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Impact and optimal timing of local therapy addition in borderline resectable or locally advanced pancreatic cancer after FOLFIRINOX chemotherapy

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ABSTRACT

Background: To evaluate the efficacy and optimal timing of local treatment in patients with borderline resectable (BR) or locally advanced pancreatic cancer (LAPC) treated with upfront FOLFIRINOX.

Method: Between 2015 and 2020, 258 patients with pancreatic ductal adenocarcinoma (PDAC) were analysed. Treatment outcomes were compared between systemic treatment group (ST) and multimodality treatment groups (MT) using Kaplan–Meier curves and log-rank test. The MT were stratified as follows: FOLFIRINOX + radiation therapy (RT) (MT1), FOLFIRINOX + surgical resection (MT2), and FOLFIRINOX + RT + surgical resection (MT3).

Results: With median follow-up period of 18 months, the 2-year overall survival (OS) for the ST was 22.0%, and it was significantly worse than MT (MT1, 46.3%; MT2, 65.7% and MT3; 90.2%; $P < .001$). The 2-year locoregional progression free survival (LRPFS) and overall PFS in ST were 10.7% and 7.0%, which were also significantly lower than those of MT (2-year LRPFS: MT1, 31.8%; MT2, 45.3%; MT3, 81.0%; 2-year overall PFS: MT1, 23.3%; MT2, 35.0%; MT3, 66.3%; $P < .001$). In time-varying multivariate Cox proportional hazard model, local treatment contributed to better treatment outcomes, with adjusted hazard ratios of 0.568 (95% confidence interval [CI], 0.398-0.811), 0.490 (95% CI, 0.331-0.726), and 0.656 (95% CI, 0.458–0.940) for OS, LRPFS, and overall PFS, respectively. The time window of 11–17 months after FOLFIRINOX appeared to demonstrate the maximal efficacy of local treatments in OS.

Conclusions: Adding local treatment in BR/LAPC patients treated with upfront FOLFIRINOX seemed to contribute in improved treatment outcomes, and it showed maximal efficacy in OS when applied 11-17 months after the initiation of FOLFIRINOX. We suggest that administration of sufficient period of upfront FOLFIRINOX may intensify the efficacy of local treatments, and well controlled prospective trials are expected.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer mortality worldwide [1]. In addition, its mortality rate has been increasing, and PDAC is anticipated to be the second leading cause of cancer-related death in 2030, only surpassed by lung cancer

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[2]. Nevertheless, unlike the remarkable improvement in treatment outcomes in tumours of other sites, that of PDAC remains poor, with a 5-year survival rate of less than 10%, which is not significantly different from that of 20 years ago [3].

Currently, the optimal treatment strategy for PDAC is decided upon depending on tumour resectability, and the prerequisite for long-term survival in PDAC is complete surgical resection. However, only 15% to 20% of PDACs are resectable at diagnosis [4]. Even in patients treated with curative resection followed by currently preferred adjuvant systemic therapies, more than half of these patients develop distant metastases [5]. Given this aggressive recurrence of PDAC, systemic chemotherapy can be considered as a primary treatment to suppress micrometastasis and to reduce the size of primary tumours so as to improve resectability not only in borderline resectable (BR) or locally advanced pancreatic cancer (LAPC) but also in cases technically determined to be resectable [6].

A modern combination of folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) has outperformed conventional gemcitabine and/or nab-paclitaxel-based regimens and is recommended as the first-line regimen in patients with BR or LAPC, despite its higher toxicity [7,8]. A multidisciplinary approach for BR or LAPC has been adopted as the new treatment paradigm, and surgical resection and/or radiation therapy (RT) after upfront FOLFIRINOX is recommended whenever possible. After neoadjuvant FOLFIRINOX administration, a considerable number of previously unresectable tumours are expected to become resectable, with surgical resection after upfront chemotherapy improving survival rates in patients with BR or LAPC [9,10]. The concept of total neoadjuvant treatment, which refers to induction chemotherapy followed by chemo-RT before surgical resection, has also been introduced for patients with BR or LAPC [11,12] to improve resectability, a margin-negative resectability rates, and downstaging [6]. Although the benefits of multimodal approaches in patients with BR or LAPC appear clear, optimal treatment schemes, especially regarding the timing of local treatment after upfront FOLFIRINOX administration, need to be investigated.

In this study, we aimed to demonstrate the efficacy of multimodal treatments in patients with BR or LAPC treated with upfront FOLFIRINOX. Furthermore, the optimal timing for maximise the effect of the local treatment was analysed in a retrospective setting.

Materials and methods

Patients

Between 2015 and 2020, 695 patients were diagnosed with PDAC, of whom 552 were treated with upfront FOLFIRINOX within 2 months of diagnosis at the XXXXXXX XXXXXXX XXXXXX. All cases of PDAC were pathologically confirmed using endoscopic biopsy. Patients with pathologic variants of exocrine or intraductal papillary mucinous neoplasm-associated carcinomas were excluded from the analysis. Tumour resectability in the present study was categorised according to the National Comprehensive Cancer Network (NCCN) guidelines, and only 'borderline' and 'locally advanced' tumours were analysed [13]. Patients with multiple primary malignancies, distant metastasis or seeding metastasis from PDAC were also excluded. The schematic flow of study population is presented in Fig. S1. This study was approved by the International Review Board of XXXXXXX XXXXXXX XXXXXX (IRB no. XXX 2022-05-139).

