의학석사 학위논문

선행항암화학요법 modified FOLFIRINOX 후 수술을 받은 췌관선암 환자에서 보조항암화학요법 시행의 임상적 필요성과 예후

Clinical relevance of adjuvant chemotherapy in patients with pancreatic ductal adenocarcinoma who underwent surgery following neoadjuvant modified FOLFIRINOX

울산대학교 대학원

의 학 과

이 소 흔

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지 도 교 수 유 창 훈

이 논문을 의학석사 학위 논문으로 제출함

2022 년 2 월

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이소흔의 의학석사 학위 논문을 인준함

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2022 년 2 월

Abstract

Background The benefit of adjuvant chemotherapy following curative-intent surgery in pancreatic ductal adenocarcinoma (PDAC) patients who had received neoadjuvant modified FOLFIRINOX (mFOLFIRINOX) is unclear. This retrospective analysis aimed to assess the survival benefit of adjuvant chemotherapy in patients in this patient population.

Methods Between January 2017 and December 2020, 219 patients with localized PDAC who received neoadjuvant mFOLFIRINOX and underwent pancreatectomy were included in this analysis. Survival outcomes were compared according to adjuvant chemotherapy administration and represented as disease-free survival (DFS) and overall survival (OS). Propensity score matching (PSM) was conducted to create balanced cohorts.

Results Adjuvant chemotherapy was administered to 149 (68.0%) patients. Patients in the adjuvant chemotherapy group received significantly fewer cycles of neoadjuvant chemotherapy (median; 7 vs. 9, $p<0.001$) compared to the observation group. Patients in the adjuvant chemotherapy group had significantly improved survival compared to the observation group, with a median DFS of 13.4 months (95% CI, 10.7–18.9) vs. 8.3 months (95% CI, 4.9–16.0) ($p=0.0039$); and a median OS of 33.4 months (95% CI, 29.9–not assessable) vs. 23.8 months (95% CI, 17.9–not assessable) ($p=0.0012$). In the PSM cohort of 59 matched pairs of patients, the survival benefit of adjuvant chemotherapy remained significant. DFS and OS were significantly better in the adjuvant chemotherapy group regardless of the lymph node status during surgery ($p=0.038$ for DFS and $p=0.016$ for OS with positive lymph node; and $p=0.028$ for DFS and $p=0.014$ for OS with negative lymph node). In the multivariate analysis, adjuvant chemotherapy was a significant favorable prognostic factor (DFS, hazard ratio [HR] 0.50 (95%CI, 0.34–0.73, $p<0.001$); OS, HR 0.35 (95%CI, 0.20–0.60, $p<0.001$).

Conclusion In PDAC patients who underwent surgery following neoadjuvant mFOLFIRINOX, adjuvant chemotherapy may be associated with improved survival. Its benefit was not affected by the lymph node status.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies with a 5-year survival rate of less than 10%. Only 20% of patients have surgically resectable disease at the time of diagnosis [1-3]. However, even after curative-intent resection, approximately 75% of patients develop recurrence within 2 years, and recurrence occurs more frequently in the absence of adjuvant chemotherapy [1].

For patients who undergo upfront surgery for localized PDAC, adjuvant chemotherapy is the standard of care [4]. Adjuvant modified FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin) and gemcitabine plus capecitabine are the preferred chemotherapy regimens as adjuvant chemotherapy for patients with resected PDAC based on the improved survival outcomes compared to gemcitabine monotherapy in the phase 3 trials [5-7].

Recently, neoadjuvant chemotherapy has been widely used for the management of patients with borderline resectable pancreatic cancer (BRPC) and locally advanced pancreatic cancer (LAPC) [8-12]. There is limited evidence to recommend a specific neoadjuvant chemotherapy regimen because of the lack of prospective comparative trials. However, FOLFIRINOX (either the original or the modified version) has been widely used based on the better objective response rates and survival outcomes compared to gemcitabine in patients with metastatic PDAC [13-15]. In meta-analyses of FOLFIRINOX for BRPC and LAPC, conversion surgery could be achieved in 67.8% of BRPC and 25.9% of LAPC patients [13, 15].

While the number of patients who undergo surgery following neoadjuvant chemotherapy is increasing, there is only limited data available to guide physicians as to whether adjuvant chemotherapy can improve the survival outcomes in this patient population [16, 17]. Therefore, we conducted a retrospective analysis to investigate the survival benefit of adjuvant chemotherapy in patients with resected PDAC after neoadjuvant FOLFIRINOX.

Methods

Patients

Between January 2017 and December 2020, a total of 1100 patients underwent surgery as localized pancreatic cancer at the Asan Medical Center, Seoul, Korea. Among them, 250 patients received

neoadjuvant modified FOLFIRINOX (mFOLFIRINOX) before surgery. After the exclusion of patients unable to undergo curative-intent surgical resection (R0 or R1) and those with histological types other than ductal adenocarcinoma, 219 patients with localized PDAC who received neoadjuvant mFOLFIRINOX and underwent pancreatectomy were included in this analysis.

Patients' characteristics including age, gender, and Eastern Cooperative Oncology Group (ECOG) performance score, tumor characteristics, and data related to treatment and survival were acquired from the review of electronic medical records of the patients. The CA 19-9 level was measured at the time of diagnosis, the tumor response evaluation, and pre-/post-operative periods within 1 and 6 weeks from surgery. Pathological findings included pathological tumor stage, node stage, resection margin status, lymphovascular invasion or perineural invasion and were graded by the American Joint Committee on Cancer (AJCC), 8th edition. R1 resection was defined as microscopic evidence of a tumor within 1 mm of the resection margin. This study was approved by the institutional review board of the Asan Medical Center, Seoul, Korea (IRB approval number: 2021-1282).

Statistical analysis

Disease-free survival (DFS) was defined as the interval between surgery and recurrence or death from any etiology, whichever occurred first, and overall survival (OS) was that between surgery and death from any etiology.

Categorical variables are presented as frequencies and proportions and continuous variables are presented as medians with interquartile ranges (IQRs). Survival was assessed using Kaplan-Meier survival curves and presented as median DFS and OS with corresponding 95% Confidence Intervals (CIs). Cox proportional hazards models were used for univariate and multivariate analyses and the outcomes are presented as the hazard ratio (HR) and 95% CI. The variables with p values <0.2 in univariate analysis were included in the multivariate analysis.

Propensity score matching (PSM) was conducted to create balanced cohorts including variables of age, sex, ECOG performance score, tumor extent at the diagnosis, pathological T stage, N stage, resection margin status, number of cycles of neoadjuvant mFOLFIRINOX and preoperative CA 19-9 level. Patients were matched based on the propensity scores using 1:1 nearest-neighbor method. Standardized mean difference was adopted with a value <0.1 indicating good balance. All analyses were performed using R Foundation statistical software, version 4.1.1.

Results

Patient characteristics

Among 219 patients with PDAC who underwent curative-intent surgery following neoadjuvant mFOLFIRINOX, adjuvant chemotherapy was administered in 149 (68.0%) patients. The patients' baseline characteristics are summarized in **Table 1**. The number of cycles of neoadjuvant mFOLFIRINOX was significantly higher in the observation group compared to the adjuvant chemotherapy group (median [IQR], 9 [IQR 7-10] vs. 7 [5-8], p<0.001). At the time of diagnosis, patients were classified into resectable pancreatic cancer (n=7, 10.0% and n=15, 10.1%), BRPC (n=40, 57.1% and n=103, 69.6%), and LAPC (n=23, 32.9% and n=30, 20.3%) in the observation group and the adjuvant chemotherapy group, respectively, and there was no statistical difference (p=0.121). There was no significant difference in any other characteristics including the tumor location, surgical types, resection margin status, pathologic stage, or tumor response to mFOLFIRINOX between the two groups.

In the observation group, adjuvant chemotherapy was not administered because of physician's choice (n=20), pathological complete response (n=3), patient's will (n=6), poor general condition (n=35), and postoperative complications (n=4). In the adjuvant chemotherapy group, mFOLFIRINOX (n=98, 65.8%) was administered most frequently followed by gemcitabine monotherapy (n=39, 26.2%), and gemcitabine-capecitabine (n=4, 2.7%).

