Sex Differences in Patients with Metastatic Pancreatic Cancer Who Received FOLFIRINOX

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Research

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Abstract

Background: The combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) is a very effectivechemotherapeutic regimen forunresectable pancreatic cancer.Previous studies have reported that female sex may be a predictor of a better response to FOLFIRINOX. This study was aimed at investigating the clinical outcomes and dose modification patterns of FOLFIRINOX by sex.

Methods: Patients with metastatic pancreatic cancer(MPC) who began FOLFIRINOX as the first-line therapy at Seoul National University Bundang Hospital between 2013 and 2018 were enrolled. The patients received at least four chemotherapy cycles. Local regression and a linear mixed model were used to analyze dose modification patterns by sex.

Results: Ninety-seven patients with MPC (54 men;43 women) were enrolled. In the first FOLFIRINOX cycle,there was a significant difference in age and body surface area between the sexes (58.8 [men] and 64.9 years [women], p =0.005 and 1.7 [men]and 1.6 m^2[women], p < 0.001, respectively). The median progression-free survival (PFS) and overall survival (OS) were 10.8 and 18.0 months, respectively. There was a trend of longerPFS (10.3 [men] and 11.9 months [women], p = 0.153) and a significantly longer OS(17.9[men] and 25.9 months [women], p=0.019)in female patients. During the first year of FOLFIRINOX treatment, there was a significant difference of the age-corrected dose reduction pattern by sex (a mean of 94.3% dose at the initial cycle and -0.34% of dose reduction per week in menversus a mean of 89.3% dose at the initial cycle and -0.51% of dose reduction per week in women, p-value of the slope:<0.001). There was no difference in the adverse event rates between the sexes.

Conclusion: Female patients showed longer OS despite a more rapid dose reduction during each cycle. Sex differences should be considered during FOLFIRINOX treatment.

Introduction

Pancreatic cancer is alethal malignancy and the fourth leading cause of cancer-related death in the United States, with a current 5-year survival rate of only approximately9%.[1]In up to 85% of patients,pancreatic cancer is diagnosed at an advanced stage because of infiltration of the surrounding vessels or distant metastasis.[2]In patients with metastatic pancreatic cancer (MPC), the combination of 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) or gemcitabine and nab-paclitaxel resulted in significantly longer overall survival(OS) than that associated with gemcitabine monotherapy.[3, 4]Furthermore, FOLFIRINOX has shown excellent efficacy in not only palliative but also adjuvant settings,[5]andthis regimenhas been used as the neoadjuvant chemotherapy in several phase III clinical trials.[6] However, the regimen has been associated with a high incidence of adverse events including grade 3 or 4 neutropenia and fatigue.

The effects of sex in cancer treatment are not generally considered in preclinical experiments, clinical trials, or real clinical settings. However, there are differences in the efficacies and toxicities of chemotherapeutic agents between male and female patients.[7] For example, 5-FU, which is the backbone

of the FOLFIRINOX regimen, degraded more slowly and was associated with higher toxicity in female patients.[8, 9] In addition, a previous study reported that female sex may be a predictor of a better response to FOLFIRINOX.[10] However, a secondary analysis within the trial PRODIGE 4/ACCORD 11 did not conclusively show a possible effect of sex on the prognosis of patients receiving FOLFIRINOX.[11] Therefore, the association remains controversial and elucidation is necessary for further evaluation of the effect of sex. The current studywas aimed at investigatingsex differencesin clinical outcomes and dose modification patterns during FOLFIRINOX chemotherapy in patients with MPC.

