas Grade 4 was a neutropenic infection). Chemotherapy was followed by chemoradiotherapy (3D conformational, median dose: 59 Gy, range 45–66 Gy) for 74 patients (94%). Ten patients were referred for radiotherapy to hospitals near their domicile, resulting in different total doses delivered. Four patients had metastatic disease and one presented local progression at the CT-scan assessment after chemotherapy and therefore did not have subsequent chemoradiotherapy. Radiotherapy was systematically associated with chemotherapy with FOLFOX regimen for 63 patients (85.1%), gemcitabine for 2 patients (2.7%), capecitabine for 6 patients (8.1%) and oxaliplatin for 1 patient. Chemoradiotherapy was well tolerated in 72 patients (97.3%) with a toxicity score inferior or equal to Grade 2. Oxaliplatin was stopped in one patient because of Grade 3 neuropathy. Three patients did not receive the entire treatment of chemoradiotherapy: two patients due to progression (peritoneum involvement revealed by ascites and small bowel occlusive syndrome) and one because of Grade 3 asthenia. In one patient, the CT-scan revealed liver metastases but also an aspect of duodenal perforation without any clinical symptom 8 weeks after the end of chemoradiotherapy.

3.3. Surgical resection

Among all patients, 37 (46.8%) underwent surgery (Whipple procedure : 30 patients, radical antegrade modular pancreatosplenectomy: 7 patients) with a complete R0 resection in 34 (94%). Regarding post-operative morbidity, 30 patients (81.1%) had a Dindo score of 1 or 2. Only five patients (13.5%) had a Dindo 3–4: two patients with post pancreatectomy haemorrhage Grade B and five patients with post operative pancreatic fistula Grade C [13,14]. Post-operative mortality was 5.4%. Two patients died within one month of surgery: one due to peritonitis and severe sepsis from post-operative fistula and the second due to haemorrhage.

Out of 74 patients who completed chemoradiotherapy, 13 were diagnosed with metastases and 16 with persistant vascular abutment at restaging by CT-scan. In addition, 7 patients had a surgical exploration but were not finally resected due to carcinomatosis [2], liver metastasis [1], nodal metastasis [1] or non resectable vascular contact [3]. Finally, 37 patients underwent surgical resection, 24 (58.5%) with BR tumours initially, and 13 (34.2%) with LA tumours initially (Fig. 1). Twenty-three of the 37 (62.2%) resected PDAC patients underwent a venous resection (portal vein and/or mesenteric vein); one of them also had a mesenteric artery resection and a hepatic artery reconstruction.

Four patients (11%) received adjuvant chemotherapy with gemcitabine. For 2 patients, adjuvant chemotherapy was indicated by the MDT but could not be delivered due to infection (1 patient) and acute renal failure (1 patient).

Table 2
Histological results according to the initial tumour classification.

Histological results	Borderline	Locally advanced
Surgical resection (N)	24 (1 no histology)	13
ypT0-T1	9	5
ypT2-T3-T4	14	8
ypN0	18	9
ypN1	5	4
ypM1	1 (node)	
R0	22	12
R1	1	1
ypT0N0R0	3	4

3.4. Pathological analysis

Among the patients operated, 34 (94.4%) had a R0 resection with 22 BR and 12 LA patients. Of note 28 patients (75.6%) had limits >1 mm (Table 2). Importantly, 13 patients had a complete or subcomplete response ypT0-T1N0 (9 patients were initially BR and 4 patients were initially LA). One LA patient had a ypT1N1R0.

3.5. Outcomes and survival

Median follow-up was 48.8 months (range: 18.6–68 months) for the entire population.