Pretreatment evaluation

Medical history was obtained and physical examination and laboratory tests were conducted for pre-treatment assessment. The level of carbohydrate antigen (CA) 19-9, a tumour marker, at the time of diagnosis was categorised into two groups: normal ($<$37 U/mL) and elevated ($\geq$37 U/mL). Baseline radiologic staging was performed for all patients using chest/abdominal computed tomography (CT) and abdominal magnetic resonance imaging (MRI), and tumour resectability was independently reviewed by certified radiologists.

Treatment

Four treatment strategies were used in this study, and the patients were categorised into groups accordingly: FOLFIRINOX only (systemic therapy [ST] alone group), FOLFIRINOX + RT (multimodal treatment [MT] group 1), FOLFIRINOX + surgical resection (MT group 2), and FOLFIRINOX + RT + surgical resection (MT group 3). One cycle of FOLFIRINOX was defined as 2 weeks per standard dose, however, a modified FOLFIRINOX dose with an extended administration cycle was also allowed, considering patients' disease status and comorbidities. After the initiation of FOLFIRINOX, surgeons evaluated the resectability of the PDAC. If the tumor was adjudged to be unresectable at that time, additional FOLFIRINOX was administered. The resectability was then reevaluated every 4∼8 cycles of additional chemotherapy. During this period, addition of RT was also discussed by a multidisciplinary team, considering the toxicity of FOLFIRINOX and disease status based on radiologic examination. Patients presenting with distant metastasis in the regular radiologic follow-up were not generally considered as candidates for local treatment application. Patients who received no local treatment after the initiation of FOLFIRINOX were only included in the ST group. These treatment processes were decided individually, and patients were retrospectively categorized into four treatment groups. In MT groups 2 and 3, if the primary pancreatic tumour was judged to be resectable after FOLFIRINOX or FOLFIRINOX + RT administration, surgical resection of the tumour was performed. In MT group 1, RT and additional FOLFIRINOX were administered with the expectation of further tumour shrinkage. For RT, we used the same approaches regardless of the resectability of tumor. All patients underwent 4-dimensional simulation CT scans using multi-detector CT to assess intra-abdominal organ movements. With the in-house respiration training protocol, appropriate candidates for respiratory gating and breath hold technique were selected. Otherwise internal target volume (ITV) based RT was conducted. Gemcitabine- or 5-fluorouracil-based concurrent chemo-RT was generally preferred for long-course RT. For short-course RT, 5–15 fractions of intensity-modulated RT (IMRT) using photons or protons were administered, however, insertion of fiducials were not conducted regardless of RT protocol. GTV was defined as the gross pancreatic tumor and enlarged lymph nodes, which are radiologically suggestive of metastasis. CTV was defined as a 0.5∼1.0 cm margin from ITV, and ENI was not a routine consideration. Then a 0.5 cm margin was added from CTV to define PTV. Particularly, planning organ at risk volumes (PRV) of the stomach, duodenum, and nearby small bowel were delineated and excluded from PTV in cases of hypofractionation. When the calculated dose to the normal organs was beyond constraints, a simultaneous integrated boost technique was used to deliver a higher radiation dose to the gross tumor, and a lower dose to the PTV. The RT dose schedules are demonstrated in Table S1(a).

A multidisciplinary team discussed individualized management after local treatment of the patients in MT groups 1–3, considering patients' disease and performance statuses.

Follow up evaluation and assessments

Follow-up evaluations consisted of physical examinations, laboratory tests (including CA19-9 levels), and radiologic evaluations. During the upfront administration of FOLFIRINOX, contrast-enhanced abdominal CT was performed at every four cycles. When the surgeons adjudged a tumor to be resectable and planned for surgical resection, abdominal MRI and positron emission tomography-CT were additionally performed to confirm the resectability of the primary tumor and evaluate the existence of distant metastatic lesions. Tumour response was evaluated according to the revised Response Evaluation Criteria in Solid Tumours

criteria [14], and the Common Terminology Criteria for Adverse Events v4.0 was used to evaluate treatment toxicity.

Statistical analysis

Patient and treatment characteristics are summarised as medians with ranges or interquartile ranges for continuous variables and frequencies with percentages for categorical variables. Patient characteristics were compared between treatment groups using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables.

The primary treatment outcome was overall survival (OS), whereas the secondary outcomes were overall progression-free survival (PFS) and locoregional PFS (LRPFS). The outcomes were estimated using the Kaplan–Meier method and were compared among the four treatment groups (ST, MT1, MT2, and MT3) via the log-rank test. Additionally, the outcomes were estimated and compared between the MT and ST groups. To determine the optimal timing of local treatment after FOLFIRINOX induction, we constructed three conditional subgroups for each outcome: For each subgroup, we performed conditional survival analysis using the Kaplan–Meier method, log-rank test, and Cox proportional hazards regression model by conditioning each window of time for local treatment application after the initiation of FOLFIRINOX, that is, 0–2 months, 2–4 months, and 4–6 months. Because the local treatment was administered in each patient at a different time after FOLFIRINOX induction, its overall effect was evaluated using time-varying Cox proportional hazards regression models, where local treatment status was considered as a time-varying covariate. Multivariable analyses were performed to test local treatment effect after adjusting for covariates such as resectability at diagnosis, initial CA19-9 level, and response to the initial four-cycle induction of FOLFIRINOX. For each treatment outcome, a fitted penalised B-spline curve was used to explore the time-varying hazard ratio for the local treatment according to its application time. We checked the proportional hazards assumption using the scaled Schoenfeld residual test and found no severe violations. Statistical significance was defined as a two-sided *P*-value of $< .05$. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.1.3 (Vienna, Austria; http://www.R-project.org/).

