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ORIGINAL ARTICLE – PANCREATIC TUMORS

# How Does Chemoradiotherapy Following Induction FOLFIRINOX Improve the Results in Resected Borderline or Locally Advanced Pancreatic Adenocarcinoma? An AGEO-FRENCH Multicentric Cohort

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## ABSTRACT

**Background.** Patients with borderline (BR) or locally advanced (LA) pancreatic adenocarcinoma (PAC) are often treated with induction FOLFIRINOX (FLX). However, the role of additional preoperative chemoradiotherapy (CRT) is controversial. The aim of this study is to evaluate its impact in patients who underwent resection after induction FLX.

**Patients and Methods.** Retrospective analysis of prospective consecutive surgical BR or LA PAC patients after induction FLX in 23 French centers between November 2010 and December 2015, treated with or without preoperative additional CRT (FLX vs FLX + CRT groups).

**Results.** Two hundred three patients were included (106 BR, 97 LA PAC). Median number of FLX cycles was 6 (range 1–30); 50% ($n$ = 102) of patients received

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additional CRT. Median duration between diagnosis and surgery was 5.4 and 8.7 months ($P = 0.001$) in the FLX and FLX + CRT group, respectively. The 90-day mortality, major complications, and pancreatic fistula rates were 4.4%, 17.7%, and 5.4%, respectively. After 45.1 months follow-up, overall survival (OS) and disease-free survival were 45.4 months and 16.2 months, respectively. Patients with additional CRT had higher R0 resection rate (89.2% vs 76.3%; $P = 0.017$), ypN0 rate (76.2% vs 48.5%; $P < 0.001$), and higher rate of pathologic major response (33.3% vs 12.9%; $P = 0.001$). In the FLX + CRT group, patients had lower rate of locoregional relapse (28.3% vs 50.7%; $P = 0.004$). Patients with additional CRT had longer OS than those receiving FLX alone (57.8 vs 35.5 months; $P = 0.007$).

**Conclusions.** Pathological results and survival data argue for interest in additional CRT. Prospective studies on an intention-to-treat basis are needed to confirm these results.

Surgery remains the cornerstone of treatment for patients with resectable PAC and the only curative approach. A subset of patients (approximately 30%) present vascular involvement prohibiting upfront resection, known as borderline resectable (BR) or locally advanced (LA) pancreatic cancers.[1,2] In these patients, gemcitabine—combined with radiotherapy—has been the standard treatment for decades, with low response rates and without clear improvement in survivals.[3]

The superiority of the FOLFIRINOX regimen (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) demonstrated in the phase III metastatic PAC setting led many centers to investigate FOLFIRINOX with or without chemoradiotherapy in patients with BR or LA tumor.[4–8] The role of radiation therapy in the management of non-resectable PAC remains controversial. Fluorouracil-based concomitant chemoradiotherapy was shown to be better than radiotherapy alone in the 1980s.[9] Later, the results of five randomized trials comparing chemoradiotherapy with chemotherapy of LA PAC patients were divergent.[10–14] Lately, the authors of the LAP07 trial reported that, among patients with LA PAC with disease controlled after 4 months of gemcitabine-based induction chemotherapy, there was no significant difference in OS with chemoradiotherapy compared with chemotherapy alone.[15]

We reported previously oncological and surgical outcomes after induction FOLFIRINOX, with 12% pathological complete response and 26% pathologic major response rates, and the prognostic value of these pathologic responses.[16] In a recent patient-level metaanalysis, Suker et al.[17] evaluated effectiveness of FOLFIRINOX as first-line treatment for patients with LA PAC. In that study, 63.5% of patients received chemoradiotherapy in the treatment sequence. However, nowadays, there is no evidence on its role and no results of randomized trials are available. The aim of this large multicentric study is therefore to investigate the impact of chemoradiotherapy after FOLFIRINOX induction therapy in patients who had secondary resection for BR or LA PAC.