At the time of analysis, 56 patients had died: 27 (65.8%) among BR patients and 29 (76.3%) among LA patients. Among operated patients, 15 (40.5%) had no sign of recurrence, whereas 18 (48.6%) saw metastatic progression (Fig. 1). Noticeably, no local relapse, without metastasis, was evidenced in operated patients, and only 4 patients (10.8%) had local relapses, but with systematic metastatic disease. In the non-operated group, only 2 patients (4.7%) saw no progression. For 8 patients (19%) progression was local, for 23 (54.7%) it was metastatic and 9 (21.4%) had both (Fig. 1). The local control rate was significantly higher in the operated group with 89.2% as compared to 59.5% in the non-operated group ($p = 0.01$).

Median overall survival for the entire population was 21.5 months [CI 95%: 18–29 months].

Overall survival and progression-free survival were significantly different ($p < 0.01$) in favour of the operated group. The median OS was 49.7 months [CI 95%: 26.7-NR] for the operated group versus 17.4 months [CI 95%: 15.2–22.2] for the non-operated group (Fig. 2) and the median PFS was 25.5 months [CI 95%: 18.8-NR] for the operated group versus 9.2 months [CI 95%: 7.6–12.7] for the non-operated group. Complete or sub-complete response ypT0-T1N0 was associated with a significantly better overall survival compared to ypT2-4 or N1 (OR: 0.26 [CI 95%: 0.15−0.45]) (Fig. 3).

3.6. Prognostic factors

In univariate analysis, the only prognostic factor of OS and of PFS was surgical resection ($p < 0.001$). Other parameters were not significantly associated. Therefore no multivariate analysis

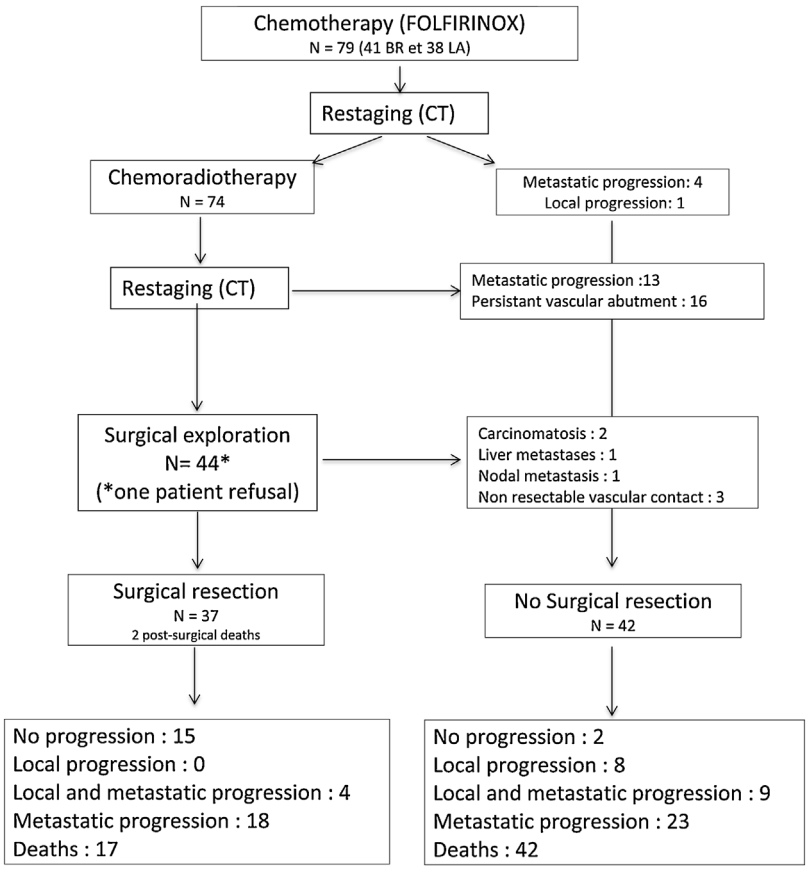

Fig. 1. Patients' outcome. PDAC: pancreatic ductal adenocarcinoma; LA: locally advanced; BR: borderline; CT: CT-scan.