Results

Patient and treatment characteristics

The baseline characteristics of 258 patients are presented in Table 1. The median age of the entire cohort was 60.5 years, and the median follow-up period of the entire study population was 18 months (range, 2–71 months). According to the NCCN guidelines, there were 108 (41.9%) patients with BR and 150 (58.1%) patients with LAPC, and pancreatic head cancer accounted for two-thirds of the study population. After FOLFIRINOX chemotherapy, 62 patients were converted to resectable status, and 59 patients received surgery. After FOLFIRINOX and RT, 22 patients became surgically resectable, and 21 patients received surgery. The conversion rates from unresectable to resectable tumors according to initial operability and treatment groups were demonstrated in Table S2. Finally, a total of 123, 55, 59, and 21 patients were in the ST, MT1, MT2, and MT3 groups, respectively. Among 178 patients who did not undergo surgical resection (ST and MT1 groups), 47 (26.4%) had BR-PDAC at the time of diagnosis; this was significantly lower than the 131 (87.3%) patients with BR-PDAC who underwent surgical resection (MT2 and MT3 groups) ($P < .001$). In the same context, the rate of clinical T3 and T4 stages was significantly higher in ST and MT1 groups than in MT2 and MT3 groups (56.7% [101/178 patients] vs. 40% [32/80 patients], $P = .007$). Age and location of PDAC were well-distributed, regardless of the treatment group. Details of the treatment strategies, including the timing of the local treatment according to the treatment group, are shown in Table 2. A total of 61 (56.5%) patients with BR-PDAC and 19 (12.7%) with LAPC finally underwent surgical resection. The timing of the local treatment stratified by initial resectability is shown in Table S3. In LAPC cases, 9 of 19 (47.4%) patients underwent surgical resection within 6 months after FOLFIRINOX initiation, whereas 48 of 61 (78.7%) of patients with BR underwent surgery within 6 months after initiation. The median number of FOLFIRINOX cycles was 8 (range, 1∼49) in the ST group, 12 (range, 2∼51) in the MT1 group, 8 (range, 2∼27) in the MT2 group, and 11 (range, 4∼36) in the MT 3 group. The number of cycles before local treatment in the MT groups were eight (MT1; range, 2∼23), five (MT2; range, 2∼17) and five (MT3; range, 3∼12).

Table 1
Patients and treatment characteristics according to treatment subgroups

Groups Variables	Total (n = 258),	ST (n = 123)	MT 1[a] (n = 55)	MT 2 (n = 59)	MT 3 (n = 21)	*P* value
Sex (Male)	141 (54.7%)	67 (54.5%)	31 (56.4%)	30 (50.8%)	13 (61.9%)	.841
Age (years)	60.5 (range, 36 - 84)	61 (range, 57-68)	59 (range, 43-77)	60 (range, 41-79)	60 (range, 47-76)	.156
Tumor location						.529
Head	172 (66.7%)	87 (70.7%)	27 (49.1%)	45 (76.3%)	12 (57.1%)	(ST+MT1 vs
Body	73 (28.3%)	27 (22.0%)	27 (49.1%)	12 (20.3%)	8 (38.1%)	MT2+ MT3)
Tail	13 (5.0%)	9 (7.3%)	1 (1.8%)	2 (3.4%)	1 (4.8%)	
Initial resectability						<.001
BR	108 (41.9%)	35 (28.5%)	12 (21.8%)	46 (78.0%)	15 (71.4%)	(ST+MT1 vs
LA	150 (58.1%)	88 (71.5%)	43 (78.2%)	13 (22.0%)	6 (28.6%)	MT2+ MT3)
Initial T stage						.007
1	18 (7.0%)	6 (4.9%)	1 (1.8%)	8 (13.6%)	3 (14.3%)	(ST+MT1 vs
2	107 (41.5%)	53 (43.1%)	17 (30.1%)	27 (45.8%)	10 (47.6%)	MT2+ MT3)
3	28 (10.9%)	18 (14.6%)	8 (14.5%)	1 (1.7%)	1 (4.8%)	
4	105 (40.7%)	46 (37.4%)	29 (52.7%)	23 (39.0%)	7 (33.3%)	
Initial N stage						.297
0	172 (66.7%)	82 (66.7%)	37 (67.3%)	37 (62.7%)	16 (76.2%)	
1 or 2	86 (33.3%)	41 (33.3%)	18 (32.7%)	22 (37.3%)	5 (23.8%)	
Baseline CA19-9						.225
Median (IQR)	136(36.4-609.4)	136(39.3-756.0)	137.58(35.3-609.1)	139.62(58.5-367.6)	51.01(15.6-833.2)	
Normal (<37 U/ml)	66 (25.6%)	29 (23.6%)	15 (27.3%)	13 (22.0%)	9 (42.9%)	
Elevated (>37 U/ml)	192 (74.4%)	94 (76.4%)	40 (72.7%)	46 (78.0%)	12 (57.1%)	

* Multimodality treatment group: MT1 (FOLFIRINOX + RT), MT2 (FOLFIRINOX + OP), MT3 (FOLFIRINOX + RT + OP).
Abbreviations: ST, systemic therapy alone group; MT, multimodality treatment group; BR, borderline resectable; LA, locally advanced; FOLFIRINOX, combination of folinic acid, 5-fluorouracil, irinotecan, oxaliplatin; RT, radiation therapy; OP, operation.