Materials And Methods

Patients

Patients with MPC who received the first-line FOLFIRINOX between January 2013 and December 2018 at the Seoul National University Bundang Hospital were retrospectively included.The exclusion criteria were as follows: (1) less than four cycles of FOLFIRINOX due to treatment intolerability, adverse events, or a loss to follow up; (2) resectable, borderline resectable, or locally advanced pancreatic cancer at the time of diagnosis; (3) use of FOLFIRINOX as the second-line or later chemotherapy; (4) a history of radiation therapy prior to FOLFIRINOX use; and (5) Eastern Cooperative Oncology Group Performance Score (ECOG PS) of 2 or higher. The clinical and pathological recordsof the patients were obtained from a retrospective review of electronic medical records and pathologic reports. This study was approved by the institutional review board of Seoul National University Bundang Hospital (IRB# B-1907/550-112).

Calculation of the modified dose of FOLFIRINOX

The FOLFIRINOX regimen was administered in 14-day cycles according to the PRODIGE 4/ACCORD 11 trial,[3] and dose reduction or increasing the intervals between cycles was decided by a physician. The response to chemotherapy was evaluated every 8 to 12 weeks by using contrast-enhanced computerized tomography and determining the carbohydrate antigen 19 (CA 19-9) level. Magnetic resonance imaging or positron emission tomography was also used for evaluation if necessary. FOLFIRINOX administration was continued until the patients showed disease progression or treatment intolerability. The relative dose intensity (RDI) of FOLFIRINOX was defined according to its definition in a previous study performed by our group (Fig. 1),[12] in which a modified Hryniuk calculation method was used.[13] Single-agent RDI is the simple proportion of the actualdose delivered compared to the standard dose of eachagent (85,180, 400, and 2400 mg/m^2 for oxaliplatin, irinotecan, 5-FU as a bolus, and 5-FU via continuous intravenous injection, respectively), and multi-drug RDI was the mathematical average of single-agent RDIs.

Study objectives

The primary outcomes were OS and progression-free survival (PFS). The secondary outcomes were the dose modification pattern of FOLFIRINOX according to time and adverse events.Data on adverse events were collected according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

All statistical analyses were performed using R version 3.6.2. Chi-square or Fisher's exact test was used for a comparative analysis of categorical data. According to the time, the dose modification pattern of FOLFIRINOX was evaluated with a local regression (LOESS) and a linear mixed model. Univariable analyses for OS and PFS were performed using the Kaplan–Meier method with log-rank tests. Statistical significance was defined as $p< 0.05$.

Results

Patients

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Discussion

FOLFIRINOX is a 5-FU–based combination chemotherapeutic regimen and very effective for patients with unresectable pancreatic cancer.[3] However, the regimen is associated with considerable grade 3 or 4 toxicities, and dose modification during the treatment is very common. The current study aimed to assess differences in FOLFIRINOX outcomes by sex with regard to not only efficacy but also the amount of chemotherapeutic agents delivered.

Factors such as tumor biology, the immune system,body composition, and drug disposition differ between the sexes. These differences are associated with sex chromosomes, the level of sex hormones,and environmental factors such as nutrition and microbiota.[14] The incidences of several cancers differ by sex, including esophageal and colorectal cancers. Besides differences in incidence or tumor location, drug pharmacology is also different. Fat-free body mass is approximately 80% and 65% in male and female patients, respectively; body composition also differs between the sexes.[15] However, the current doses of chemotherapy are based on body surface area or body mass index, and sex is not considered in the calculation of chemotherapy doses.[14]

5-FU is a drug with substantial inter-individual variability in clearance; the impact of sex on 5-FU clearance is significant, with the exposure in female patients being 26% higher than that in male patients.[16] A previous study showed that women were at a higher risk of grade 3/4 hematologic toxicities of 5-FU, and the higher clearance of 5-FU in men likely explains the higher toxicity of 5-FU in women with colorectal cancer.[9] It was also reported that the clearance of irinotecan in female patients is 30 to 38% less than that in male patients.[17-19]Consequently, adverse events were more frequently observed in women for most regimens.[20]