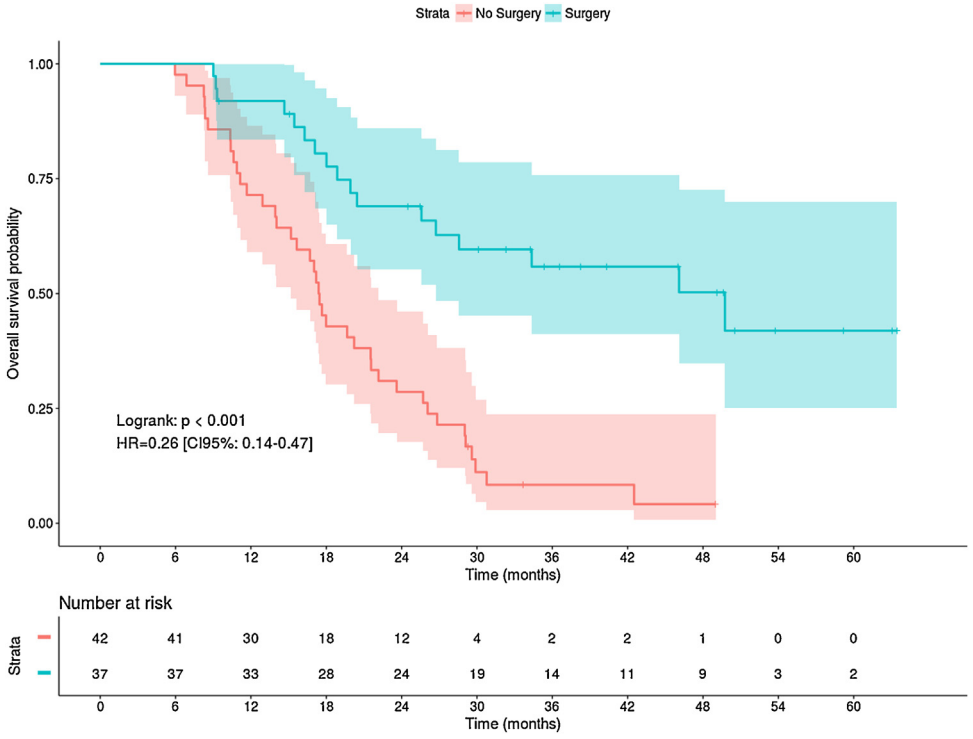

Fig. 2. Overall survival according to surgery.
Kaplan–Meier estimates of overall survival (OS) were significantly different ($p < 0.01$) in favour of operated versus non-operated patients. The median survival time was estimated to be 49.7 months [CI 95%:26.7-NR] in the operated group versus 17.4 months [CI 95%:15.2–22.2] in the non-operated group.