## PATIENTS AND METHODS

### *Patients*

All consecutive patients with diagnosis of BR or LA PAC who underwent pancreatic resection following induction FOLFIRINOX with or without chemoradiotherapy between November 2010 and December 2015 were prospectively included in this multicentric (23 centers) observational French study and retrospectively analyzed. All patients had histologically or cytologically proven PAC. Because some patients were referred secondary to participating expert centers for surgery, it was not possible to evaluate the exact number of patients receiving induction FOLFIRINOX on an intention-to-treat basis.

The American Hepato-Pancreatico-Biliary Association consensus-based National Comprehensive Cancer Network (NCCN) guidelines were used to classify patients as having BR or LA tumor at diagnosis.[1]

### *Induction Treatment*

Patients received upfront chemotherapy according to the FOLFIRINOX regimen every 2 weeks as described before.[4,7] Data on dates of the first and last cycle, and the total number of cycles delivered were collected. The total number of cycles of FOLFIRINOX and the indication of additional chemoradiotherapy were determined for each patient, after multidisciplinary discussion in a tumor board and at the discretion of each participating center.

Radiation therapy delivered a median dose of 54 Gy in 30 daily fractions over 6 weeks. All patients first underwent a planning computed tomography (CT) scan. Target volume delineation and organ at risk constraints followed the American–French guidelines.[18] Recommended concurrent chemotherapy regimen included fluoropyrimidine (IV 5-fluorouracil or oral capecitabine). Radiological tumor response was evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria on CT scan. The results of the preoperative assessment and eligibility for potential curative therapeutic plan were discussed at a tumor board gathering medical and radiation oncologists, surgeons, and radiologists. Surgical exploration was proposed after induction sequence in case of clinical benefit (pain and weight), stabilization or decrease

of CA 19-9, and stabilization or response of the tumor at CT scan assessment.[19]

*Surgical Procedures*

All surgical procedures were carried out by conventional laparotomy. For tumors located in the pancreatic head, pancreaticoduodenectomy was performed (Whipple procedure). Partial or circular venous resection was performed when necessary according to perioperative findings. The pancreatic anastomosis was done by pancreaticogastric or pancreaticojejunal anastomosis. For body or tail tumors, caudal pancreatectomy with splenectomy was performed. Postoperative complications during 90 days after surgery were evaluated using the Clavien–Dindo classification.[20] Pancreatic fistula was graded according to the International Study Group on Pancreatic Fistula (ISGPF) recently updated definitions.[21]

*Histological Assessment*

In most centers, the superior mesenteric vein (SMV) groove and superior mesenteric artery (SMA) resection margins were anchored with multicolor inks.[22] The distance from tumor to the closest margin was microscopically assessed. Tumor differentiation according to the WHO classification, perinervous and vascular invasion, and node involvement were also analyzed. Curative resection (R0) was defined as lack of tumor tissue microscopically detectable at resection margins. R1 resection indicated microscopic residual tumor at ink (positive margins).[1,23] Pathological complete response (pCR) was defined as no evidence of cancer on resected specimen (ypT0N0 stage), and pathological major response (pMR) as ypT0-1N0 stage disease.

*Statistical Analysis*

Demographic, pre-, and perioperative characteristics of patients were compared by Chi squared or Fisher's exact test. Continuous data were analyzed by independent-samples *t* test. Statistical analyses were done for the entire population, according to NCCN classification (BR vs LA) and according to sequence of induction treatment [FOLFIRINOX alone (FLX) vs FOLFIRINOX + chemoradiotherapy (FLX + CRT)]. The cutoff date for analysis was 30 January 2018. Follow-up was calculated using reverse Kaplan–Meier method. Survival rates were calculated by Kaplan–Meier method.[24] The Cox proportional-hazards regression model was used to perform univariate analysis with 95% confidence interval (CI) in the whole population. Parameters with $P$ value $< 0.1$ were entered into a final multivariable Cox regression model, after considering collinearity among variables with a correlation matrix (Supplementary Methods). All statistical analyses were performed using SPSS software version 21.0 (SPSS Inc., Chicago, IL). $P$ value $\leq 0.05$ was considered as significant.