A recent study about the FOLFIRINOX regimen by sex within the PRODIGE 4/ACCORD 11 trial reported longer median OS (13.1 versus 10.3 months) and PFS (7.2 versus 5.9 months) in women, although the differences between the sexes were not significant ($p = 0.101$ and 0.169, respectively).[11]. Similar outcomes were also reported in another study which showed a longer tendency of PFS (5.0 versus 3.0 months, $p = 0.099$) and a higher disease control rate (91.7 versus 48.0%, $p = 0.001$) in women.[10] Although these studies failed to conclusively show a definite effect of sex on the FOLFIRINOX regimen, they suggested the possibility of an effect. Compared to these studies, in this study, the median OS in the female patients was significantly longer than that in the male patients (25.9 months versus 17.9 months, $p = 0.019$) despite the sex-related differences in PFS being non-significant(11.9 in female patients versus

10.3 months in male patients, p = 0.153). Therefore, our results also suggested the possibility of better outcomes in female patients who received the FOLFIRINOX regimen. Additional research is necessary to determine whether these different outcomesof the FOLFIRINOXregimen are attributable to sex.

In addition to the chemotherapy response, this study focused on dose modification. Compared to previous studies, which only presented the average or median dose of FOLFIRINOX,[12] in this study, we calculated the modified dose for each cycle and compared the pattern of dose modification by sex according to time. As a result, female patients on average received 90% of the original dose in the first cycle and 65% of the original dose at 1 year. The doses seemed vastly different from those administered to male patients, who on average received 95% of the original dose in the first cycle and 83% of the original dose at 1 year. For statistical comparison of the dose modification pattern, a linear mixed model was adopted and the negative slope was significantly different by sex. Considering that there was no difference in the rates of grade 3 or 4 adverse event or number of visits to the emergency department due to chemotherapy-related adverse events, our study suggested that better outcomes could be expected in female patients even with smaller doses of FOLFIRINOX.

There were several limitations of this study. First, it was a retrospective single-center study. Therefore, further studies are necessary for the generalization of our results. Second, the median OS and PFS in this study seemed longer than those in previous studies because the current study excluded patients who underwent fewer than four cycles of FOLFIRINOX for the comparison of the dose modification pattern. Therefore, there was a possibility of selection bias for a good response in both sexes. Third, no pharmacodynamic or pharmacokinetic data were available for the regimen. Lastly, half of the patients received second-line chemotherapy, which was mainly a gemcitabine-based regimen. Therefore, there was a possibility that second-line therapy might contribute to a difference in OS, although the regimens were heterogeneous. In conclusion, female patients showed better survival outcomes in spite of more reduction in the dose of FOLFIRINOX in this study, and more attention should be focused on the effect of sex on FOLFIRINOX treatment in patients with MPC.

Perspectives and Significance

Cancer incidences are increasing and the treatment methods are getting more complex. For a long time, sex differences have not been considered in the development or the real practice, however, they should be considered because sex is one of the basic demographic considerations.

Tables

Table 1
Baseline characteristics of the patients

	Men (N=54)	Women (N=43)	Total(N=97)	p
Age, years				0.005
Median	58.8	64.9	61.1	
Range	55.0-64.2	58.7-69.9	55.9-68.7	
Tumor location, no. (%)				0.211
Head	19 (35.8)	21 (48.8)	40 (41.7)	
Body	7 (13.2)	6 (14)	13 (13.5)	
Tail	26 (49.1)	13 (30.2)	39 (40.6)	
Multiple	1 (1.9)	3 (7)	4 (4.2)	
Metastatic site, no. (%)				0.704
Liver	30 (37.0)	23 (36.5)	53 (36.8)	
Peritoneum	19 (23.5)	10 (15.9)	29 (20.1)	
Lung	7 (8.6)	9 (14.3)	16 (11.1)	
Lymph node	22 (27.2)	19 (30.2)	41 (28.5)	
Bone	3 (3.7)	2 (3.2)	5 (3.5)	
BMI (kg/m^2)				0.248
Median	22.7	24.1	23.1	
Range	20.5-24.9	20.8-26	20.7-25.7	
BSA (m^2)				<0.001
Median	1.7	1.6	1.6	
Range	1.6-1.8	1.5-1.6	1.5-1.8	
CA19-9 (U/mL)				0.413
Median	900.0	620.0	760.0	
Range	192.6-3800.0	64.0-2100.0	118.0-2100.0	
ECOG PS score (%)				0.326
0	21 (38.9)	21 (48.8)	42 (43.3)	
1	33 (61.1)	22 (51.2)	55 (56.7)	
Use of G-CSF				0.647

