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ORIGINAL ARTICLE

Efficacy of modified FOLFIRINOX neoadjuvant chemotherapy combined with surgery on resectable pancreatic cancer

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Summary

Purpose: *To explore the clinical efficacy and safety of modified FOLFIRINOX neoadjuvant chemotherapy (NACT) combined with surgery in the treatment of resectable pancreatic cancer.*

Methods: *A total of 88 patients with resectable pancreatic cancer were randomly divided into the NACT group (n=44, treated with preoperative modified FOLFIRINOX NACT combined with surgery) and the control group (n=44, treated with direct surgery). The tumor down-staging after NACT and efficacy and adverse reactions of NACT were analyzed, and the R_0 resection rate, surgery conditions, postoperative complications and changes in the levels of serum tumor markers were compared.*

Results: *In the NACT group, the median cycle of NACT was 6.3 cycles (3-13 cycles), and the effective rate was 50% (22/44). T and N down-staging occurred in 12 cases (31.6%) and 14 cases (36.8%), respectively, and the total down-staging rate reached 36.8% after NACT. The R_0 resection rate in the NACT group was obviously higher than in the control group. In the NACT group, the levels of serum carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) greatly declined after NACT, while they were greatly lower than in the control group at 1 d before surgery. At 7 d after surgery, the levels of serum CA19-9 and CEA markedly declined in the two groups, while they were markedly lower in the NACT group than in the control group. The median overall survival (OS) was 22.6 months and 19.2 months, and the median progression-free survival (PFS) was 13.4 months and 11.5 months, respectively, in the NACT group and the control group. Log-rank test revealed that both OS and PFS in the NACT group were remarkably better than in the control group.*

Conclusion: *Modified FOLFIRINOX NACT is safe and feasible in the treatment of resectable pancreatic cancer, which can effectively reduce the tumor stage, raise the R_0 resection rate, and greatly improve the patient's survival status and disease progression.*

Key words: *modified FOLFIRINOX regimen, neoadjuvant chemotherapy, pancreatic cancer, efficacy*

Introduction

The incidence rate of pancreatic cancer is 90.1/100,000 in China, ranking 10th among all malignant tumors, and its mortality rate is 79.4/100,000, ranking 6th [1]. Pancreatic cancer is highly malignant, and the 5-year survival rate of patients is less than 5%. Radical resection is the only possible means of cure for pancreatic cancer [2]. However, due to the insidious onset and rapid progression, only 20-30% of pancreatic cancers are resectable at the time of diagnosis, whereas borderline resectable pancreatic cancer (BRPC) or unresectable pancreatic cancer is more common [3]. Surgery is still used as the preferred treatment for BRPC by some physicians. However, patients with BRPC have a low R_0 resection rate and far worse prognosis than those with resectable disease. There is increasing

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evidence that preoperative neoadjuvant chemotherapy (NACT) and radiotherapy are effective ways to improve the prognosis of patients [4,5].

At present, FOLFIRINOX has been adopted by the National Comprehensive Cancer Network (NCCN) as the first-line chemotherapy regimen for advanced pancreatic cancer patients with good general conditions [6-8]. However, such a regimen has serious adverse reactions in Asian populations, reducing the patients' quality of life. Therefore, the modified FOLFIRINOX chemotherapy regimen has been studied in some medical centers in China and foreign countries [9-11].The results of a clinical trial showed that the efficacy of modified FOLFIRINOX chemotherapy regimen is comparable to that of the old one, but the incidence rate of grade 3-4 adverse reactions of the former significantly declined [12]. In this study, the clinicopathologic data of 88 patients with resectable pancreatic cancer were retrospectively analyzed, and the efficacy and safety of the modified FOLFIRINOX NACT combined with surgery were analyzed, so as to provide a reasonable basis for clinical decision-making.

Methods

Objects of study

The clinicopathologic data of 88 patients with resectable pancreatic cancer treated in the 2nd Xiangya hospital of Central South University from January 2017 to March 2020 were collected. There were 53 males and 35 females aged 26-76 years old (median 59.6). *Inclusion criteria* were as follows: 1) patients diagnosed with pancreatic ductal adenocarcinoma by histologic and cytologic examinations, 2) those with resectable pancreatic cancer evaluated by CT, MRI and EUS and discussed by a multidisciplinary team, and 3) those with a Karnofsky performance scale (KPS) score ≥70 points. *Exclusion criteria* were as follows: 1) patients unable to undergo NACT due to severe adverse reactions during treatment that could not be greatly improved by symptomatic treatment, 2) those who underwent NACT for <2 cycles, or 3) those with a history of malignant tumors or pancreatic surgery.