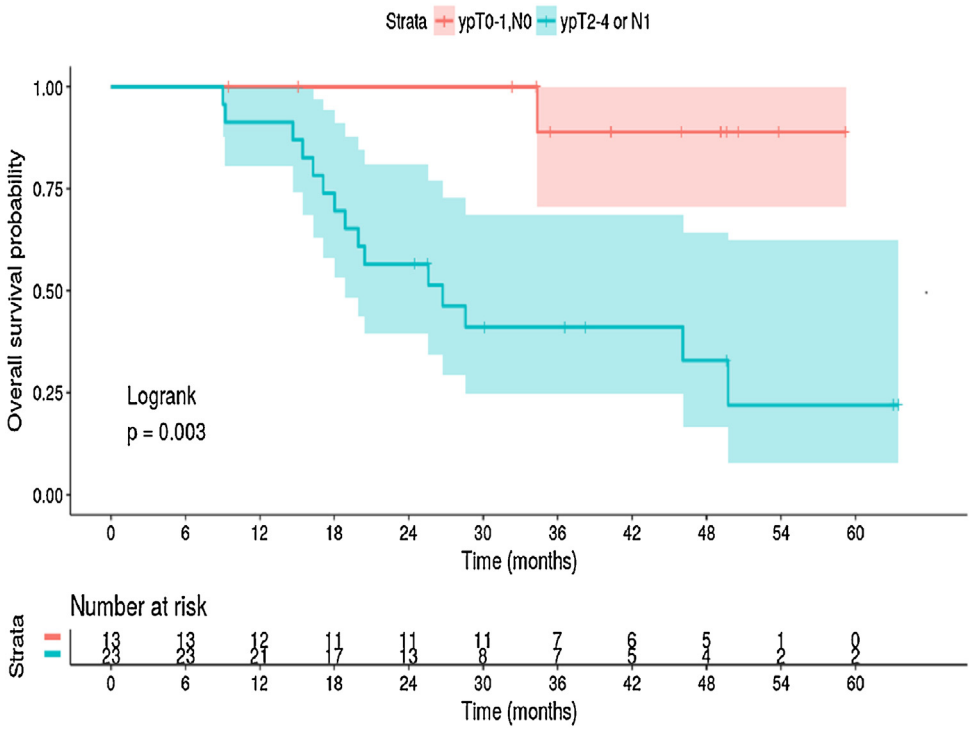

Fig. 3. Overall survival according to complete/sub-complete response.
Kaplan–Meier estimates of overall survival (OS) in months were significantly different in favour of patients with complete or sub-complete response. Median survival time was not reached for patients achieving ypT0-1, N0 versus 26.6 months for patients with ypT2-4 or N1 (OR: 0.26 [CI 95%: 0.15−0.45]).

was performed. Five main factors were significantly related to decreased probability of secondary surgery: abutment with the superior mesenteric artery and hepatic artery, arterial contact, initial classification as LA, and post-chemoradiotherapy CA 19-9 ≥ 20 U/mL. In the case of abutment with the superior mesenteric artery, only 34.9% of patients were operated versus 61.1% with no contact (p = 0.022, OR = 0.34 [0.14−0.85]). For hepatic artery abutment, this ratio was 28 versus 55.6% of patients (p = 0.026, OR = 0.31 [0.11−0.87]). Initial classification as BR was linked to increased probability of surgery (p = 0.032, OR = 2.71 [1.09–6.77]) compared with LA (Table 3). Finally 36.7% of patients with a post-chemoradiotherapy Ca19.9 ≥ 20 U/mL were operated versus 64.3% of patients with a CA 19-9 < 20 U/mL (p = 0.036, OR = 3.11 [1.06–9.09]).

4. Discussion

The aim of this retrospective study was to determine the tolerance, secondary resection rate and patient outcome after a neoadjuvant or induction strategy including FOLFIRINOX-based chemotherapy followed by chemoradiotherapy, for patients with BR or LA pancreatic cancers. R0 resection is associated with a better outcome [2,5]. We therefore hypothesized that neoadjuvant treatment could allow secondary resection in PDAC considered as locally advanced at baseline and increase the R0 resection rate in BR cancers. This was further supported by the fact that even if a tumour is considered as BR and can be resectable at the cost of venous resection, the risk of R1 resection remains major. Furthermore, even if R0 resections are achieved, venous resection has been identified as an unfavourable prognostic factor [15].

Firstly, we found that neoadjuvant treatment was well-tolerated with less than 3% of Grade 3–4 toxicity, and 90% of patients completing the treatment schedule. This is in agreement with the results of the AGEO cohort with FOLFIRINOX neoadjuvant chemotherapy [16]. Furthermore, post-operative mortality was 5%, similar to published results of upfront pancreatectomy [17], and in agreement with Liu's meta-analysis that found similar post-operative mortality rates between patients operated with or without neoadjuvant chemoradiotherapy in resectable patients [18]. Interestingly, some authors report even less frequent post-operative complications in patients operated after neoadjuvant chemoradiotherapy in particular regarding pancreatic fistula [19,20].