Yes	46 (85.2)	38 (88.4)	84 (86.6)	
No	8 (14.8)	5 (11.6)	13 (13.4)	
Surgery (%)				0.793
Yes	2 (3.7)	3 (7.0)	5 (5.2)	
No	52 (96.3)	40 (93.0)	92 (94.8)	
Second-line chemotherapy, no. (%)				0.733*
Gemcitabine	4 (7.4)	3 (7.0)	7 (7.2)	
Gemcitabine plus erlotinib	8 (14.8)	4 (9.3)	12 (12.4)	
Gemcitabine plus cisplatin	4 (7.4)	2 (4.7)	6 (6.2)	
Gemcitabine plus nab-paclitaxel	8 (14.8)	7 (16.3)	15 (15.5)	
TS-1	3 (5.6)	7 (16.3)	10 (10.3)	
None	27 (50.0)	20 (46.5)	47 (48.5)	

BMI, body mass index; BSA, body surface area; CA 19-9, carbohydrate antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group performance score; G-CSF, granulocyte colony-stimulating factor; *, second-line chemotherapy vs. no additional chemotherapy

Table 2
Treatment-related grade 3 or 4 adverse events

	Men (N=54)	Women (N=43)	Total(N=97)	p
Hematologic				
Neutropenia	17 (31.5)	20 (46.5)	37 (38.1)	0.192
Febrile neutropenia	6 (11.1)	9 (20.9)	15 (15.5)	0.296
Anemia	0 (0.0)	1 (2.3)	1 (1.0)	0.909
Thrombocytopenia	1 (1.9)	4 (9.3)	5 (5.2)	0.235
Non-hematologic				
Anorexia	1 (1.9)	1 (2.3)	2 (2.1)	>0.99
Nausea	12 (22.2)	8 (18.6)	20 (20.6)	0.853
Vomiting	6 (11.1)	3 (7.0)	9 (9.3)	0.730
Diarrhea	4 (7.4)	2 (4.7)	6 (6.2)	0.892
Fatigue	0 (0.0)	2 (4.7)	2 (2.1)	0.378
Sensory neuropathy	7 (13.0)	3 (7.0)	10 (10.3)	0.531

Table 3
Number of visits to the emergency department due to chemotherapy-related adverse events

	Men (N=54)	Women (N=43)	Total (N=97)	p
				0.239
0	36 (66.7)	25 (58.1)	61 (62.9)	
1~2	17 (31.5)	14 (32.6)	31 (32.0)	
More than 3	1 (1.9)	4 (9.3)	5 (5.2)	

Declarations

Ethics approval and consent to participate

- This study was approved by the institutional review board of Seoul National University Bundang Hospital (IRB# B-1907/550-112).

Consent for publication

- Not applicable

Availability of data and material

- The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

- The authors declare that they have no competing interests.

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Authors' contributions

- Conceptualization; Jinkook Kim and Jaihwan Kim
- Data curation; Jinkook Kim

- Formal analysis; Eunjeong Ji and Jong-chan Lee
- Investigation; Methodology; Kwangrok Jung, In Ho Jung, and Jaewoo Park[1]
- Supervision; Jin Won Kim and Jin-Hyeok Hwang
- Visualization; Eunjeong Ji
- Roles/Writing - original draft; Jinkook Kim
- Roles/Writing - review & editing: Jaihwan Kim