## RESULTS

*Study Population*

A total of 203 patients with BR ($n$ = 106; 52%) or LA ($n$ = 97; 48%) PAC were included (Table 1). Median age of patients was 61.7 years. Median largest basal tumor diameter was 31.5 mm (range 15–110 mm). CA 19-9 was available for 151 patients at diagnosis. Forty-five patients (29.8%) presented a normal biomarker, 106 (70.2%) had an abnormal one, and 77 (51%) a value greater than 150 UI/L.[25] Baseline characteristics of patients in the BR and LA groups were similar (Table 1).

*Induction Treatment*

One hundred one (50%) patients were treated with FOLFIRINOX alone, and 102 (50%) with additional chemoradiotherapy after induction FOLFIRINOX. The patients received a median of 6 cycles (range 1–30) of FOLFIRINOX. However, significantly more patients received more than six cycles of FOLFIRINOX in the LA group (31% vs 18%, $P$ = 0.023). Patients in the FLX + CRT group received a median dose of 54 Gy (range 45–59 Gy) of radiation therapy. Twenty patients (19.6%) included before 2013 were treated with three-dimensional conformal radiation therapy (3DCRT). All others ($n$ = 82) were treated with intensity-modulated radiation therapy (IMRT). Ninety-six patients received concurrent fluoropyrimidine-based chemotherapy at standard doses, and six had concurrent gemcitabine. The interval between end of CRT and surgery was 10.4 weeks (range 3.6–39.6 weeks). The interval between diagnosis and surgery was 7.4 months (range 3.0–20.8 months) for the entire cohort, but significantly longer in the FLX + CRT group (8.7 vs 5.4 months; $P$ = 0.001) (Table 2). Before surgery, all patients had normal level of CA 19-9 or a dramatic decrease compared with baseline (Supplementary Data 1).

*Surgical Outcomes*

Vascular resection was required in 88 patients (43.3%). Eight needed arterial resection [right hepatic artery $n$ = 6 (6.7%); celiac trunk $n$ = 2 (2.3%)]. For the whole population, the rate of major (grade III–V) Clavien–Dindo complications was 17.7% ($n$ = 36). Eleven patients (5.4%) had pancreatic fistula.[21] Length of hospital stay and the 90-day mortality rate were 15 days (1–73 days) and 4.4%

**TABLE 1** Demographics and clinicopathologic characteristics of study population

| Variable | Total $N = 203$ | BR $N = 106$ | LA $N = 97$ | $P$ | FLX $N = 101$ | FLX + CRT $N = 102$ | $P$ |
|---|---|---|---|---|---|---|---|
| Sex | | | | ns | | | 0.220 |
| Male | 119 (58.6%) | 62 (58.5%) | 57 (58.8%) | | 56 (55.4%) | 63 (61.8%) | |
| Female | 84 (41.4%) | 44 (41.5%) | 40 (40.2%) | | 45 (44.6%) | 39 (38.2%) | |
| Age (years) | 61.7 (28.3–78.9) | 61.8 (28.3–78.9) | 60.7 (35.3–78.8) | ns | 62.4 (28.3–78.9) | 60.0 (38.3–75.3) | 0.063 |
| BMI (kg/m$^2$) | 23.4 (14.5–38) | 23.2 (17.6–38) | 23.7 (14.5–35) | ns | 23.3 (17–38) | 23.7 (14.5–35.6) | ns |
| Tumor location | | | | **0.008** | | | 0.090 |
| Head and isthm | 167 (82.2%) | 95 (89.6%) | 72 (74.3%) | | 89 (88.1%) | 78 (76.4%) | |
| Body | 28 (13.8%) | 4 (9.4%) | 18 (18.5%) | | 9 (8.9%) | 19 (18.6%) | |
| Tail | 8 (4%) | 1 (1%) | 7 (7.2%) | | 3 (3%) | 5 (5%) | |
| Tumoral size[a] (mm) | 31.5 (15–110) | 31.5 (15–70) | 31.5 (15–110) | ns | 32 (10–86) | 31 (16–110) | ns |
| NCCN classification | | | | | | | 0.110 |
| Borderline | 106 (52.2%) | – | – | | 57 (56.4%) | 49 (48%) | |
| Locally advanced | 97 (47.8%) | – | – | | 44 (43.6%) | 53 (52%) | |
| CA 19-9[a] (UI/mL) ($N = 151$) | 152 (2–12,578) | 175.5 (2–12,450) | 134 (2–12,578) | 0.638 | 136.4 (2–12,450) | 208.3 (2–12,578) | 0.170 |