Secondly, we found that this neoadjuvant strategy achieved 47% of secondary resections with 94% R0 resections when R0 resection means >0 mm but 75.6% if R0 means ≥1 mm. These results are slightly comparable to the 69.5% (CI 62.1%–76.4%) rate of exploration with resection in 77.9% (CI 72.4%–82.9%) of cases published in the meta-analysis by Gillen et al. combining the results of 111 studies, including LA and BR patients [4]. However, our complete resection rate was higher than or in the range of previously published rates (72.4–85.2%) depending on R0 definition (>0 mm or ≥ 1 mm) [4,21,22]. Differences in the proportion of LA versus BR pancreatic cancers in the published studies might explain variations in resection rates. Interestingly, a secondary resection was possible for 34.2% of LA initially non resectable tumours, with 92.3% R0 resection, compared to 26% in the meta-analysis of Suker et al. which included 355 patients treated by induction FOLFIRINOX for LA PDAC. Of note, 63.5% of patients received chemoradiotherapy after induction chemotherapy. Our result is in agreement with the one third of secondary resection rate published in 3 different meta-analyses [4,22,23]. This carries strong clinical value, given the fact that chemoradiotherapy still remains controversial in this context. Indeed, chemoradiotherapy is considered as an option after neoadjuvant chemotherapy since it results in improved time without treatment compared to chemotherapy alone, but without improvement in survival [24]. Chemoradiotherapy may enable vascular abutments to be sterilized. Therefore, it is a strong therapeutic option from the point of view of converting non resectable tumours to resectability, or in increasing the rate of complete R0 resection, as shown in the AGEO study [25]. It might also play a role in iden-

Table 3
Parameters associated with resectability :OR (odds ratio), CI (confidence interval).

Parameters	Modality	N	%	OR	CI	P value
SMA contact						
	No Contact	36	61.1	–		
	Contact	43	34.9	0.34	0.14–0.85	**0.022**
Coeliac axis contact						
	No contact	60	51.7	–		
	Contact	19	31.6	0.43	0.14–1.29	0.132
Hepatic artery contact						
	No contact	54	55.6	–		
	Contact	25	28	0.31	0.11–0.87	**0.026**
Arterial contact						
	No contact	20	70	–		
	Contact	59	39	0.27	0.09–0.81	**0.02**
Retroportal infiltration						
	No	37	43.2	–		
	Yes	42	50	1.31	0.54–3.19	0.548
SMV contact						
	No contact	19	42.1	–		
	Contact	60	48.3	1.29	0.45–3.65	0.636
SMV stenosis						
	0	56	42.9	–		
	Inferior to 50%	7	85.7	8	0.9–70.93	0.062
	Superior to 50%	16	43.8	1.04	0.34–3.18	0.949
Venous contact						
	No contact	7	42.9	–		
	Contact	72	47.2	1.19	0.25–5.72	0.825
Classification						
	Locally advanced	38	34.2	–		
	Borderline	41	58.5	2.71	1.09–6.77	0.032
Pre-CRT Ca19.9 (Ui/ml)						
	<175	33	57.6	–		
	≥175	33	36.4	0.42	0.16–1.13	0.087
After CRT Ca 19.9 (Ui/ml)						
	≥20	30	36.7			
	<20	28	64.3	3.11	1.06–9.08	**0.036**
Age (years)						
	<65	50	46			
	≥65	29	48.3	1.1	0.44–2.74	0.845
Performance status (OMS)						
	0	48	41.7			
	1	24	41.7	2.33	0.85–6.38	0.099
	2	7	28.6	0.56	0.1–3.18	0.513
Tumor size (mm)						
	<35	37	56.8	–		
	≥35	39	35.9	0.43	0.17–1.07	0.07

Bold letters highlight significant results.

tifying patients with rapid progressive or metastatic disease, for whom frontline surgery would not be beneficial.

For BR tumours, our study found a 58.5% secondary resection rate, R0 in 95% of cases, consistent with published results, which however show great variability. Several reasons can explain the wide heterogeneity of published R0 resection rates [4,18–20].