PSM was performed and 59 matched pairs of patients were generated. Absolute values of standardized difference of matched variables were all <10%. The baseline characteristics of patients in the matched cohort are also summarized in **Table 1**.

Table 1. Baseline characteristics in unmatched and matched cohorts

	Unmatched cohort			Matched cohort		
	Observation (n=70)	Adjuvant chemotherapy (n=149)	p-value	Observation (n=59)	Adjuvant Chemotherapy (n=59)	p-value
Sex						
Male	39 (55.7%)	68 (45.6%)	0.213	33 (55.9%)	31 (52.5%)	0.853
Female	31 (44.3%)	81 (54.4%)		26 (44.1%)	28 (47.5%)	
Age, years, median (IQR)	64 (58-70)	61 (56-67)	0.062	64 (58-70)	64 (59-69)	0.859
ECOG PS						
0-1	66 (94.3%)	143 (96.0%)	0.730	55 (93.2%)	54 (91.5%)	1.000
≥2	4 (5.7%)	6 (4.0%)		4 (6.8%)	5 (8.5%)	
Tumor extent at the diagnosis						
Resectable	7 (10.0%)	15 (10.1%)	0.121	7 (11.9%)	6 (10.2%)	0.947
BRPC	40 (57.1%)	103 (69.6%)		37 (62.7%)	37 (62.7%)	
LAPC	23 (32.9%)	30 (20.3%)		15 (25.4%)	16 (27.1%)	
Location of tumor						
Head	44 (62.9%)	114 (76.5%)	0.132	39 (66.1%)	44 (74.6%)	0.619
Body	13 (18.6%)	20 (13.4%)		10 (16.9%)	9 (15.3%)	
Tail	12 (17.1%)	14 (9.4%)		9 (15.3%)	6 (10.2%)	
Multicentric	1 (1.4%)	1 (0.7%)		1 (1.7%)	0 (0.0%)	
Tumor differentiation						
Well	5 (7.1%)	20 (13.9%)	0.374	5 (8.5%)	9 (15.5%)	0.416
Moderate	60 (85.7%)	114 (79.2%)		51 (86.4%)	45 (77.6%)	
Poorly	5 (7.1%)	10 (6.9%)		3 (5.1%)	4 (6.9%)	
Surgical type						
PPPD/PD	47 (67.1%)	113 (75.8%)	0.388	42 (71.2%)	44 (74.6%)	0.840
Distal pancreatectomy	19 (27.1%)	30 (20.1%)		13 (22.0%)	13 (22.0%)	
Total pancreatectomy	4 (5.7%)	6 (4.0%)		4 (6.8%)	2 (3.4%)	
Vascular resection						
Vein resection	37 (52.9%)	63 (42.3%)	0.187	31 (52.5%)	25 (42.4%)	0.357
Artery resection	10 (14.3%)	17 (11.4%)	0.701	6 (10.2%)	8 (13.6%)	0.776
Pathological T stage						
Pathologic CR	0 (0.0%)	5 (3.3%)	0.385	52 (88.1%)	50 (84.7%)	0.788
ypT1-T2	62 (88.6%)	128 (85.9%)				
ypT3-T4	8 (11.4%)	16 (10.7%)		7 (11.9%)	9 (15.3%)	

	Unmatched cohort			Matched cohort		
	Observation (n=70)	Adjuvant chemotherapy (n=149)	p-value	Observation (n=59)	Adjuvant Chemotherapy (n=59)	p-value
Pathological N stage						
ypN0	40 (57.1%)	85 (57.0%)	0.999	33 (55.9%)	31 (52.5%)	0.853
ypN1	24 (34.3%)	51 (34.2%)		26 (44.1%)	28 (47.5%)	
ypN2	6 (8.6%)	13 (8.7%)				
Pathologic tumor stage						
Pathologic CR	0 (0.0%)	5 (3.4%)	0.558	0 (0.0%)	2 (3.4%)	0.517
Stage IA/IB	37 (52.9%)	72 (48.3%)		30 (50.8%)	27 (45.8%)	
Stage IIA/IIB	25 (35.7%)	54 (36.2%)		23 (39.0%)	21 (35.6%)	
Stage III	8 (11.4%)	18 (12.1%)		6 (10.2%)	9 (15.3%)	
Lymphovascular invasion						
Negative	46 (65.7%)	87 (58.4%)	0.375	40 (67.8%)	38 (64.4%)	0.846
Positive	24 (34.3%)	62 (41.6%)		19 (32.2%)	21 (35.6%)	
Perineural invasion						
Negative	25 (35.7%)	55 (36.9%)	0.983	20 (33.9%)	22 (37.3%)	0.848
Positive	45 (64.3%)	94 (63.1%)		39 (66.1%)	37 (62.7%)	
Resection margin status						
Resection margin negative	58 (82.9%)	126 (84.6%)	0.902	47 (79.7%)	48 (81.4%)	1.000
Resection margin positive	12 (17.1%)	23 (15.4%)		12 (20.3%)	11 (18.6%)	
Number of cycles of neoadjuvant mFOLFIRINOX, median (IQR)	9 (7-10)	7 (5-8)	<0.001	8 (7-10)	8 (7-9)	0.943
Best response to neoadjuvant mFOLFIRINOX						
Partial response	22 (34.4%)	47 (32.4%)	0.906	19 (35.2%)	17 (28.8%)	0.600
Stable disease	42 (65.6%)	98 (67.6%)		35 (64.8%)	42 (71.2%)	
Pathologic response *						
0-1	9 (13.0%)	14 (9.9%)	0.645	9 (15.5%)	5 (8.9%)	0.432
≥2	60 (87.0%)	128 (90.1%)		49 (84.5%)	51 (91.1%)	
Baseline CA 19-9 level						
WNL	24 (41.4%)	38 (30.4%)	0.196	21 (42.0%)	15 (31.9%)	0.414
>UNL	34 (58.6%)	87 (69.6%)		29 (58.0%)	32 (68.1%)	
Preoperative CA						

	Unmatched cohort			Matched cohort		
	Observation (n=70)	Adjuvant chemotherapy (n=149)	p-value	Observation (n=59)	Adjuvant Chemotherapy (n=59)	p-value
19-9 level						
WNL	28 (52.8%)	68 (56.2%)	0.806	24 (53.3%)	23 (52.3%)	1.000
>UNL	25 (47.2%)	53 (43.8%)		21 (46.7%)	21 (47.7%)	
Postoperative CA 19-9 level						
WNL	49 (80.3%)	126 (86.3%)	0.383	41 (80.4%)	50 (86.2%)	0.577
>UNL	12 (19.7%)	20 (13.7%)		10 (19.6%)	8 (13.8%)	

Data are median (interquartile range) or n (%).

Abbreviations. IQR=interquartile range. ECOG PS=Eastern Cooperative Oncology Group performance score. BRPC=borderline resectable pancreatic cancer. LAPC=locally advanced pancreatic cancer. PPPD=pylorus-preserving pancreaticoduodenectomy. PD=pancreaticoduodenectomy. CR=complete response. mFOLFIRINOX=modified FOLFIRINOX. WNL=within normal range. UNL=upper normal limit.