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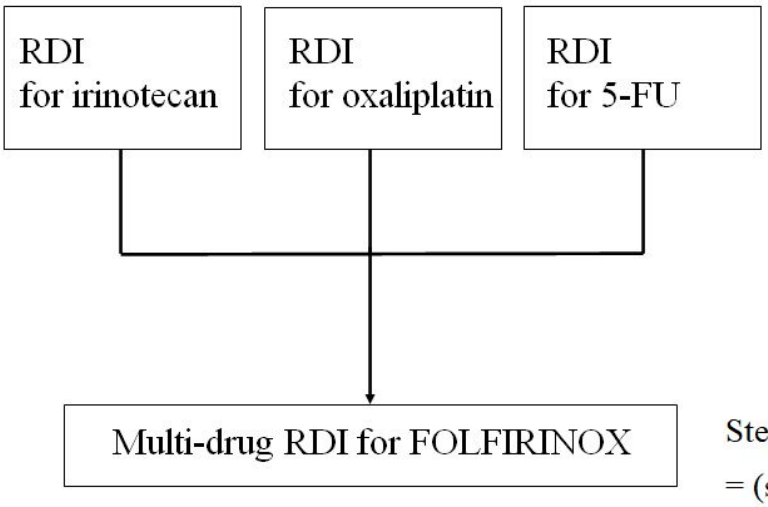
- Not applicable

References

1. 1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:1:7-34.
2. 2. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. 2014;371:22:2140-1.
3. 3. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:19:1817-25.
4. 4. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:18:1691-703.
5. 5. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med. 2018;379:25:2395-406.
6. 6. Lambert A, Schwarz L, Borbath I, Henry A, Van Laethem JL, Malka D, et al. An update on treatment options for pancreatic adenocarcinoma. Ther Adv Med Oncol. 2019;11:1758835919875568.
7. 7. Kim HI, Lim H, Moon A. Sex Differences in Cancer: Epidemiology, Genetics and Therapy. Biomol Ther (Seoul). 2018;26:4:335-42.
8. 8. Milano G, Etienne MC, Cassuto-Viguier E, Thyss A, Santini J, Frenay M, et al. Influence of sex and age on fluorouracil clearance. J Clin Oncol. 1992;10:7:1171-5.
9. 9. Sloan JA, Goldberg RM, Sargent DJ, Vargas-Chanes D, Nair S, Cha SS, et al. Women experience greater toxicity with fluorouracil-based chemotherapy for colorectal cancer. J Clin Oncol. 2002;20:6:1491-8.
10. 10. Hohla F, Hopfinger G, Romeder F, Rinnerthaler G, Bezan A, Stattner S, et al. Female gender may predict response to FOLFIRINOX in patients with unresectable pancreatic cancer: a single institution retrospective review. Int J Oncol. 2014;44:1:319-26.
11. 11. Lambert A, Jarlier M, Gourgou Bourgade S, Conroy T. Response to FOLFIRINOX by gender in patients with metastatic pancreatic cancer: Results from the PRODIGE 4/ ACCORD 11 randomized trial. PLoS One. 2017;12:9:e0183288.