Firstly, resectability criteria are still debated. Several definitions have been proposed for LAPC depending on the extent of vascular contact, such as the M.D.Anderson or the Callery consensus [26]. The main classification used is the NCCN classification which is, however, regularly updated, leading to potential retrospective differences in the distribution of patients among the groups (BR versus LA) [3]. Secondly, resection rates could also depend on the multidisciplinary decision at assessment after neoadjuvant treatment. Indeed, analysis of resectability after neoadjuvant treatment is even more challenging since post-treatment images are difficult to analyze. The ability to predict R0 resectability with a CT-scan was reduced in the case of neoadjuvant treatment (58% vs 83%, p = 0.039) mostly due to overestimation of tumour size and vascular contacts and a diffuse peripancreatic inflammation [26–28].

Biopsies by laparoscopy are recommended to rule out secondary site or persistence of vascular abutment. Thirdly, the sequential surgical strategy carried out in our institution could also influence the secondary resection rate. After the absence of carcinomatosis has been verified, biopsies of persistent arterial vascular abutment are carried out with extemporaneous histopathological analysis. Resection is continued only in the case of sterilization of biopsies, with venous resection if necessary [6] Fourthly, R0 resection is also dependent on a systematic and standardized histopathological analysis protocol. Resection specimen orientation and margin inking by the surgeon are critical. In addition, R0 rates vary among studies, between 77% if R0 means margins are over 0 mm, and 29% if R0 means margins are over 2 mm [5,29].

Prognostic factors associated with secondary resection were as already published, in particular arterial abutments with SMA, and were in agreement with definition of LA. Venous invasion, initial tumour size and initial CA19-9 were not associated with resectability [29,30]. However, a post-chemoradiotherapy Ca19.9 under 20 was associated with resectability.

Our survival results are in the range (13.7–24.2 months) found for LA PDAC treated with FOLFIRINOX regimen as a first line treatment [22]. Importantly, overall survival results were remarkably high in operated patients (49.7 [IC95%: 26.7-NR]). In addition, overall survival was significantly higher in patients with complete or sub-complete ypT0-T1N0M0 response (respectively NR versus 26.6 months, (OR: 0.26 [CI95%: 0.15−0.45])), which may be an argu-

ment for intensification of neoadjuvant treatment. Noticeably, the local control rate was high in patients treated by chemoradiotherapy and surgery with no local relapse, without metastasis and only 10.8% local relapses but with systematic metastatic disease, whereas frontline surgery is usually associated with 35–86% of local relapse [31–33], suggesting the high relevance of this strategy even for patients with initially resectable tumours.

Therefore we can not exclude a bias of selection of patients, leading to favourable results. Indeed, our recruitment was mainly done by the hepato-biliary and pancreatic surgery department, with patients referred for surgery from primary and secondary centres, explaining our high rate of BR patients (52%), which does not reflect the general recruitment in this pathology. However, this also proves the expertise of our centre, practicing >65 pancreatectomies per year, knowing that the annual caseload of pancreatectomy has been shown to be an independent predictor of mortality [17].

In addition, the decision for resectability could vary among physicians according to the time of decision, since classification has evolved during the timeline of the cohort treatment. To address this issue, we decided to carry out a central review of all patient CT-scan imaging according to the latest version of classification at the time of analysis, in order to make patient distribution consistant according to resectability criteria.

In conclusion, our data confirms that neoadjuvant treatment consisting of FOLFIRINOX chemotherapy followed by chemoradiotherapy is an efficient strategy for patients with BR and LA pancreatic cancers, resulting in a good rate of secondary complete surgical resection and pathological response. Furthermore, well-tolerated, this strategy results in high local control of the disease. Ongoing randomized prospective clinical trials are currently testing this therapeutic approach.

Conflict of interest statement

Dr. Blanc reports personal fees from Baxalta, outside the submitted work. No COI to disclose for the other authors.

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