* Pathologic response was graded according to the CAP grade

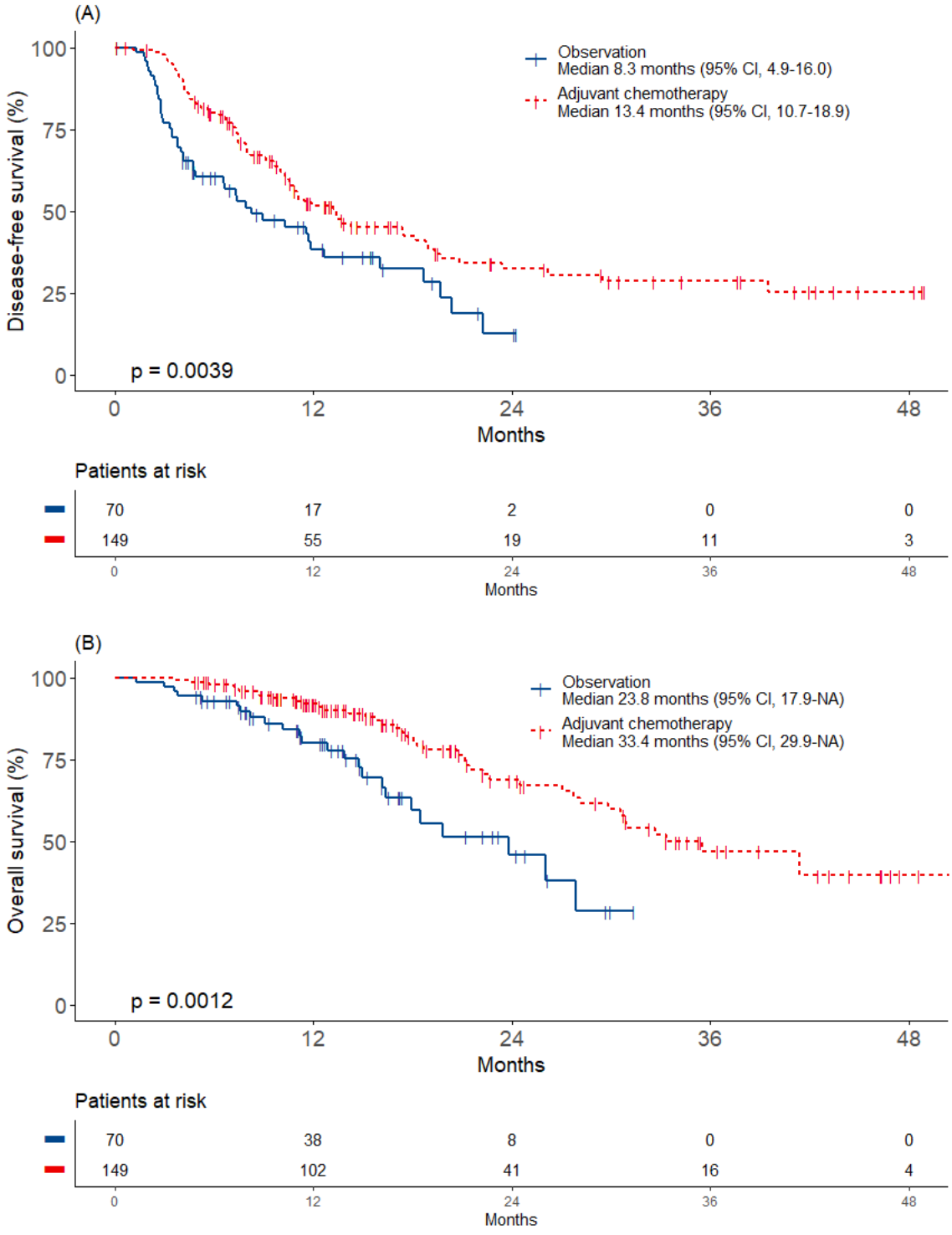
Survival outcomes

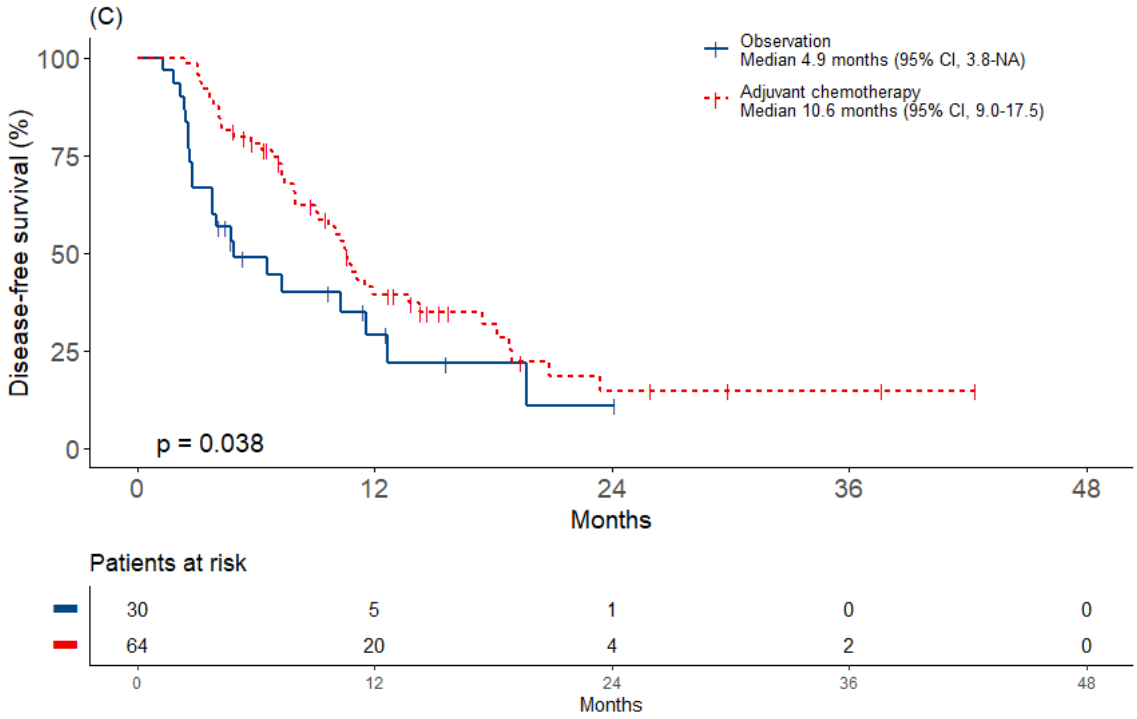
With a median follow-up duration of 17.2 months (95% CI, 15.2–21.2), patients in the adjuvant chemotherapy group showed significantly better survival outcomes compared to those in the observation group, with a median DFS of 13.4 months (95% CI, 10.7–18.9) vs. 8.3 months (95% CI, 4.9–16.0), respectively (p=0.0039); and a median OS of 33.4 months (95% CI, 29.9–not assessable[NA]) vs. 23.8 months (95% CI, 17.9–NA), respectively (p=0.0012) **(Figure 1. A-B)**.

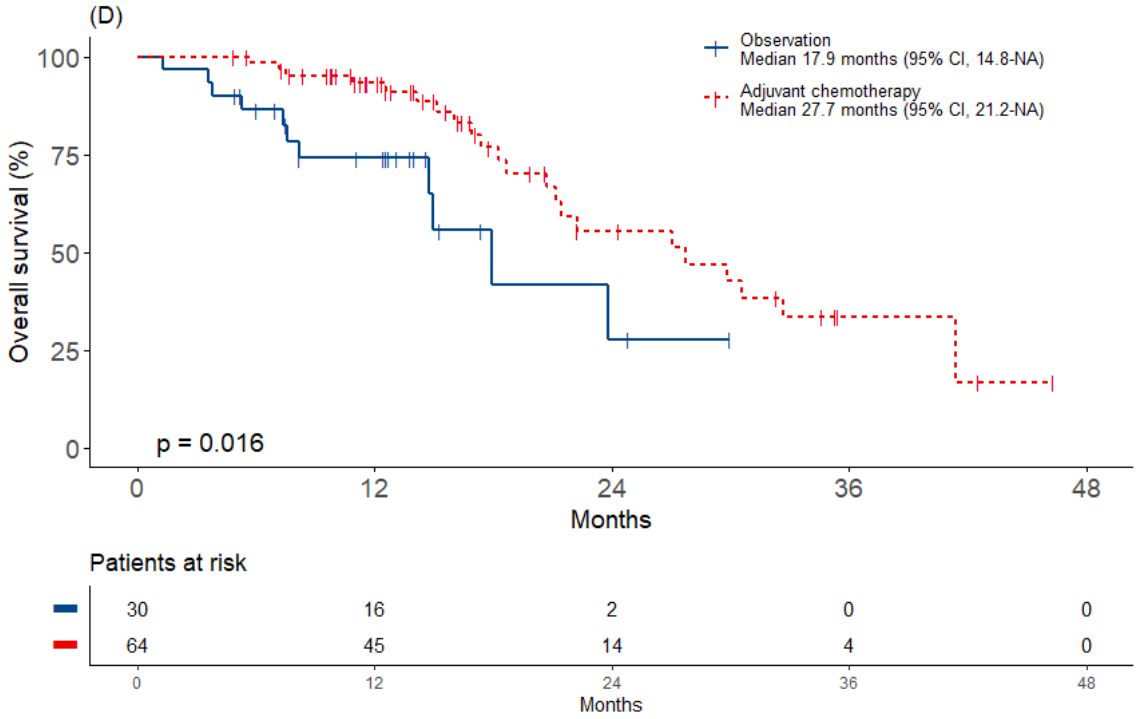
In subgroup analysis according to the lymph node status, DFS and OS were significantly better in the adjuvant chemotherapy group compared to the observation group for both patients with positive lymph nodes (ypN+; p=0.038 and p=0.016, respectively) and negative lymph nodes (ypN0; p=0.028 and p=0.014, respectively) **(Figure 1. C-F)**.