Table 2
Treatment characteristics according to treatment groups

	ST (n = 123)	MT1 (n = 55)	MT2 (n = 59)	MT3 (n = 21)
Total number of FOLFIRINOX cycles, median (range)	8 (1-49)	12 (2~51)	8 (2~27)	11 (4~36)
FOLFIRINOX cycles before local treatment	-			
1~4		13 (23.6%)	24 (40.7%)	10 (47.6%)
5~8		20 (36.4%)	23 (39.0%)	5 (23.8%)
>8		22 (40.0%)	12 (20.3%)	6 (28.6%)
Timing of surgical resection after FOLFIRINOX	-			
0-2 months (1~4 cycles of FOLFIRINOX)		-	2 (3.4%)	0 (0.0%)
2-4 months (5~8 cycles of FOLFIRINOX)		-	29 (49.2%)	5 (23.8%)
4-6 months (9~12 cycles of FOLFIRINOX		-	16 (27.1%)	5 (23.8%)
≥6 months (13~ cycles of FOLFIRINOX)		-	12 (20.3%)	11 (52.4%)
Timing of RT after FOLFIRINOX	-			
0-2 months (1~4 cycles of FOLFIRINOX)		1 (1.8%)	-	0 (0.0%)
2-4 months (5~8 cycles of FOLFIRINOX)		13 (23.6%)	-	10 (47.6%)
4-6 months (9~12 cycles of FOLFIRINOX		8 (14.5%)	-	5 (23.8%)
≥6 months (13~ cycles of FOLFIRINOX)		33 (60.0%)	-	6 (28.6%)
Surgical resection according to initial resectability				
BR		-	46 (78.0%)	15 (71.4%)
LAPC		-	13 (22.0%)	6 (28.6%)
Adjuvant treatment after local treatment	-			
No		27 (49.1%)	4 (6.8%)	3 (14.3%)
FOLFIRINOX		19 (34.5%)	28 (47.5%)	12 (57.1%)
Gemcitabine based CTx		9 (16.4%)	20 (33.9%)	8 (38.1%)
CCRT +/- adjuvant CTx		0 (0%)	7 (11.9%)	0 (0%)

Abbreviations: FOLFIRINOX = combination of folinic acid, 5-fluorouracil, irinotecan, oxaliplatin; OP = operation; CTx = cytotoxic chemotherapy; CCRT = concurrent chemoradiation therapy; RT = radiation therapy; BR = borderline resectable; LAPC = locally advanced pancreatic cancer.
ST (systemic therapy alone) group: FOLFIRINOX only.
MT (multimodal treatment) group 1: FOLFIRINOX + RT.
MT group 2: FOLFIRINOX + OP.
MT group 3: FOLFIRINOX + RT + OP.

Overall treatment outcomes

In the entire study population, the 2-year OS, LRPFS, and PFS were 43.3%, 31.5%, and 23.7%, respectively (Fig. S2). The treatment results according to treatment subgroups are shown in Fig. S3.

The 2-year OS for ST, MT1, MT2, and MT3 groups were 22.0%, 46.3%, 65.7%, and 90.2%, respectively (Fig. S3A, $P < .001$). The 2-year LRPFS and overall PFS for each treatment group were as follows: ST group, 12.0% and 8.7%; MT1 group, 31.8% and 23.3%; MT2 group, 45.3% and 35.0%; and MT3 group, 81.0% and 66.3% (Figs. S3B and S3C, $P < .001$). The 2-year OS, LRPFS, and overall PFS were also compared in BR (Figs. S3D~F) and LAPC (Figs. S3G~I) separately. The corresponding rates in BR were 21.9%, 15.4%, and 7.1% in the ST group; 37.5%, 22.2%, and 21.2% in the MT1 group; 68.4%, 49.1%, and 30.7% in the MT2 group; and 100.0%, 80.0%, and 72.7% in the MT3 group. The corresponding rates in LAPC were 10.9%, 9.2%, and 7.1% in the ST group; 48.4%, 35.3%, and 30.2% in the MT1 group; 57.1%, 32.5%, and 23.4% in the MT2 group; and 66.7%, 83.3%, and 50.0% in the MT3 group. To evaluate the efficacy of the local treatment, oncologic outcomes were compared between the ST and MT groups (Fig. 1). The 2-year OS of the ST group was 22.0%, which was significantly worse than that of the MT groups (62.2%; Fig. 1A; $P < .001$). The 2-year LRPFS rate and overall PFS in the ST group were 10.7% and 7.0%, respectively, which were also significantly lower than those of the MT groups (48.1% and 34.8, respectively; Figs. 1B and C, respectively; $P < .001$ for both). The benefits of including the local treatment were also confirmed in the multivariate conditional Cox proportional hazards regression analysis, even after adjusting for confounding factors such as operability, CA19-9 level, and treatment response (Table 3). Detailed results of multivariable time-varying Cox proportional hazard regression analyses are demonstrated in Table S4.

Timing of local treatment application

Kaplan–Meier curves of conditional survival analyses are shown in Figure 2. Figure 2 shows the OS, LRPFS, and overall PFS of each conditional subgroup (Fig. 2[A-1 to 3] : subgroup (A), Fig. 2[B-1 to 3] : subgroup (B), Fig. 2[C-1 to 3] : subgroup (C)) as calculated from the application of the local treatment. Except for the conditional subgroup (A), administering the local treatment after FOLFIRINOX resulted in a better OS, LRPFS, and overall PFS, with statistical significance. Table S5 (a) shows the conditional Cox regression analysis for each conditional subgroup adjusted for the potential confounding factors. Administering the local treatment yielded significantly higher OS, LRPFS, and PFS rates, except in the conditional subgroup (A). Detailed results of Cox regression model with potential variables are shown in Table S5(b).