Bold value indicates statistical significance ($P < 0.05$)

*BR* borderline, *LA* locally advanced, *FLX* FOLFIRINOX, *CRT* chemoradiotherapy

[a]Median

**TABLE 2** Induction treatment strategies and oncological outcomes according to tumor stage at diagnosis and induction treatment sequence

| Variable | Total $N = 203$ | BR $N = 106$ | LA $N = 97$ | $P$ | FLX $N = 101$ | FLX + CRT $N = 102$ | $P$ |
|---|---|---|---|---|---|---|---|
| Number of FLX cycles[a] | 6 (1–30) | 5 (3–14) | 6 (1–30) | **0.020** | 6 (2–24) | 6 (1–30) | 0.850 |
| Number of cycles > 6 | 49 (24%) | 19 (17.9%) | 30 (30.9%) | **0.023** | 25 (24.7%) | 24 (23.5%) | 0.870 |
| Additional CRT | 102 (50%) | 49 (48%) | 53 (52%) | 0.110 | | | |
| Median dose[a] (Gy) | – | – | – | – | – | 54 (45–59) | – |
| Diagnosis to surgery[a] (months) | | 7.0 (3.0–18.9) | 7.67 (3.7–20.8) | 0.053 | 5.4 (3.0–16.6) | 8.7 (4.5–20.8) | **0.001** |
| Resection margins | | | | | | | |
| R0 | 169 (83.3%) | 85 (80.2%) | 84 (86.6%) | 0.261 | 78 (76.3%) | 91 (89.2%) | **0.017** |
| ypT stage | | | | **0.037** | | | **0.017** |
| T0 | 22 (10.8%) | 14 (13.2%) | 8 (8.2%) | | 5 (5%) | 17 (16.7%) | |
| T1 | 28 (13.7%) | 9 (8.5%) | 19 (19.6%) | | 10 (9.9%) | 18 (17.6%) | |
| T2 | 22 (10.8%) | 16 (15.1%) | 6 (6.2%) | | 14 (13.9%) | 8 (7.8%) | |
| T3 | 125 (61.5%) | 65 (61.3%) | 60 (61.2%) | | 68 (67.3%) | 57 (55.9%) | |
| T4 | 6 (3%) | 2 (1.9%) | 4 (4.1%) | | 4 (4%) | 2 (2%) | |
| ypN stage | | | | 0.667 | | | < **0.001** |
| N0 | 127 (62.6%) | 68 (64.2%) | 59 (60.8%) | | 49 (48.5%) | 78 (76.5%) | |
| N1 | 76 (37.4%) | 38 (35.8%) | 38 (39.2%) | | 52 (51.5%) | 24 (23.5%) | |
| ypTN stage | | | | 0.410 | | | **0.001** |
| T0-1N0 | 47 (23.2%) | 22 (20.8%) | 25 (25.8%) | | 13 (12.9%) | 34 (33.3%) | |
| T2-4Nx | 156 (76.8%) | 84 (79.2%) | 72 (74.2%) | | 88 (87.1%) | 68 (66.7%) | |
| Adjuvant chemo | 116 (57.1%) | 60 (56.6%) | 56 (57.7%) | 1.000 | 73 (72.2%) | 43 (42.1%) | **0.001** |

Bold values indicate statistical significance ($P < 0.05$)

*BR* borderline, *LA* locally advanced, *FLX* FOLFIRINOX, *CRT* chemoradiotherapy

[a]Median

($n = 9$) respectively. Postoperative outcomes were not different in the defined subgroups (Supplementary Data 2).