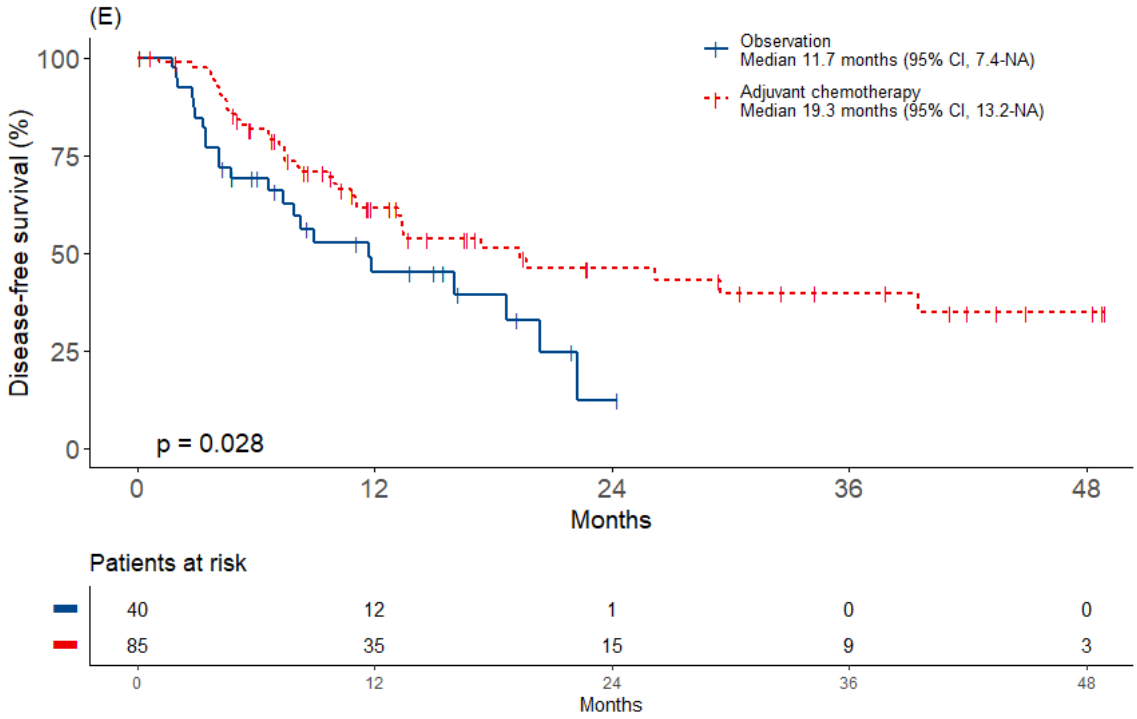
In the adjuvant chemotherapy group, there was no significant difference in the survival outcomes between the patients with adjuvant gemcitabine-based chemotherapy and mFOLFIRINOX with a median DFS of 10.9 months (95% CI, 9.6–39.5) vs. 13.4 months (95% CI, 10.8–19.3), p=0.82; and a median OS of 33.4 months (95% CI, 27.7–NA) vs. Not Reached (95% CI, 27.1–NA), p=0.4.

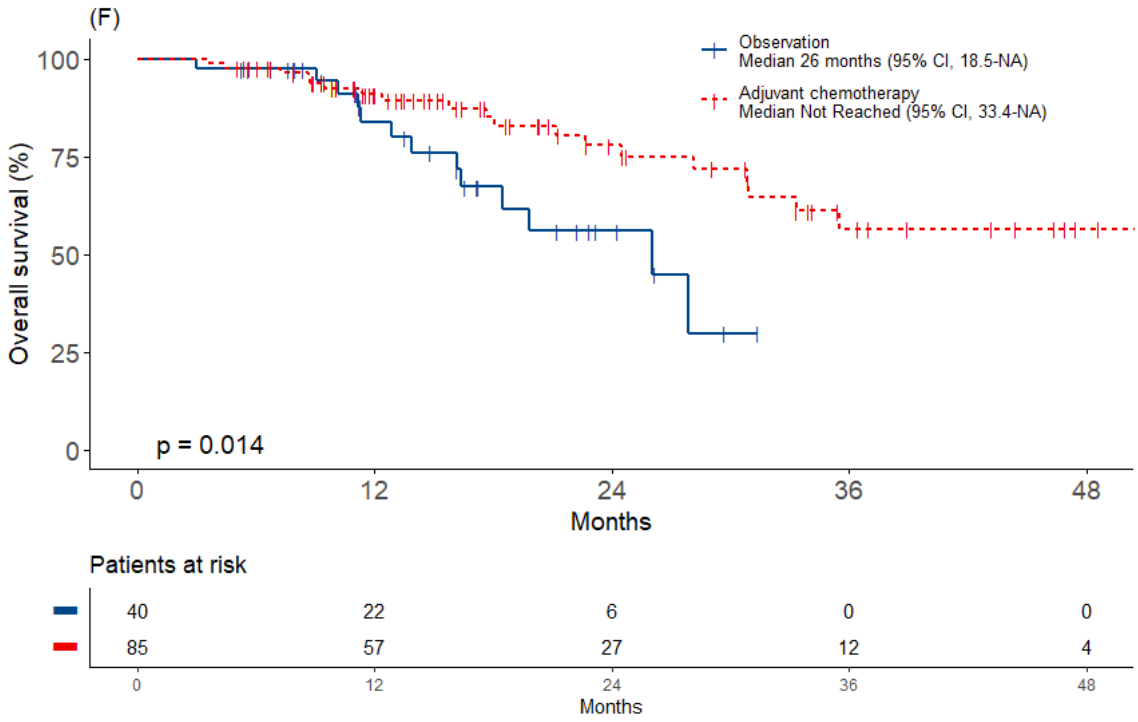
Figure 1. Survival outcomes according to the adjuvant chemotherapy administration in the unmatched cohort. (A) Disease-free survival in overall patients, (B) Overall survival in overall patients, (C) Disease-free survival in patients with positive lymph nodes, (D) Overall survival in patients with positive lymph nodes, (E) Disease-free survival in patients with negative lymph nodes, and (F) Overall survival in patients with negative lymph nodes.