12. 12. Lee JC, Kim JW, Ahn S, Kim HW, Lee J, Kim YH, et al. Optimal dose reduction of FOLFIRINOX for preserving tumour response in advanced pancreatic cancer: Using cumulative relative dose intensity. Eur J Cancer. 2017;76:125-33.
13. 13. Hryniuk W, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol. 1984;2:11:1281-8.
14. 14. Wagner AD, Oertelt-Prigione S, Adjei A, Buclin T, Cristina V, Csajka C, et al. Gender medicine and oncology: report and consensus of an ESMO workshop. Ann Oncol. 2019;30:12:1914-24.
15. 15. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44:10:1051-65.
16. 16. Mueller F, Buchel B, Koberle D, Schurch S, Pfister B, Krahenbuhl S, et al. Gender-specific elimination of continuous-infusional 5-fluorouracil in patients with gastrointestinal malignancies: results from a prospective population pharmacokinetic study. Cancer Chemother Pharmacol. 2013;71:2:361-70.
17. 17. Berg AK, Buckner JC, Galanis E, Jaeckle KA, Ames MM, Reid JM. Quantification of the impact of enzyme-inducing antiepileptic drugs on irinotecan pharmacokinetics and SN-38 exposure. J Clin Pharmacol. 2015;55:11:1303-12.
18. 18. Klein CE, Gupta E, Reid JM, Atherton PJ, Sloan JA, Pitot HC, et al. Population pharmacokinetic model for irinotecan and two of its metabolites, SN-38 and SN-38 glucuronide. Clin Pharmacol Ther. 2002;72:6:638-47.
19. 19. Wu H, Infante JR, Keedy VL, Jones SF, Chan E, Bendell JC, et al. Population pharmacokinetics of PEGylated liposomal CPT-11 (IHL-305) in patients with advanced solid tumors. Eur J Clin Pharmacol. 2013;69:12:2073-81.
20. 20. Cristina V, Mahachie J, Mauer M, Buclin T, Van Cutsem E, Roth A, et al. Association of Patient Sex With Chemotherapy-Related Toxic Effects: A Retrospective Analysis of the PETACC-3 Trial Conducted by the EORTC Gastrointestinal Group. JAMA Oncol. 2018;4:7:1003-6.

Figures



Step 1. Single agent RDI (%)

$$= \frac{\text{administered dose of single agent}}{\text{standard dose of single agent}} \text{ X } 100$$

Step 2. Multi-drug RDI (%)

$$= (sRDI_{ox} + sRDI_{ir} + \frac{sRDIfb + 6 \text{ X } sRDIfc}{7}) \text{ X } 1/3$$

Figure 1

The modified Hryniuk model. 5-FU could be divided into sRDIfb and sRDIfc. The effect of the administration (bolus versus continuous intravenous) was not considered, which means that only the dose (mg) was used for calculations. RDI, relative dose intensity; ox, oxaliplatin; ir, irinotecan; fb, 5-FU bolus; fc, 5-FU continuous intravenous (Figure modified from reference 12).