*Pathological Results*

R0 resection was achieved in 169 patients (83.3%). pCR occurred in 22 patients (10.8%) and pMR in 47 (23.2%) of the entire cohort. No difference was observed between BR and LA patients concerning tumor downstaging. R0 resection, ypN0 stage, and pMR were significantly higher in the FLX + CRT group (Table 2). In the FLX group, the number of FOLFIRINOX cycles ($\leq 6$ vs $> 6$) was not correlated with pathological results (R0, ypN0, pMR; data not shown).

*Adjuvant Treatment*

Adjuvant chemotherapy was completed in 116 patients (57.1%). Seventy-eight (67.2%) patients received gemcitabine, 27 (23.3%) received 5-fluorouracil (5-FU)-based treatment with additional oxaliplatin or irinotecan, and 11 (9.5%) received FOLFIRINOX as during induction period. Patients of the FLX group received more frequently adjuvant treatment than those in the FLX + CRT group [74 (73.2%) vs 42 (41.2%); $P = 0.002$].

*Survival*

Median follow-up was 45.1 months (95% CI 41.2–49.0 months) from diagnosis and 36.8 months (95% CI 34.0–39.6 months) after surgery. During follow-up, tumor relapse occurred in 130 patients (64%) and 96 (47.3%) of them died. In total, 105 deaths occurred.

In the FLX + CRT group, patients had lower rate of locoregional relapse than those in the FLX group (28% vs 51%; $P = 0.004$). The rate of distant metastasis was similar in the two groups (34% vs 42%; $P = 0.248$).

For the whole population, disease-free survival (DFS) was 16.2 months (95% CI 13.7–19.3 months), OS from diagnosis was 45.4 months (95% CI 37.9–52.7 months), and OS from surgery was 37.4 months (95% CI 28.9–45.9 months). Survival rates were not significantly different between the BR and LA groups. Patients with additional chemoradiation had significantly longer OS than those receiving FOLFIRINOX alone [57.8 months (95% CI 42.6–73.0 months) vs 35.5 months (95% CI 30.4–40.6 months); $P = 0.007$], and longer OS from surgery [47.9 months (95% CI 33.6–62.2 months) vs 30.5 months (95% CI 24.3–36.6 months); $P = 0.030$] (Fig. 1). However, there was no significant difference in DFS between the two groups [17.7 months (95% CI 9.9–25.5 months) vs 13.5 months (95% CI 9.7–17.3 months) in the FLX + CRT and FLX group, respectively; $P = 0.121$] (Fig. 2). Patients who received adjuvant treatment did not have longer OS compared with those who did not (data not shown).

*Prognostic Factors*

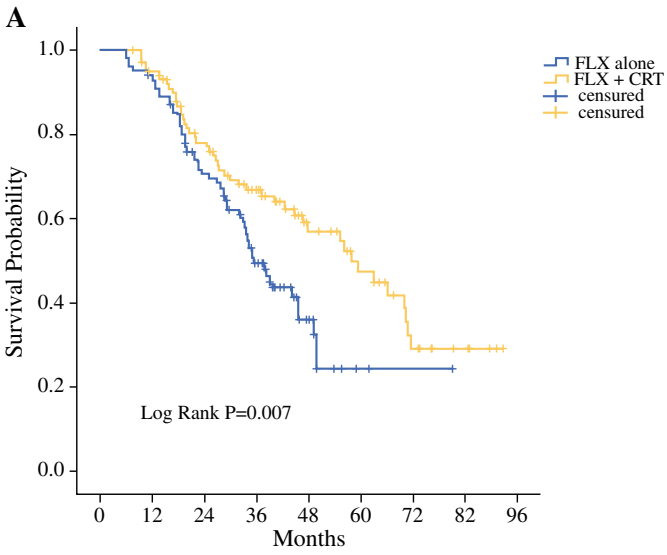
Lack of venous resection was the only factor independently associated with DFS [hazard ratio (HR) = 0.69; 95% CI 0.48–0.98; $P = 0.039$] (Table 3). Concerning OS from diagnosis, preoperative chemoradiotherapy ($P = 0.008$), lack of venous resection ($P = 0.024$), and R0 resection ($P = 0.013$) were prognostic factors. On multivariate analysis, preoperative chemoradiotherapy (HR = 0.61; $P = 0.018$) and lack of venous resection (HR = 0.67; $P = 0.048$) were independently associated with OS (Table 3).