(C)
Observation
Median 4.9 months (95% CI, 3.8-NA)
Adjuvant chemotherapy
Median 10.6 months (95% CI, 9.0-17.5)
Disease-free survival (%)
100
75
50
25
0
p = 0.038
0
12
24
36
48
Months
Patients at risk
30 5 1 0 0
64 20 4 2 0
0
12
24
36
48
Months


(D)
Observation
Median 17.9 months (95% CI, 14.8-NA)
Adjuvant chemotherapy
Median 27.7 months (95% CI, 21.2-NA)
Overall survival (%)
100
75
50
25
0
p = 0.016
0
12
24
36
48
Months
Patients at risk
30 16 2 0 0
64 45 14 4 0
0
12
24
36
48
Months

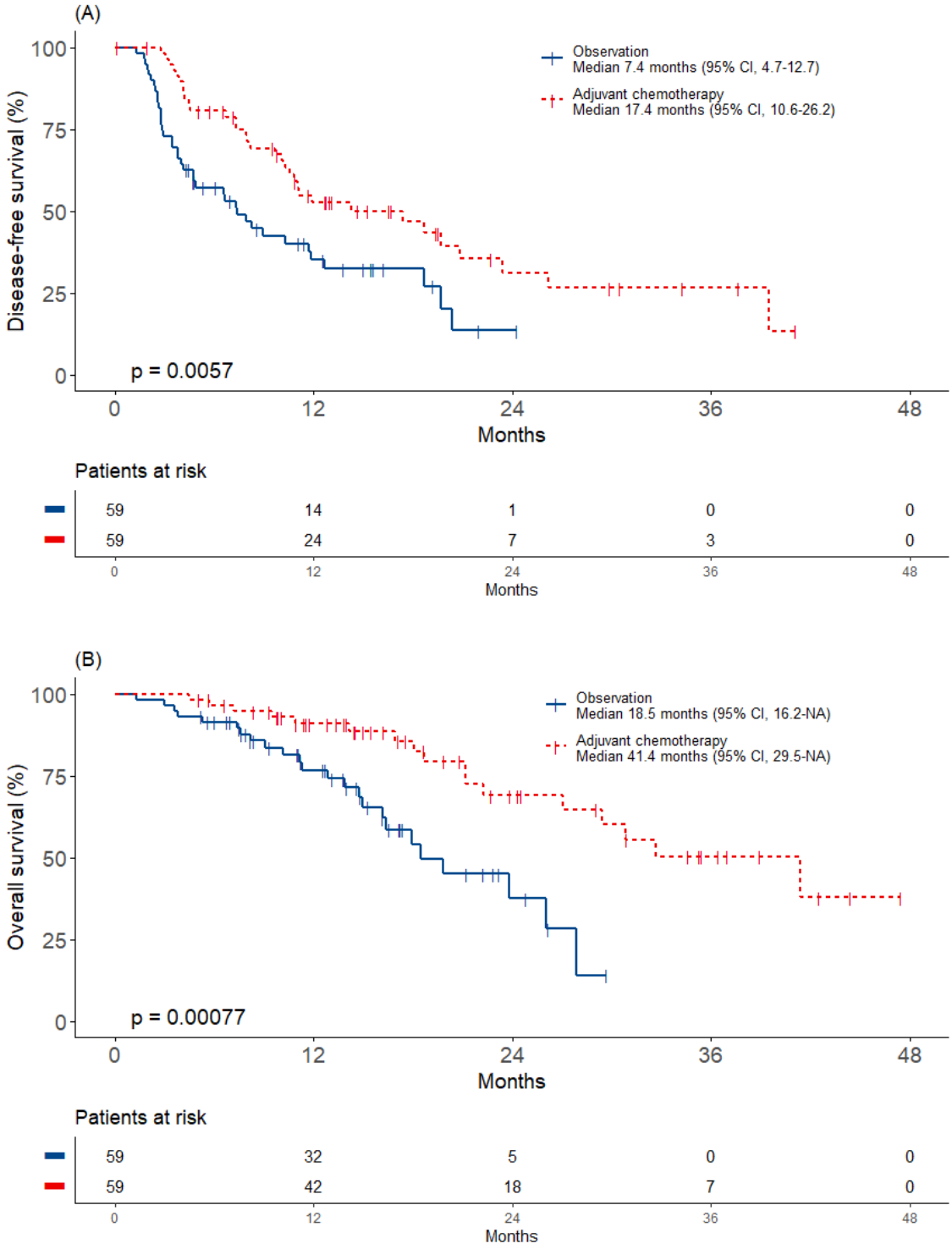

(E)
Observation
Median 11.7 months (95% CI, 7.4-NA)
Adjuvant chemotherapy
Median 19.3 months (95% CI, 13.2-NA)
Disease-free survival (%)
100
75
50
25
0
p = 0.028
0
12
24
36
48
Months
Patients at risk
40 12 1 0 0
85 35 15 9 3
0
12
24
36
48
Months

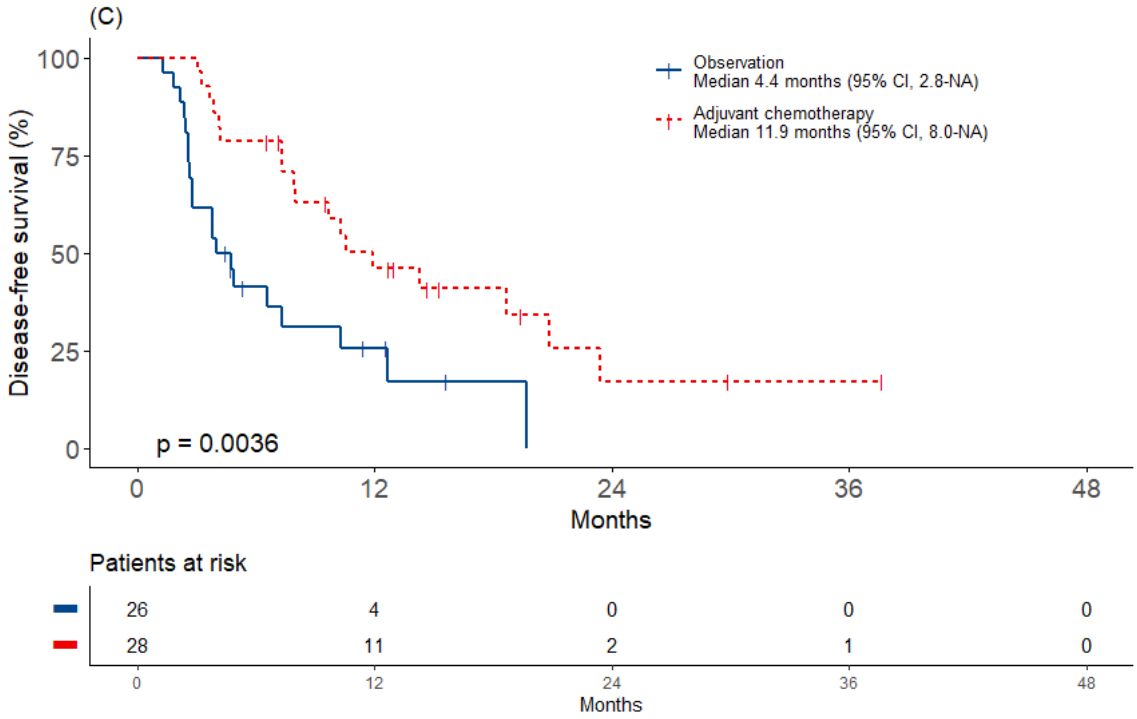

(F)
Observation
Median 26 months (95% CI, 18.5-NA)
Adjuvant chemotherapy
Median Not Reached (95% CI, 33.4-NA)
Overall survival (%)
100
75
50
25
0
p = 0.014
0
12
24
36
48
Months
Patients at risk
40 22 6 0 0
85 57 27 12 4
0
12
24
36
48
Months