According to different treatment methods, the patients were divided into the NACT group (n=44, treated with preoperative modified FOLFIRINOX NACT combined with surgery) and the control group (n=44, treated with direct surgery).There were no statistically significant differences in clinical baseline data between the two groups (Table 1, p>0.05). All patients enrolled were informed of this study in accordance with the *Declaration of Helsinki*, approved by the Hospital Ethics Committee, and signed the informed consent form.

Treatment methods

Modified FOLFIRINOX NACT regimen consisted of 135 mg/m^2 irinotecan, 64 mg/m^2 oxaliplatin, 400 mg/m^2 calcium folinate and 2400 mg/m^2 5-fluorouracil, and it was conducted once every 2 weeks. If there was obstructive jaundice prior to NACT, percutaneous transhepatic cholangial drainage was performed to alleviate jaundice. The levels of alanine aminotransferase, aspartate aminotransferase and total bilirubin were adjusted to ≤1.5 times of normal values and that of albumin >30 g/L, followed by chemotherapy.Upper abdominal computed tomography (CT) or magnetic resonance imaging (MRI) examination were performed to evaluate the effect of previous NACT before each NACT and after every 3 cycles of NACT. During NACT, blood routine and hepatic-renal function examinations were reviewed every 5 d. The chemotherapy regimen was changed in the case of tumor progression or drug resistance.

At 3 weeks after NACT, electrocardiography, chest + abdomen enhanced CT, head MRI, whole body bone scan, blood routine, routine biochemistry, coagulation function, tumor markers and other auxiliary examinations were performed to comprehensively evaluate the

Table 1. Baseline characteristics of the studied patients

Parameters	*NACT group (n=44)* *n(%)*	*Control group (n=44)* *n(%)*	*p value*
Age (years)	58.9±10.3	60.3±9.9	0.517
Gender (Male/ Female)	29/15	24/20	0.384
Tumor location			0.493
Head and neck	32 (72.7)	28 (63.6)	
Body and tail	12 (27.3)	16 (36.4)	
Maximal tumor diameter (cm)	3.6±1.8	3.4±2.0	0.623
Pretreatment pathological stage			0.817
I	3 (6.8)	4 (9.1)	
II	8 (18.2)	9 (20.5)	
III	18 (40.9)	15 (34.1)	
IV	15 (34.1)	16 (36.4)	
Karnofsky performance status	89.3±8.8	87.8±8.4	0.416

NACT: neoadjuvant chemotherapy.

patient's general conditions and tumor burden and assess the feasibility of surgery. According to the tumor site, pancreaticoduodenectomy and pancreatectomy were performed, and vascular resection and reconstruction were combined in the case of involvement of portal vein or superior mesenteric vein.After surgery, the NACT regimen was continued.

Observation indexes

The efficacy was evaluated in accordance with the Response Evaluation Criteria In Solid Tumors (V1.1). Complete response (CR): All target lesions disappear, and the short diameter of metastatic lymph nodes is <10 mm. Partial response (PR): The sum of the long diameter of target lesions is decreased by ≥30%. Stable disease (SD): The sum of the long diameter of target lesions is decreased less than PR, or increased less than progressive disease (PD). PD: The sum of the long diameter of target lesions is increased by ≥20% and the measured value is increased by ≥5mm, or there are new lesions. Objective response rate= (CR + PR)/total cases × 100%.

The NACT adverse events were graded based on the Common Terminology Criteria for Adverse Events (V3.0), and the main adverse reactions were recorded, including gastrointestinal reactions, bone marrow suppression, mild liver damage and peripheral neuropathy. After surgery,pathological TNM staging was based on the American Joint Committee on Cancer (AJCC) pancreatic cancer staging system (8th Edition) [13]. The operation time, intraoperative blood loss, R_0 resection rate, postoperative hospital stay, and incidence rate of postoperative complications were recorded in the two groups. The changes in the levels of serum carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) were determined *via* radioimmunoassay before treatment and at 1 d before surgery, and 7 d and 1 month after surgery.