In Figure 3, the time hazard ratio plots for the OS, LRPFS, and overall PFS are shown. Administering the local treatment, especially at 11–17 months after the initiation of FOLFIRINOX, significantly improved OS (Fig. 3A). Generally, administering the local treatment resulted in a better LRPFS and overall PFS, albeit without statistical significance, when such treatments were applied within 2 years after the initiation of FOLFIRINOX (Figs. 3B and C).

RT vs. surgery

We compared treatment outcomes between conventional RT and surgery, and between hypofractionated RT and surgery.

The R0 resection rate of our study population who underwent surgery was 83.8% (67/80). The rates according to treatment schemes were 81.4% (48/59) for MT2 group, and 90.5% (19/21) for MT3 group, respectively. ($P = .331$).

We compared the treatment outcomes of patients who had undergone surgical resection (with/without preoperative conventional fractionation RT, n = 65) or conventional RT (without surgery, n = 25; all patients underwent photon IMRT). The surgical resection and conventional RT groups showed 2-year OS rates of 59.6% and 34.2% ($P < .001$), respectively; LRPFS of 45.5% and 7.4% ($P = .003$), respectively; and overall PFS rates of 35.4% and 7.1% ($P = .001$), respectively, demonstrating superior treatment results in the surgical resection group.

As some of our patients in the RT group received hypofractionated RT with a high biologically effective dose (BED) of ≥70 gray (Gy), we additionally compared the treatment outcomes of groups who underwent surgical resection or hypofractionated RT (without surgery; 25 patients underwent proton beam therapy [PBT] and 5 underwent photon IMRT) after FOLFIRINOX induction (Fig. S4). The most commonly used dose scheme was a total dose of 60 Gy with 12 Gy per fraction (14 patients underwent PBT and 2 underwent IMRT). RT dose schemes and techniques applied in the hypofractionated RT group are described in Table S1(b). The 2-year OS for the hypofractionated RT

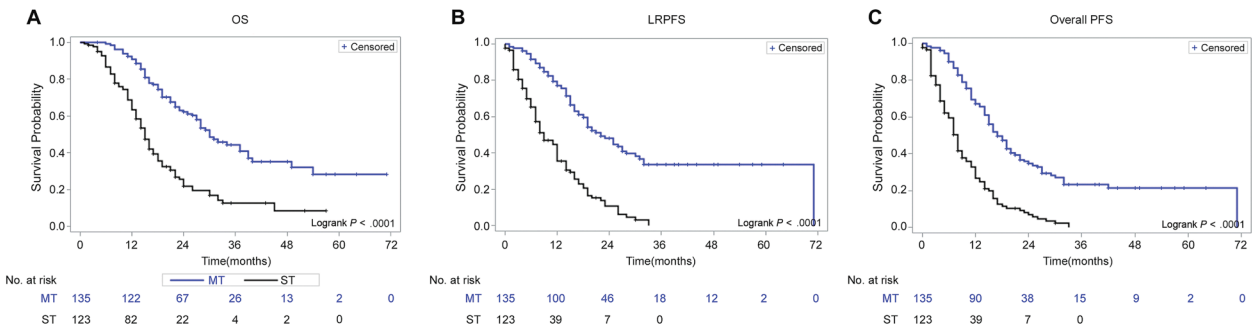

Fig. 1. (A) OS, (B) LRPFS, and (C) overall PFS according to the treatment groups (ST vs MT). *Abbreviations:* ST = systemic therapy alone; MT = multimodal treatment; OS = overall survival; LRPFS = locoregional progression free survival.

Table 3
Overall Effect of local treatment on OS, LRPFS, and overall PFS using time-varying Cox proportional hazard regression models

Local treatment (any vs no)[a]	Crude HR	Adjusted HR[b]	95% C.I.[b]	*P* value
OS	0.423	0.568	(0.398, 0.811)	0.0018
LRPFS	0.437	0.490	(0.331, 0.726)	0.0004
Overall PFS	0.541	0.656	(0.458, 0.940)	0.0214

Abbreviations: OS, overall survival; LRPFS, locoregional progression free survival; FOLFIRINOX, combination of folinic acid, 5-fluorouracil, irinotecan, oxaliplatin.

[a] Considered as a time-varying covariate since the time of local treatment application varied across patients.

[b] Multivariable analyses with adjustment for resectability at diagnosis, initial CA19-9 level, and response for 4-cycle FFX induction.

group was 65.8%, which was comparable to that for the surgical resection group (59.6%; Fig. S4A; $P = .580$). The 2-year LRPFS and overall PFS rates also showed no significant difference (Fig. S4B; 2-year LRPFS; 48.7% in hypofractionated RT vs. 45.5% in surgery; $P = .499$; Fig. S4C; 2-year overall PFS; 32.5% in hypofractionated RT vs 35.4 in surgery; $P = .901$). Only eight patients experienced grade 1 or 2 toxicity in the gastroduodenal area. None of the patients experienced hypofractionated RT-related toxicities of grade ≥3. RT related toxicity profiles are shown in Table S6.

Discussion

Using real-world single-institutional data, we demonstrated that multimodal approaches after upfront FOLFIRINOX administration were beneficial for the treatment outcomes in patients with BR or LAPC. In the conditional survival analysis, administering the local treatment within 6 months of upfront FOLFIRINOX administration contributed to a better OS, LRPFS, and overall PFS, except for patients with very early application of local treatment (0–2 months after FOLFIRINOX; Fig. 2). In the time-varying Cox regression analysis, the treatment outcomes of patients who received the local treatment were consistently beneficial, regardless of the timing of application. In particular, the time window of 11–17 months after FOLFIRINOX initiation appears to be the most effective timing for local treatment according to the penalised B-spline curve, showing a significantly lower hazard ratio in OS.