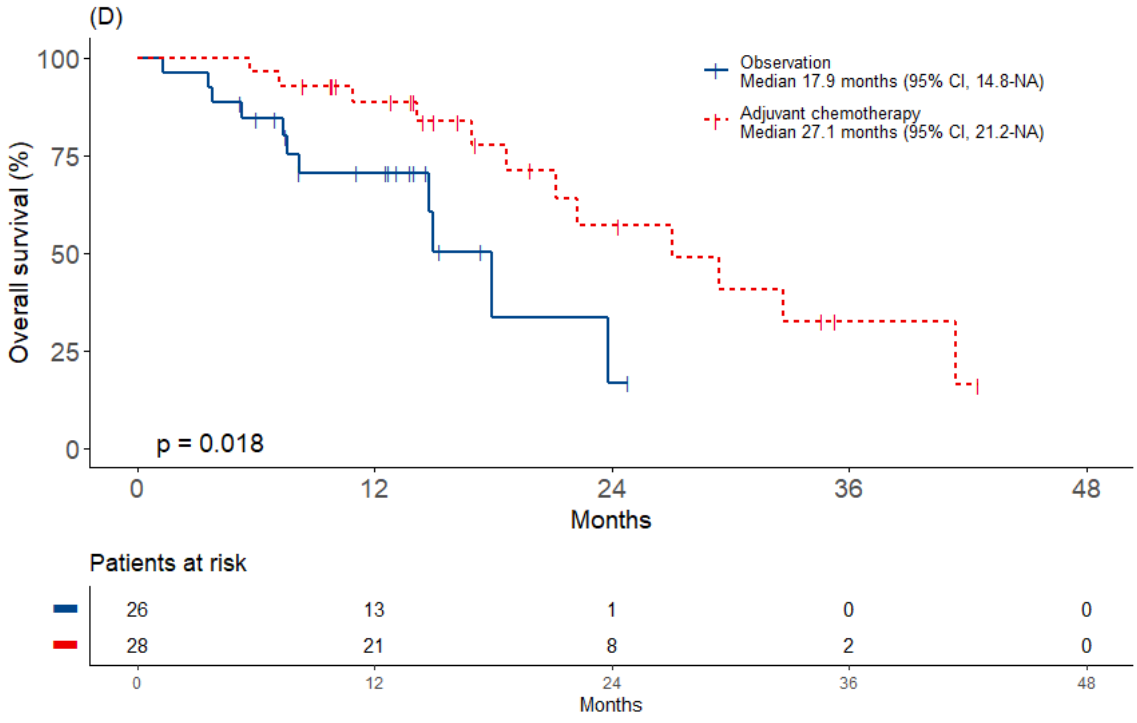
In the PSM cohorts, the survival benefits of adjuvant chemotherapy remained significant: adjuvant chemotherapy vs. observation; a median DFS of 17.4 months (95% CI, 10.6–26.2) vs. 7.4 months (95% CI, 4.7–12.7), respectively (p=0.0057) and a median OS of 41.4 months (95% CI, 29.5–NA) vs. 18.5 months (95% CI, 16.2–NA), respectively (p=0.00077) **(Figure 2. A-B)**.

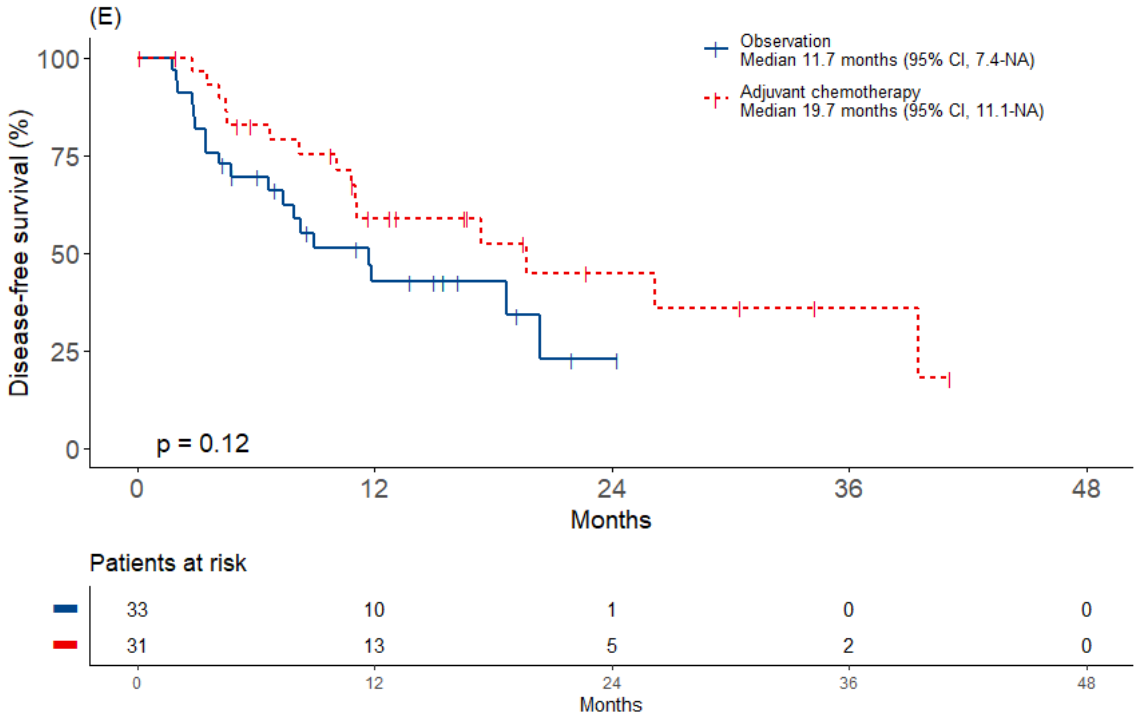
The median DFS and OS were statistically better in the adjuvant chemotherapy group than in the observation group for subgroups of patients with positive and negative lymph nodes, while adjuvant chemotherapy showed a tendency for better DFS than observation in patients with negative lymph nodes (DFS and OS; ypN+, p=0.0036 and p=0.018, respectively, and ypN0, p=0.12 and p=0.0052, respectively) **(Figure 2. C-F)**.

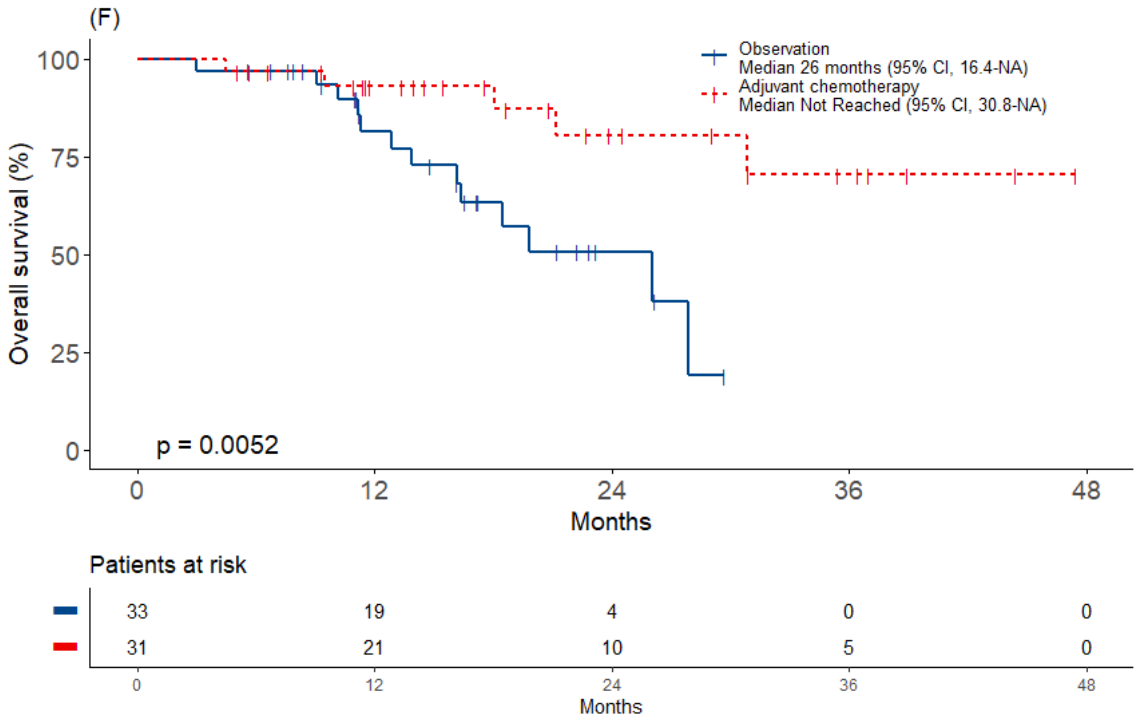
Figure 2. Survival outcomes according to the adjuvant chemotherapy administration in the matched cohort. (A) Disease-free survival in overall patients, (B) Overall survival in overall patients, (C) Disease-free survival in patients with positive lymph nodes, (D) Overall survival in patients with positive lymph nodes, (E) Disease-free survival in patients with negative lymph nodes, and (F) Overall survival in patients with negative lymph nodes.