## DISCUSSION

This study is, to the best of the authors' knowledge, the first large-scale report on the impact of chemoradiotherapy after induction FOLFIRINOX in secondary resected BR or LA PAC. This aggressive approach in selected patients allowed higher rates of tumor downstaging (ypN, pMR) and R0 resection, a decrease of local recurrence, and longer OS than a strategy with FOLFIRINOX alone, whatever the BR or LA initial tumor stage. Interest in chemoradiotherapy has been recently challenged by the absence of its benefit on OS in the LAP07 trial.[15] However, chemoradiotherapy was associated with longer progression-free survival and duration without treatment, and less locoregional progression, positioning this treatment not as a standard but a really interesting option in selected patients. Our results raise this interest and bring the first surgical and oncological elements to the discussion on this strategy in the "post-FOLFIRINOX era."

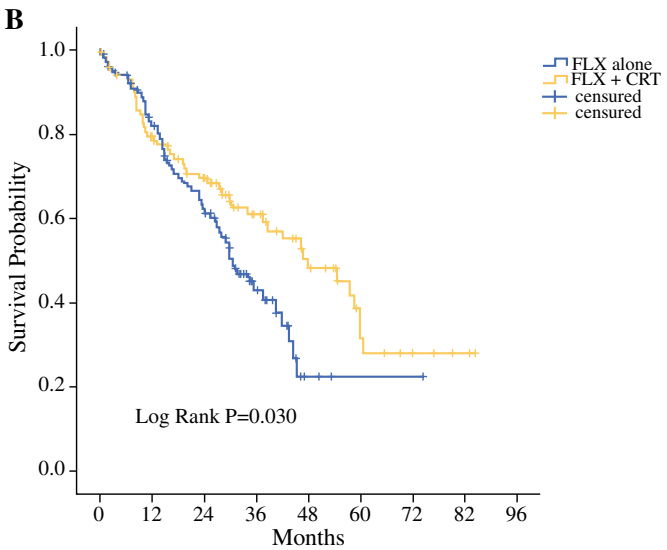
Several prior studies reported pathological response in patients who had secondary resection after induction FOLFIRINOX.[16,26–28] The definition of pathological response in PAC is not clear and differently assessed. Recently, He et al. reported a retrospective single-institution cohort study on pCR after induction treatment (multiple regimens) in 186 patients.[28] pCR was an independent prognostic factor of DFS. In our study, the pCR and pMR rates were 11% and 24%, respectively, and pMR was an independent prognostic factor, consistent with prior reported data. These data lend support to use of pathological response as an endpoint for future prospective trials.

Induction radiation therapy remains controversial in PAC despite some prospective randomized trials. Long-term outcomes in secondary resected patients after FOLFIRINOX induction with chemoradiotherapy were, to date,




Number of patients at risk

| | 0 mo | 6 mo | 12 mo | 18 mo | 24 mo | 30 mo | 36 mo | 42 mo | 48 mo |
|---|---|---|---|---|---|---|---|---|---|
| FLX | 101 | 100 | 93 | 82 | 65 | 53 | 32 | 17 | 7 |
| FLX+RCT | 102 | 100 | 92 | 81 | 70 | 57 | 47 | 36 | 20 |