The treatment paradigm in BR or LAPC is shifting towards a multimodality approach of systemic therapy induction followed by local treatment. When focusing on recurrence patterns, studies have demonstrated that 76% of sites of initial recurrence involve distant metastasis in patients with resectable or BR-PDAC [15–16]. In addition, the CONKO-001 randomized control trial reported that 50% of patients who underwent upfront surgical resection without adjuvant chemotherapy showed a median distant failure survival of 6.7 months [17]. Accordingly, a point of view exists that PDAC should be approached as a systemic disease regardless of the initial resectability status, and upfront systemic chemotherapy is increasingly being adopted as the mainstay of treatment for PDAC [18]. Despite the evolution of systemic agents with the introduction of FOLFIRINOX, locoregional recurrence is the most common treatment failure and contributes to substantial mortality [19–20]. Therefore, administering the local treatment after upfront systemic therapy in PDAC is gaining interest, and the harmony of these multimodal treatment methods is considered key for prolonged survival outcomes in this disease entity.

In particular, neoadjuvant approaches for the treatment of unresectable PDAC at diagnosis have advanced considerably since FOLFIRINOX was found to outperform gemcitabine-based regimens in metastatic PDAC [8]. A recently reported PREOPANC phase III randomized trial showed OS benefits in resectable or BR pancreatic cancer with gemcitabine based neoadjuvant treatment in the long term analysis, and the treatment outcomes are currently expected to improve with the FOLFIRINOX regimen [21]. Although the toxicity of the combined regimens might be intolerable in some patients, FOLFIRINOX may downstage LAPCs into resectable (or BR) tumours, and surgical resection after neoadjuvant treatment can result in improved survival outcomes [9,22,23]. The overall resection rate in our study was 56.5% in BR and 12.7% in LAPC, which is similar to that of the large-scale Trans-Atlantic Pancreatic Surgery Consortium, wherein patients were treated with the same modalities in the same patient groups (53.1% in BR vs. 17.6% in LAPC) [24]. A higher chance of receiving the local treatment was observed in the BR group than in the LAPC group (67.6% in BR vs. 40.7% in LAPC). Moreover, 12.7% of patients with LAPC (19/150) were able to undergo surgical resection after FOLFIRINOX administration, which induced similar OS and LRPFS rates as those of patients with surgically resected BR (2-year OS: 76.8% in BR vs. 60.2% in LAPC, $P = .530$ and 2-year LRPFS: 57.5% in BR vs. 49.6% in LAPC, $P = .783$). Swedish data also reported improved survival after neoadjuvant therapy followed by surgical resection in patients with BR or LAPC [23]. Fifty-four patients (34.6%) used the FOLFIRINOX regimen, and only 40.3% of patients received a 'full dose' neoadjuvant chemotherapy regimen. The median OS after neoadjuvant treatment for patients who underwent resection was 22.4 months, which was significantly better than that for patients who did not (12.7 months; $P < .0001$).

However, whether including RT in the treatment of BR or LAPC can be beneficial in oncologic outcomes, such as the conversion rate of unresectable to resectable tumours or survival results, remains controversial. To date, most prospective studies that investigated the efficacy of long-course chemo-RT in patients with BR or LAPC used gemcitabine-based regimens rather than FOLFIRINOX, and they showed low response rates, without a clear improvement in survival outcomes [25–27]. The controversy grew after the gemcitabine-based randomised phase III LAP07 trial demonstrated no survival benefits after chemo-RT [25]. A