(C)
Disease-free survival (%)
100
75
50
25
0
Observation
Median 4.4 months (95% CI, 2.8-NA)
Adjuvant chemotherapy
Median 11.9 months (95% CI, 8.0-NA)
p = 0.0036
0
12
24
36
48
Months
Patients at risk
26 4 0 0 0
28 11 2 1 0
0
12
24
36
48
Months


(D)
Overall survival (%)
100
75
50
25
0
Observation
Median 17.9 months (95% CI, 14.8-NA)
Adjuvant chemotherapy
Median 27.1 months (95% CI, 21.2-NA)
p = 0.018
0
12
24
36
48
Months
Patients at risk
26 13 1 0 0
28 21 8 2 0
0
12
24
36
48
Months


(E)
Observation
Median 11.7 months (95% CI, 7.4-NA)
Adjuvant chemotherapy
Median 19.7 months (95% CI, 11.1-NA)
Disease-free survival (%)
100
75
50
25
0
p = 0.12
0
12
24
36
48
Months
Patients at risk
33 10 1 0 0
31 13 5 2 0
0
12
24
36
48
Months


(F)
Observation
Median 26 months (95% CI, 16.4-NA)
Adjuvant chemotherapy
Median Not Reached (95% CI, 30.8-NA)
Overall survival (%)
100
75
50
25
0
p = 0.0052
0
12
24
36
48
Months
Patients at risk
33 19 4 0 0
31 21 10 5 0
0
12
24
36
48
Months

Prognostic factor analysis

The results of the univariate and multivariate analyses for DFS and OS are summarized in **Table 2 and Table 3**. In the multivariate analysis, adjuvant chemotherapy was a significant favorable prognostic factor (DFS, hazard ratio [HR] 0.50 (95% CI, 0.34–0.73, p<0.001); OS, HR 0.35 (95% CI, 0.20–0.60, p<0.001)). In addition, elevated preoperative CA 19-9 levels were significantly associated with worse survival outcomes (DFS, HR 1.99 (95% CI, 1.37–2.89, p<0.001); OS, HR 2.02 (95% CI, 1.21–3.37, p=0.007)). An advanced pathological T stage was significantly associated with a worse OS (HR 2.15, 95% CI, 1.08–4.29, p=0.03).

After PSM, an adjusted HR of adjuvant chemotherapy remained significant (DFS, HR 0.51 (95% CI, 0.32–0.83, p=0.007); OS, HR 0.32 (95% CI, 0.16–0.64, p=0.001)).

Table 2. Univariate and multivariate analysis for disease-free survival

Disease-free survival				
	Univariate analysis		Multivariate analysis	
Variable	HR (95%CI)	P value	HR (95%CI)	P value
Sex				
Female	Ref			
Male	1.09 (0.77-1.55)	0.614		
Age				
< 65	Ref			
≥65	0.99 (0.69-1.42)	0.96		
ECOG PS				
0-1	Ref			
≥2	1.35 (0.59-3.07)	0.477		
Resectabilty				
Resectable	Ref			
BRPC	0.91 (0.48-1.71)	0.768		
LAPC	0.91 (0.45-1.81)	0.782		
Location				
Head	Ref			
Body	1.00 (0.60-1.68)	0.993		
Tail	1.29 (0.78-2.14)	0.329		
Multicenteric	1.31 (0.18-9.44)	0.790		
Tumor differentiation				
Well	Ref			
Moderate	1.57 (0.86-2.86)	0.139		
Poor	1.58 (0.64-3.86)	0.321		
Surgical type				
PPPD/PD	Ref			
Distal pancreatectomy	1.04 (0.69-1.58)	0.844		
Total pancreatectomy	1.31 (0.57-2.99)	0.526		
Vein resection	1.29 (0.91-1.84)	0.152	1.05 (0.73-1.50)	0.812
Artery resection	0.92 (0.54-1.59)	0.774		
Pathological T stage				
ypT0-2	Ref			
ypT3/4	1.40 (0.81-2.39)	0.227		
Pathological N stage				

ypN0	Ref		Ref	
ypN1/2	1.72 (1.21-2.44)	0.003	1.43 (0.98-2.10)	0.063
Lymphovascular invasion	1.69 (1.19-2.42)	0.004	1.42 (0.97-2.09)	0.074
Perineural invasion	1.38 (0.94-2.00)	0.097	1.16 (0.78-1.71)	0.467
Status of surgical margins				
Resection margin negative	Ref		Ref	
Resection margin positive	1.59 (1.02-2.49)	0.041	1.52 (0.96-2.41)	0.074
Number of cycles of neoadjuvant mFOLFIRINOX				
<6cycles	Ref			
≥6cycles	1.11 (0.72-1.72)	0.631		
Best response to neoadjuvant mFOLFIRINOX				
Partial response	Ref			
Stable disease	1.29 (0.86-1.92)	0.213		
Pathologic response				
0-1	Ref		Ref	
≥2	2.02 (1.02-4.00)	0.044	1.16 (0.56-2.39)	0.691
Adjuvant chemotherapy				
No	Ref		Ref	
Yes	0.58 (0.40-0.85)	0.004	0.50 (0.34-0.73)	<0.001
Adjuvant regimen				
No	Ref			
Gemcitabine-based	0.57 (0.35-0.93)	0.024		
mFOLFIRINOX	0.60 (0.40-0.90)	0.014		
CA-19-9 (preoperative)				
Within normal range	Ref			
Elevated	1.86 (1.27-2.73)	0.002	1.99 (1.37-2.89)	<0.001

Abbreviations. ECOG PS=Eastern Cooperative Oncology Group performance score. BRPC=borderline resectable pancreatic cancer. LAPC=locally advanced pancreatic cancer. PPPD=pylorus-preserving pancreaticoduodenectomy. PD=pancreaticoduodenectomy. mFOLFIRINOX=modified FOLFIRINOX

Table 3. Univariate and multivariate analysis for overall survival

Overall survival				
	Univariate analysis		Multivariate analysis	
Variable	HR (95%CI)	P value	HR (95%CI)	P value
Sex				
Female	Ref			
Male	1.21 (0.75-1.98)	0.435		
Age				
< 65	Ref			
≥65	0.99 (0.60-1.65)	0.984		
ECOG PS				
0-1	Ref			
≥2	1.13 (0.35-3.61)	0.84		
Resectabilty				
Resectable	Ref			
BRPC	0.58 (0.26-1.29)	0.182		
LAPC	0.57 (0.24-1.39)	0.216		
Location				
Head	Ref			
Body	0.80 (0.34-1.86)	0.597		
Tail	1.21 (0.63-2.33)	0.570		
Multicenteric	1.63 (0.22-11.88)	0.630		
Tumor differentiation				
Well	Ref			
Moderate	1.29 (0.61-2.70)	0.508		
Poor	1.14 (0.30-4.33)	0.844		
Surgical type				
PPPD/PD	Ref			
Distal pancreatectomy	0.97 (0.55-1.71)	0.915		
Total pancreatectomy	1.41 (0.44-4.56)	0.563		
Vein resection	1.37 (0.84-2.23)	0.212		
Artery resection	1.09 (0.55-2.13)	0.812		
Pathological T stage				
ypT0-2	Ref		Ref	
ypT3/4	2.45 (1.27-4.71)	0.008	2.15 (1.08-4.29)	0.030
Pathological N stage				
ypN0	Ref		Ref	

ypN1/2	1.82 (1.12-2.97)	0.015	1.46 (0.85-2.50)	0.172
Lymphovascular invasion	1.70 (1.05-2.78)	0.033	1.45 (0.84-2.49)	0.184
Perineural invasion	1.66 (0.98-2.81)	0.058	1.28 (0.74-2.23)	0.378
Status of surgical margins				
Resection margin negative	Ref		Ref	
Resection margin positive	1.58 (0.86-2.91)	0.141	1.34 (0.72-2.52)	0.357
Number of cycles of neoadjuvant mFOLFIRINOX				
<6cycles	Ref			
≥6cycles	1.06 (0.55-2.05)	0.863		
Best response to neoadjuvant mFOLFIRINOX				
Partial response	Ref			
Stable disease	1.00 (0.59-1.68)	0.99		
Pathologic response				
0-1	Ref		Ref	
≥2	1.85 (0.79-4.31)	0.155	1.10 (0.45-2.64)	0.838
Adjuvant chemotherapy				
No	Ref		Ref	
Yes	0.43 (0.25-0.73)	0.002	0.35 (0.20-0.60)	<0.001
Adjuvant regimen				
No	Ref			
Gemcitabine-based	0.51 (0.27-0.96)	0.037		
mFOLFIRINOX	0.39 (0.21-0.72)	0.002		
CA-19-9 (preoperative)				
Within normal range	Ref		Ref	
Elevated	2.01 (1.21-3.33)	0.007	2.02 (1.21-3.37)	0.007