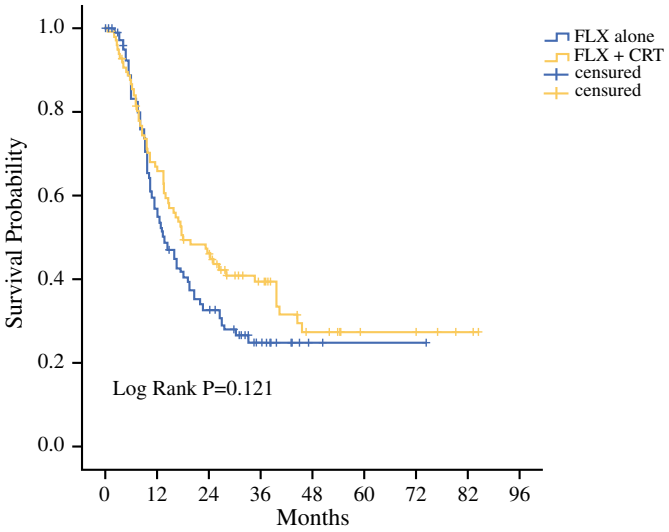



Number of patients at risk

| | 0 mo | 6 mo | 12 mo | 18 mo | 24 mo | 30 mo | 36 mo | 42 mo | 48 mo |
|---|---|---|---|---|---|---|---|---|---|
| FLX | 101 | 94 | 79 | 67 | 54 | 33 | 17 | 8 | 1 |
| FLX+RCT | 102 | 90 | 72 | 65 | 53 | 39 | 32 | 26 | 13 |

**FIG. 1** Survival curves according to induction treatment with or without additional chemoradiotherapy. Overall survival from diagnostic (**a**); overall survival from surgery (**b**)

difficult to assess due to the small number of patients in reported series and/or short-term follow-ups.[26,27] In this cohort, after median follow-up from diagnosis of 45.1 months, preoperative chemoradiotherapy was associated with increased tumor downstaging (ypT and ypN), R0 resection margins, and OS. Histological response after radiation therapy has been previously reported. Sadot et al.[27] reported a subgroup of 31 patients stratified by radiotherapy. In the radiotherapy group ($N$ = 16), patients had a higher N0 rate than those treated with FOLFIRINOX




Number of patients at risk

| | 0 mo | 6 mo | 12 mo | 18 mo | 24 mo | 30 mo | 36 mo | 42 mo | 48 mo |
|---|---|---|---|---|---|---|---|---|---|
| FLX | 98 | 80 | 50 | 37 | 28 | 18 | 9 | 4 | 1 |
| FLX+RCT | 100 | 80 | 59 | 49 | 36 | 26 | 22 | 15 | 6 |