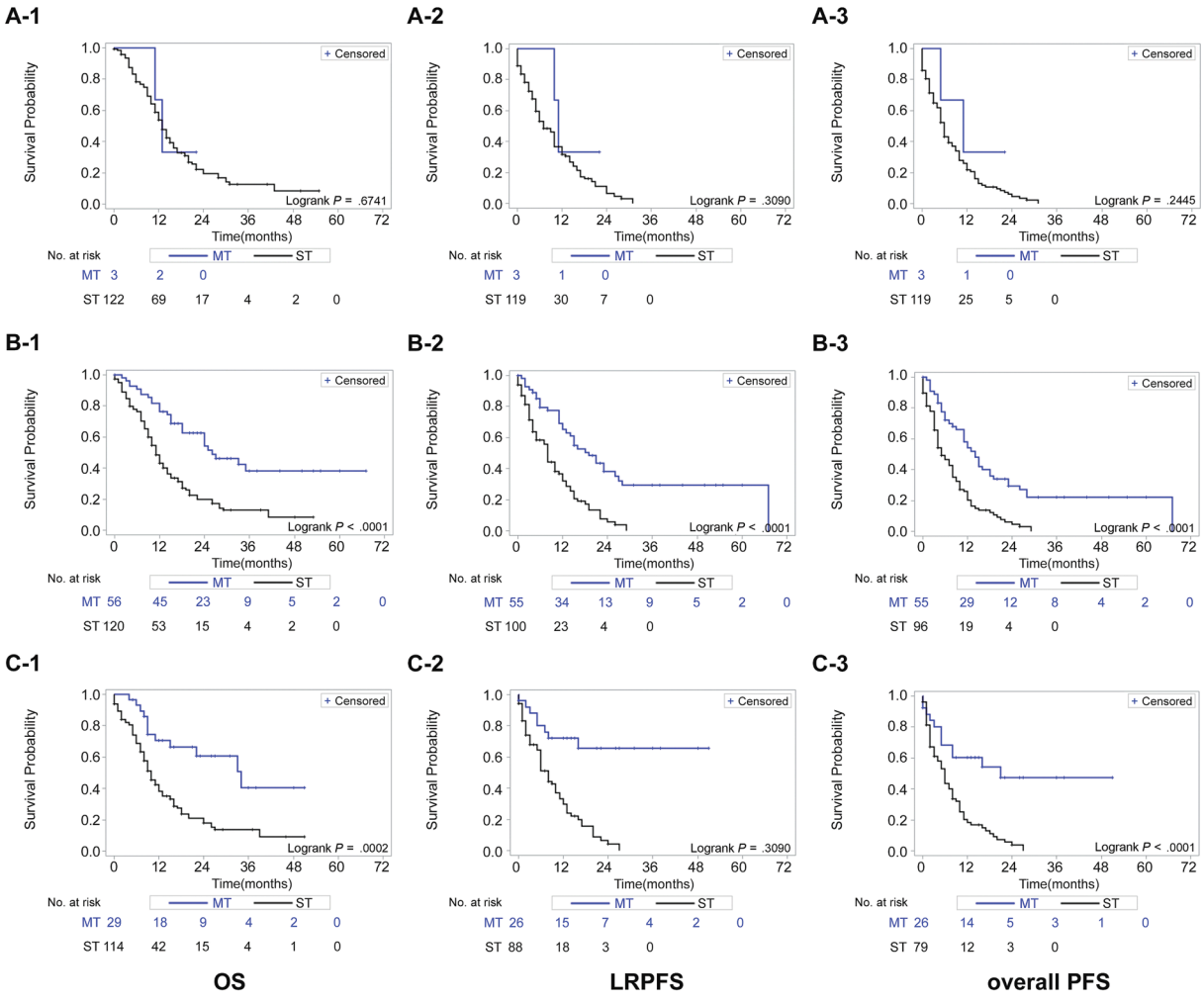

Fig. 2. Conditional OS (A-1, B-1, C-1), LRPFS (A-2, B-2, C-2), and overall PFS (A-3, B-3, C-3) in each conditional subgroups stratified by the timing of local treatment after induction FOLFIRINOX. Conditional subgroups were defined as follows; Subgroup (A) [Figure A-1 to 3), patients—without or with local treatment application within 2 months—had no progression event within 2 months after FOLFIRINOX induction; Subgroup (B) [Figure B-1 to B3], patients—without local treatment application within 4 months or with local treatment application within 2–4 months—had no progression event within 4 months after FOLFIRINOX induction; Subgroup (C) [Figure C-1 to 3], patients—without local treatment application within 6 months or with local treatment application within 4–6 months—had no progression event within 6 months after FOLFIRINOX induction. *Abbreviations:* OS = overall survival; LRPFS = locoregional progression free survival.

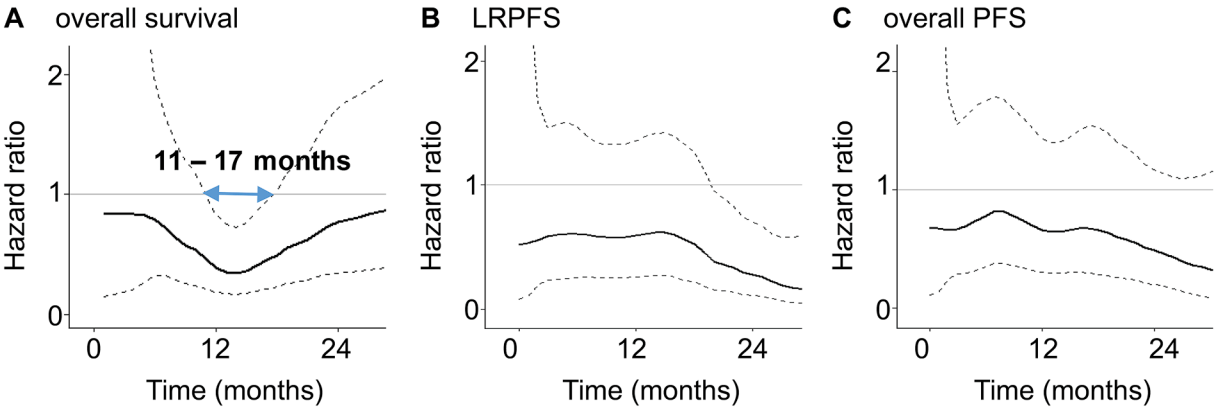

Fig. 3. Time-varying hazard ratio for treatment outcomes according to application time of local treatments, using the fitted penalized B-spline curve for each treatment outcome. Figure (A), (B) and (C) respectively represent time-varying hazard ratio and 95% CI for OS, LRPFS, and overall PFS. *Abbreviations:* CI = confidence interval; OS = overall survival = LRPFS = locoregional progression free survival.

French multicentre retrospective study that gained attention reported the oncologic outcomes of patients with BR and LAPC regarding the effectiveness of administering chemo-RT before surgery after FOLFIRINOX induction [28]. In addition to an improved OS (median OS: 57.8 months of FOLFIRINOX plus chemo-RT vs. 35.5 months with only FOLFIRINOX, $P = .007$), the R0 resection, ypN0, and pathologic major response rates were significantly higher in the FOLFIRINOX plus chemo-RT group than in the FOLFIRINOX only group. Regarding short-course radiation, a BR-PDAC phase II occurred [29]. After 4–8 cycles of FOLFIRINOX, patients received 25 Gy of capecitabine- and proton-based chemo-RT therapy in five fractions, the 2-year OS and PFS rates were 56% and 43%, respectively, with an R0 resection rate of 97%. Nevertheless, the benefits of including RT in the treatment of anatomically advanced PDAC in a neoadjuvant treatment setting requires additional confirmative evidence via a randomised phase III trial, and our data may contribute to the literature as a reference that favours the administration of RT after upfront FOLFIRINOX treatment.