The patients were followed up till March 2020, and the survival status was recorded. The overall survival (OS) refers to the duration from the first day of treatment to the death or last follow-up. Progression-free survival (PFS) refers to the duration from the first day of treatment to the disease progression or recurrence and metastasis.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation (x±s), and t-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test was performed for intergroup comparison. The survival curves were plotted using the Kaplan-Meier method, and log-rank test was adopted for survival analysis. P<0.05 suggested statistically significant difference.

Table 2. Clinical effective rates and adverse reactions of patients that received neoadjuvant chemotherapy

	Cases (n=44) *n (%)*
Clinical effective rates	
CR	0 (0)
PR	22 (50.0)
SD	16 (36.4)
PD	6 (13.6)
ORR	22 (50.0)
Hematologic toxicities	
Leukocytopenia	27 (61.4)
Neutropenia	23 (52.3)
Lymphopenia	21 (47.7)
Thrombocytopenia	24 (54.5)
Anemia	26 (59.1)
Non-hematologic toxicities	
Fever	19 (43.2)
Nausea and vomiting	31 (70.5)
Diarrhea	26 (59.1)
Anorexia	24 (54.5)
Liver function damage	13 (29.5)
Peripheral neuropathy	7 (15.9)

NACT: neoadjuvant chemotherapy, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: objective response rate.

Results

Short-term efficacy and adverse reactions of NACT

In the NACT group, the median cycle of NACT was 6.3 cycles (3-13), and there were 22 cases of PR, 16 cases of SD and 6 cases of PD. The levels of CA19-9 and CEA continuously rose in 4 PD cases during NACT, and the expansion of primary lesions was confirmed *via* imaging examination, including 1 case of liver metastasis evaluated as primary drug resistance. Among the 6 cases of PD, 3 cases were switched to gemcitabine combined with albumin-bound paclitaxel chemotherapy regimen, and another 3 cases were switched to gemcitabine combined with S-1 chemotherapy regimen. The main adverse reactions of NACT included fever, gastrointestinal reactions, bone marrow suppression, liver damage, anorexia and peripheral neuropathy, and they were improved after symptomatic treatment. No severe adverse reactions affecting the treatment occurred.Grade 3-4 adverse reactions mainly included leukopenia in 6 cases, neutropenia in 3 cases, lymphopenia in 3 cases, thrombocytopenia in 4 cases, nausea and vomiting in 5 cases, diarrhea in 3 cases, and peripheral neuropathy in 2 cases (Table 2).

Comparison of surgery-related indexes and postoperative pathology between the two groups

The operation time was 195.5±47.6 min and 208.4±42.9 min, respectively, in the NACT group and control group, and the difference was not sta-

tistically significant (p=0.185). The NACT group had significantly less intraoperative blood loss and significantly shorter average postoperative hospital stay than the control group [226.1±34.3 mL vs. 247.3±30.9 mL, 14.5±6.9 d vs. 17.4±7.6 d] (p=0.003, p=0.043). The main postoperative complications included incision infection, pancreatic fistula, biliary fistula, delayed gastric emptying, anastomotic bleeding and lymphatic leakage, and the difference in the incidence of complications was not statistically significant between the two groups (p>0.05) (Table 3).

In the NACT group, 38 cases underwent radical pancreatectomy, including 24 cases of pancreaticoduodenectomy, and 14 cases of distal pancreatectomy combined with splenectomy. In the control group, 26 cases underwent pancreaticoduodenectomy, and 18 cases were subjected distal pancreatectomy combined with splenectomy. There were no statistically significant differences (p=0.721). The portal vein and superior mesenteric vein were resected and reconstructed in 9 cases, and the celiac trunk was resected in 2 cases. The R_0 resection rate in NACT group was obviously higher than in the control group [60.5% (23/38) vs. 36.4% (16/44)] (p=0.045). In terms of the postoperative pathological TNM stage, there were 9 cases and 13 cases in stage I-II, 23 cases and 24 cases in stage III, and 6 cases and 7 cases in stage IV, respectively, in the NACT and the control group. In the NACT group, T and N down-staging occurred in 12 cases (31.6%) and 14 cases (36.8%) after surgery compared with that before NACT, and the total down-staging rate reached 36.8%.All patients in the NACT group received chemotherapy after surgery, and the old regimen was continued for 6 patients who did not undergo surgery (Table 4).