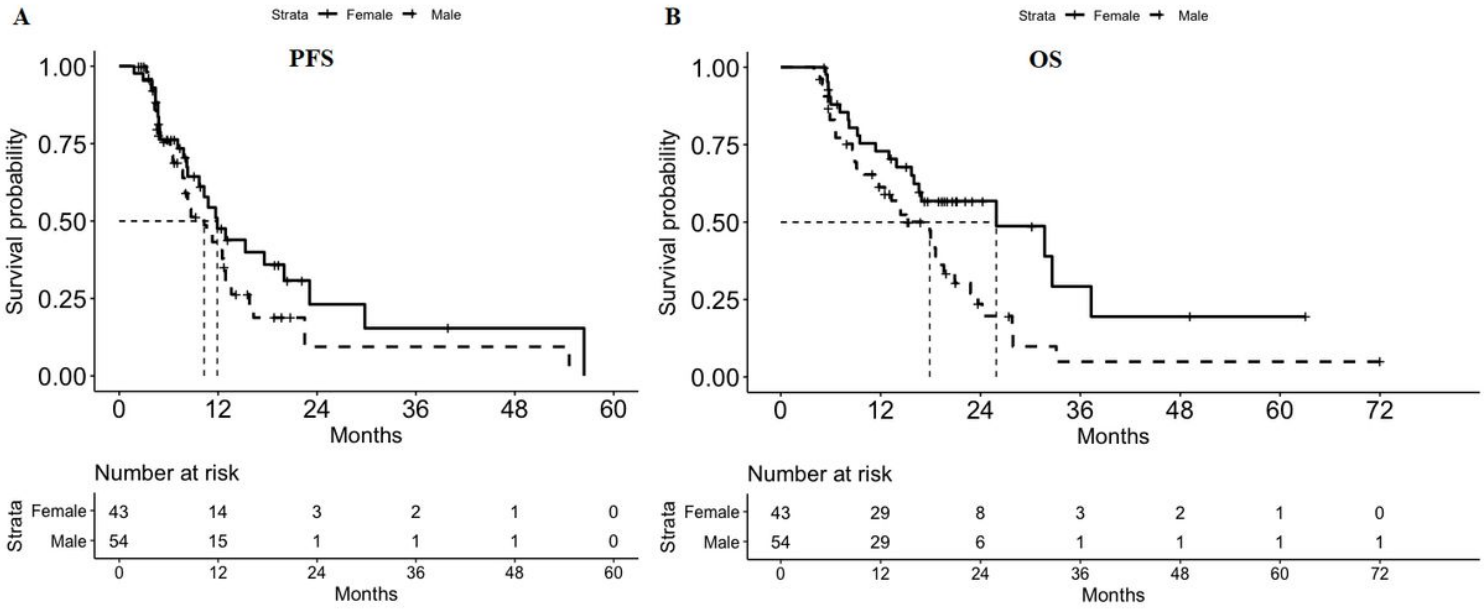


Figure 2

Median progression-free survival (A) and overall survival (B). A, The median PFS of male and female patients was 10.3 and 11.9 months, respectively (p = 0.153). B, The median OS of male and female patients was 17.9 and 25.9 months, respectively (p = 0.019). PFS, progression-free survival; OS, overall survival

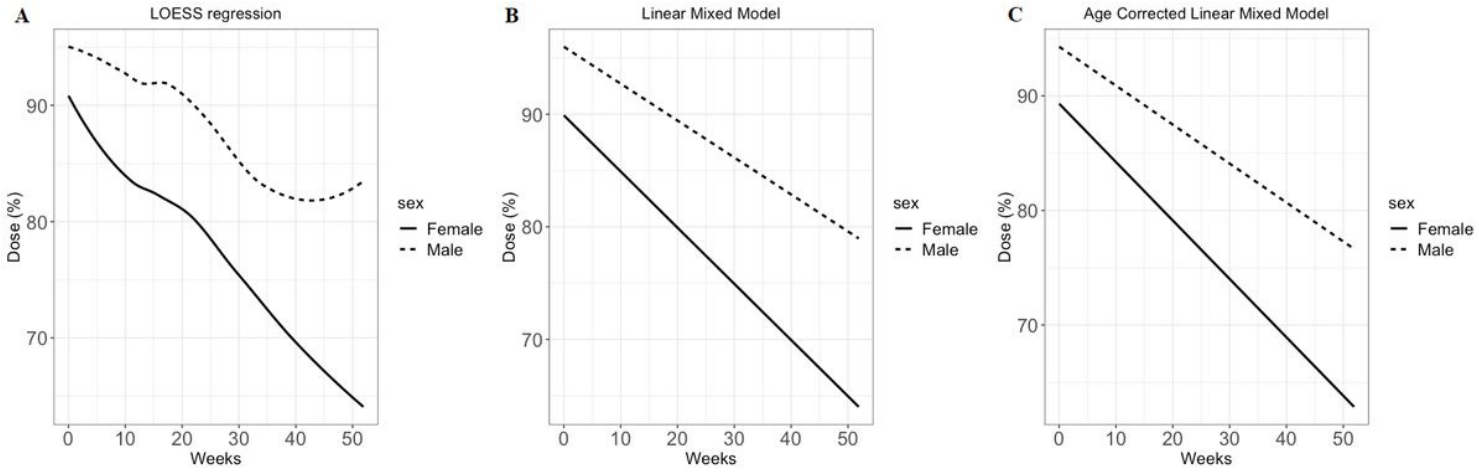


Figure 3

FOLFIRINOX dose modification model. There was a significant difference in the slope between plots B and C (p < 0.001). A, Local regression (LOESS) plot. B, Linear mixed model without age correction. C, Age-corrected linear mixed model.