Abbreviations. ECOG PS=Eastern Cooperative Oncology Group performance score. BRPC=borderline resectable pancreatic cancer. LAPC=locally advanced pancreatic cancer. PPPD=pylorus-preserving pancreaticoduodenectomy. PD=pancreaticoduodenectomy. mFOLFIRINOX=modified FOLFIRINOX

Discussion

This retrospective study assessed the clinical implications of adjuvant chemotherapy in 219 patients who underwent curative-intent surgery after neoadjuvant mFOLFIRINOX for localized PDAC. In the current study, patients who received adjuvant chemotherapy showed significantly better OS (median 33.4 months vs. 23.8 months) and DFS (median 13.4 months vs. 8.3 months) compared with those who did not. Furthermore, the benefit of adjuvant chemotherapy for DFS and OS was not affected by the status of regional lymph node metastasis. In the multivariate analysis including other prognostic factors, adjuvant chemotherapy was significantly associated with favorable DFS and OS. Its benefit remained significant after PSM.

There are no high-level data supporting the use of adjuvant chemotherapy after neoadjuvant chemotherapy and pancreatectomy. Several retrospective analyses have yielded conflicting results, particularly in the subgroup that benefited from adjuvant chemotherapy [16-22]. Some studies have suggested that postoperative chemotherapy was significantly associated with improved survival for patients with a lower lymph node burden [18, 19], whereas one study reported a survival benefit for patients with lymph node positive disease [20]. These early studies, however, included various drugs as neoadjuvant chemotherapy, and a large proportion of patients received only chemoradiation without chemotherapy for preoperative treatment [18-20]. A retrospective cohort study using the US National Cancer database showed that adjuvant chemotherapy was associated with a longer survival only in patients with a lymph node ratio (LNR) between 0.01 and 0.149, not in node-negative patients or those with a LNR greater than 0.15 [21], and a recent nationwide retrospective study by Kamarajah et al.[16] found that adjuvant chemotherapy was associated with a survival benefit in patients with ypN0 and ypN1, but not ypN2. These studies are limited mainly because of the inclusion of various neoadjuvant chemotherapeutic regimens and treatment modalities. Considering that the efficacy of modern-era multiagent chemotherapy regimens such as FOLFIRINOX or gemcitabine plus nab-paclitaxel has been much improved compared to old-fashioned treatments for patients with PDAC, the study population should be homogeneous in terms of neoadjuvant therapy to avoid potential bias.

Our study was based on a homogeneous study population as we included only patients who underwent neoadjuvant mFOLFIRINOX followed by surgical resection. The only other study that has assessed the role of adjuvant chemotherapy following FOLFIRINOX and surgery was recently published by the European-African Hepato-Pancreato-Biliary Association [17]. This cohort study included 520 patients who underwent surgical resection after neoadjuvant FOLFIRINOX and showed that adjuvant chemotherapy was associated with improved survival only in the lymph node positive subgroup [17].

In contrast, our findings showed that adjuvant chemotherapy was associated with better survival outcomes compared to observation in the overall patient population and in both lymph node positive and negative groups. As there were the discrepancies in the use of adjuvant chemotherapy (mFOLFIRINOX 65.3% in the current study vs. 19.8% in the prior international study and gemcitabine-based chemotherapy (28.7% vs. 58.6%)), this might be a potential reason for discrepancies in the outcomes between these studies. Although there were no significant differences in terms of DFS and OS according to the adjuvant chemotherapy regimens in our study, this could be attributable to the small sample size. Further prospective studies are warranted to establish the evidence in regard to the role of adjuvant chemotherapy and optimal chemotherapy regimens in patients with resected PDAC after neoadjuvant chemotherapy.

In the multivariate analysis, adjuvant chemotherapy remained significant for better DFS and OS. In addition, an elevated preoperative CA 19-9 level was significantly correlated with a worse DFS and OS. Although a relationship was not shown for DFS, an advanced pathological T stage was significantly associated with a worse OS. Prognostic implications of CA 19-9 level and the tumor size have been reported in previous studies [23-26]. Although the number of chemotherapy cycles, tumor differentiation, and pathologic response to neoadjuvant therapy have been suggested as prognostic factors in previous studies [16, 23, 27], these were not significantly associated with DFS and OS in the multivariate analysis in the current study.

Our study has limitations. This was a non-randomized, retrospective study, susceptible to bias. Although PSM was applied to minimize the selection bias, this may not totally exclude the potential biases. Furthermore, patients who could not recover from surgery may be included in the observation group.

Conclusion

In PDAC patients who underwent surgery following neoadjuvant mFOLFIRINOX, adjuvant chemotherapy may be associated with improved survival outcomes. Its benefit was not affected by the lymph node status. These findings suggest that adjuvant chemotherapy could be considered in all patients who have completed neoadjuvant chemotherapy and curative-intent surgery, whenever patients are medically fit for chemotherapy. Further large-scale, multinational, multicenter studies are necessary to confirm our findings.

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국문요약

연구배경 : modified FOLFIRINOX 로 선행항암화학치료 후 완치 목적의 수술을 받은 췌관선암 환자에서 보조항암치료의 이득은 아직 명확히 밝혀지지 않았다. 이 연구는 후향적 연구로서 선행항암화학요법 modified FOLFIRINOX 후 수술을 받은 췌관선암 환자들에서 보조항암치료 시행의 생존연장이득을 분석해보고자 하였다.

연구방법 : 본 연구는 2017 년 1 월부터 2020 년 12 월까지 서울아산병원에서 선행항암화학요법 modified FOLFIRINOX 시행 후 췌장 절제 수술을 받은 219 명의 환자들을 대상으로 하였다. 생존 예후는 보조항암화학요법 투약 유무에 따라 비교하였고, 무질병 생존기간과 전체 생존기간으로 나타내었다. 코호트 균형을 맞추기 위해 propensity score matching (PSM)을 시행하였다.

연구결과 : 149 명 (68.0%)의 환자들이 보조항암화학요법을 투약받았다. 보조항암치료를 받은 환자들은 그렇지 않은 환자들보다 더 적은 횟수의 선행항암화학치료를 받았다 (평균 횟수, 7 vs. 9, p<0.001). 보조항암치료를 받은 환자들은 그렇지 않은 환자들보다 무질병생존기간과 전체생존기간 모두에서 유의하게 향상된 생존 예후를 보였다 (무질병생존기간 13.4 개월(95% CI, 10.7–18.9) vs. 8.3 개월 (95% CI, 4.9–16.0) (p=0.0039), 전체생존기간 33.4 개월 (95% CI, 29.9–not assessable) vs. 23.8 개월 (95% CI, 17.9–not assessable) (p=0.0012)). 각 59 명의 환자들로 구성된 PSM 코호트에서도 보조항암치료 시행의 생존이득은 유지되었다. 무질병생존기간과 전체생존기간은 수술 중 확인된 림프절 전이 여부와 관계없이 보조항암치료를 받은 군에서 유의하게 높았고, 다변량 분석에서 보조항암치료는 무질병생존기간에 대한 위험비 (hazard ratio, HR) 0.50 (95%CI, 0.34–0.73, p<0.001), 전체생존기간에 대한 HR 0.35 (95%CI, 0.20–0.60, p<0.001)으로 좋은 예후인자였다.

연구결론 : 선행항암화학요법 modified FOLFIRINOX 후 수술을 받은 췌관선암 환자에서 보조항암화학요법 시행은 생존 예후 향상과 관련이 있었다. 이는 림프절 전이 여부와 무관하게 나타났다.