Stereotactic body radiation therapy (SBRT) or particle beam RT can be considered alternative treatment options to surgical resection when tumours are still inoperable after neoadjuvant treatments, and some evidences suggest better treatment outcomes after ablative RT than after chemotherapy only [30–34]. Some trials have demonstrated the role of high-dose RT for BR or LAPC in a neoadjuvant FOLFIRINOX setting. In the LAPC-1 trial, RT of 40 Gy in five fractions following eight cycles of FOLFIRINOX showed 1-year OS and PFS rates of 64% and 34%, respectively. A total of 6 among 50 patients (12%) underwent a resection, all of which were R0 resections [33]. The long-term outcome of the study was reported in 2021, and the median OS of the SBRT group was 18 months, which was significantly higher than the 5 months of the non-SBRT group ($P < .001$) [31]. In the Alliance A021501 trial, patients with BR-PDAC were randomised to either receive extended neoadjuvant FOLFIRINOX or eight cycles of induction FOLFIRINOX plus hypofractionated RT (25–40 Gy in five fractions). The results were published in 2021 as an abstract, and no OS benefits were observed in the chemo-RT group [35]. The AGITG MASTERPLAN randomised phase II study [36] is currently recruiting patients with BR or LAPC, and the locoregional control rate will be compared between two groups: FOLFIRINOX only versus induction FOLFIRINOX followed by SBRT of 40 Gy in five fractions groups. In our study, 30 patients received high-dose radiation of BED $\geq$70 Gy by either photon-based IMRT or IMPBT, and the 2-year OS was 65.8%, which was similar to that of the patients who underwent surgical resection (59.6%). No significant differences were observed in the LRPFS and overall PFS rates between the surgical resection and hypofractionated RT groups. No grade $\geq$3 hypofractionated RT-related toxicities were observed, presenting a similar toxicity profile to that of long-course RT. The strength of our study is that some patients were treated with PBT, which is expected to overcome the limitations of conventional IMRT and to potentiate the accurate delivery of high doses to the target [37]. Kim *et al.* reported the efficacy and feasibility of hypofractionated PBT in LAPC. This study used a simultaneous integrated boost technique delivering 45–50 Gy in 10 fractions for the planning target volume. In our results, the median OS of patients who received PBT after upfront chemotherapy was 26.1 months (95% confidence interval, 17.8–34.3 months), and no acute and late grade $\geq$3 PBT related toxicities were observed. The results of two phase II studies are expected imminently (NCT02598349 and NCT01494155); however, there is no ongoing phase III randomised trial regarding PBT, as the Phase III CIPHER trial (NCT03536182) that initially planned to compare photon- and proton-based RT recently withdrew patient recruitment. Further studies are required to optimise the dose schemes and concurrent chemotherapeutic options for the treatment of BR or LAPC.

However, most of these results regarding local treatments do not compensate for the duration and cycles of induction chemotherapy and the timing of local interventions. Considering that malignant lesions finally show resistance to systemic agents, the optimal induction cycle of FOLFIRINOX and the timing of local treatment should be investigated in patients with BR/LAPC. We used time-varying Cox regression analysis to determine the optimal timing of local treatment after upfront FOLFIRINOX. We assumed that the timing of RT or surgery after upfront FOLFIRINOX may affect the treatment outcomes, that is, the proportional hazards assumption of the conventional Cox regression model does not fit our situation. After compensating for the potential risk factors, such as resectability and tumour marker levels, we determined the specific timing of local treatment which is beneficial for OS. Although our results must be interpreted with caution, this is the first study to analyse the optimal schedules in combination with upfront FOLFIRINOX and local treatments in BR or LAPC. The advantages of our study in analysing the timing of local treatments are as follows: first, single-institutional data increase the reliability of the treatment outcomes, as treatment principles after induction FOLFIRINOX and/or local treatments are similar between each patient; and second, a relatively large study population was analysed with a unified induction chemotherapy regimen.

A limitation of our study is the potential selection bias originating from the retrospective nature of the study. Confounding factors that can affect treatment outcomes, such as surgical techniques, RT technique, dose variation, and use of systemic treatments after local treatment, were not statistically compensated in our study. Particularly, the present study presents a significant variation in the number of FOLFIRINOX cycles, which can induce a potential selection bias due to the retrospective nature of the study. A longer period of chemotherapy might have been administered for patients with good tolerance and response to chemotherapy, affecting the outcomes of the present study. In addition, the optimal timing of surgery or RT was not analysed separately, although the efficacy of surgery and RT can differ in tumour control. Therefore, prospective studies with well-controlled treatment schemes and appropriate patient selection are required.

Conclusion

Our study provides additional evidence that a multidisciplinary approach for patients with BR/LAPC can result in favourable treatment outcomes after induction chemotherapy. In addition, this study is the first to analyse the appropriate timing of local treatments in the era of the FOLFIRINOX regimen, using conditional survival analysis and a time-varying covariate regression method. In our study, adding local therapy induced maximal efficacy in 11-17 months after the initiation of FOLFIRINOX, and we assume that administration of sufficient duration of FOLFIRINOX may control the microscopic disease, intensifying the role and efficacy of local therapy. Further prospective analyses with a well-controlled study population are required to evaluate optimal multimodal treatment schemes in patients with BR/LAPC.

Authors' contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

All patients included in this study provided written informed consent and the study protocol was approved by the institutional review board of XXXXXXX XXXXXXX XXXXXX (IRB no. XXX 2022-05-139). This study was performed in compliance with the Declaration of Helsinki.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100732.

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