**FIG. 2** Disease free survival curve according to induction treatment with or without additional chemoradiotherapy

**TABLE 3** Prognostic factors for disease-free and overall survival on univariate and multivariate analysis

| | *N* = 203 | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | Hazard ratio (95% CI) | *P* | Hazard ratio (95% CI) | *P* |
| Disease-free survival | | | | | |
| Gender (M vs F) | 119 | **0.70 (0.49–0.99)** | **0.044** | 0.73 (0.50–1.04) | 0.079 |
| Age ≥ 65 years | 66 | 0.77 (0.53–1.12) | 0.172 | | |
| BR versus LA | 97 | 1.07 (0.76–1.51) | 0.706 | | |
| ≤6 cycles of FOLFIRINOX | 154 | 0.78 (0.53–1.15) | 0.215 | | |
| Chemoradiotherapy | 102 | 0.71 (0.50–1.02) | 0.062 | 0.77 (0.53–1.04) | 0.154 |
| No venous resection | 119 | **0.60 (0.42–0.85)** | **0.005** | **0.60 (0.42–0.86)** | **0.005** |
| R0 resection | 169 | **0.56 (0.37–0.85)** | **0.006** | 0.66 (0.43–1.04) | 0.072 |
| ypT0-1N0 | 47 | **0.41 (0.26–0.66)** | **< 0.001** | Not considered[a] | |
| Adjuvant chemotherapy | 116 | 1.36 (0.95–1.98) | 0.094 | | |
| *Overall survival* | | | | | |
| Gender (M vs F) | 119 | 0.77 (0.52–1.12) | 0.176 | | |
| Age ≥ 65 years | 66 | 0.86 (0.57–1.31) | 0.491 | | |
| BR versus LA | 97 | 1.07 (0.73–1.57) | 0.726 | | |
| ≤6 cycles of FOLFIRINOX | 154 | 1.07 (0.69–1.67) | 0.767 | | |
| Chemoradiotherapy | 102 | **0.58 (0.39–0.87)** | **0.008** | **0.61 (0.41–0.92)** | **0.018** |
| No venous resection | 119 | **0.64 (0.43–0.94)** | **0.024** | **0.67 (0.45–0.99)** | **0.048** |
| R0 resection | 169 | **0.55 (0.35–0.88)** | **0.013** | 0.65 (0.41–1.05) | 0.079 |
| ypT0-1N0 | 47 | **0.32 (0.18–0.56)** | **< 0.001** | Not considered[a] | |
| Adjuvant chemotherapy | 116 | 1.13 (0.76–1.68) | 0.546 | | |

Bold values indicate statistical significance ($P < 0.05$)

*BR* Borderline, *LA* locally advanced

[a]A correlation matrix was used to detect statistically significant correlations between investigated parameters. When a correlation was identified, only the most clinically relevant variable was considered in the multivariable model (Supplementary Methods)

alone (80% vs 28%). In our cohort, we report comparable ypN downstaging (77%) in the FLX + CRT group, and pMR in 33% of them. In our study, secondary resection after additional chemoradiotherapy seemed to increase local control of the disease. Patients in the FLX + CRT group had a lower rate of locoregional relapse (28.3% vs 50.7%; $P = 0.004$). In the LAP-07 study, Hammel et al.[15] reported similar results with less locoregional progression in the chemoradiotherapy group (32% vs 46%).

One of the important results reported concerns the prognostic impact of preoperative chemoradiotherapy. Chemoradiotherapy was associated with a significant increase in OS from diagnosis or surgery, and a non-significant trend in DFS. Moreover, additional chemoradiotherapy seemed to be an independent prognostic factor of OS. According to the design of this study, the absence of randomization of chemoradiotherapy, and the impossibility of obtaining robust data on an intention-to-treat basis, these results must be considered with great caution. The duration of induction treatment was significantly longer in the FLX + CRT group, with a difference of more than 3 months compared with the FLX group. Thus, the differences observed between the two groups, for pathological data as for survival data, could be explained by the fact that CRT addition allowed better selection of patients with chemosensitive PAC in the FLX + CRT group. Only prospective trials with randomization of chemoradiotherapy and analysis on an intention-to-treat basis will be able to conclude definitively regarding its effect on pathological response and prognostic impact. In all cases, and despite these questions, addition of chemoradiotherapy seemed to allow better selection of patients for secondary resection compared with chemotherapy alone. Considering the mortality and morbidity rates of pancreatectomy, and the cost of such surgical resections, optimal selection of patients seems to be a real goal to develop and diffuse this treatment strategy.

## CONCLUSIONS

We assessed here for the first time the impact of additional preoperative chemoradiotherapy on BR or LA PAC after FOLFIRINOX induction in a large cohort of patients. The nonrandomized nature of this study clearly limits the level of evidence of its results. Initial staging, evaluation of tumor response, decision regarding chemoradiotherapy addition, and intent of secondary resection were defined independently by each center. Thus, patients included in this study were highly selected by each step of the induction strategy, in real-life conditions. Despite these limitations, our results argue for interest in chemoradiotherapy following FOLFIRINOX induction, potentially based on an increase in tumor downstaging and a survival benefit, but certainly for better patient selection.

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