Table 3. Comparison of surgical parameters and complications of patients in the two studied groups

Parameters	*NACT group (n=44)*	*Control group (n=44)*	*p value*
Operation time (min)	195.5±47.6	208.4±42.9	0.185
Blood loss (ml)	226.1±34.3	247.3±30.9	0.003
Postoperative hospital stay time (day)	14.5±6.9	17.4±7.6	0.043
Complications, n(%)			
Incision infection	1 (2.3)	2 (4.5)	0.557
Pancreatic fistula	3 (6.8)	5 (11.4)	0.458
Biliary fistula	2 (4.5)	4 (9.1)	0.398
Delayed gastric emptying	6 (13.6)	8 (18.2)	0.560
Anastomotic bleeding	4 (9.1)	7 (15.9)	0.334
Lymphatic leakage	2 (4.5)	3 (6.8)	0.645
Abdominal abscess	1 (2.3)	2 (4.5)	0.557
Ileus	2 (4.5)	3 (6.8)	0.645

NACT: Neoadjuvant chemotherapy.

Table 4. Parameters related to surgery and pathologic details

Parameters	*NACT group (n=38)*	*Control group (n=44)*	*p value*
Surgical method, n(%)			0.721
Pancreaticoduodenctomy	24 (63.2)	26 (59.1)	
Pancreatic body and tail resection + Splenectomy, n(%)	14 (36.8)	18 (40.9)	
Incision margin, n(%)			0.045
R0	23 (60.5)	16 (36.4)	
R1	15 (39.5)	28 (63.6)	
Postoperative TNM staging,n(%)			0.711
I-II	9 (23.7)	13 (29.5)	
III	23 (60.5)	24 (54.5)	
IV	6 (15.8)	7 (15.9)	
Posttreatment T down-staging, n(%)	12 (31.6)		
Posttreatment N down-staging, n(%)	14 (36.8)		

NACT: neoadjuvant chemotherapy.

Comparison of serum tumor markers between the two groups before and after treatment

The levels of serum tumor markers CA19-9 and CEA had no statistically significant differences before treatment between the two groups (p=0.577, p=0.629). In the NACT group, the levels of serum CA19-9 and CEA greatly declined from 613.6±57.0 U/mL and 39.3±5.6 U/mL to 323.9±74.3 U/mL and 24.6±4.2 U/mL, respectively, after NACT, while they were greatly lower than those in the control group 1 d before surgery (p<0.001). At 7 d after surgery, the levels of serum CA19-9 and CEA markedly declined from 202.1±56.2 U/mL and 11.8±3.1 U/mL to 175.7±61.7 U/mL and 10.5±2.7 U/mL, respectively,in the two groups, while they were markedly lower in the NACT group than those in the control group (p=0.039, p=0.038). The above indexes had no statistically significant differences between the two groups 1 month after surgery (p=0.061, p=0.131) (Figure 1).

Follow-up results of patient's survival

All patients were followed up for 5-36 months, (median 22.3 months). The median OS was 22.6 months and 19.2 months, and the median PFS was 13.4 months and 11.5 months, respectively, in the NACT group and control group. The survival curves of patients were plotted using the Kaplan-Meier method (Figure 2). The results of log-rank test revealed that both OS and PFS in the NACT group were remarkably better than those in the control group (p=0.041, p=0.015).

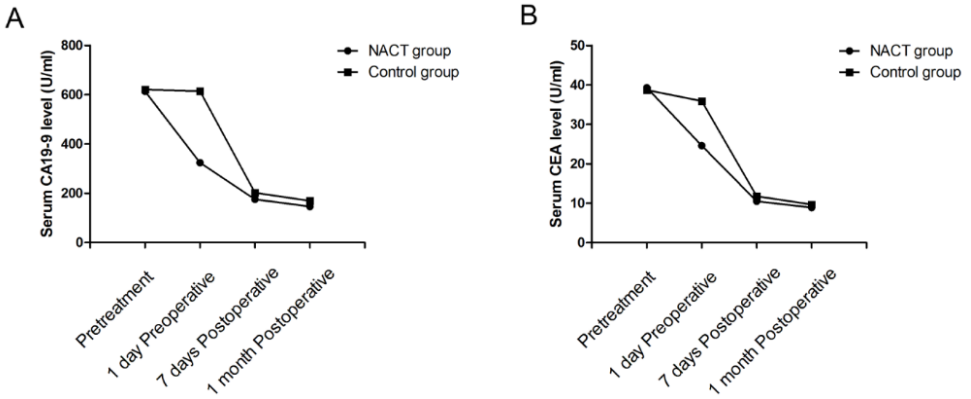

Figure 1. Comparison of pretreatment and posttreatment serum tumor markers of the studied patients. The difference between pretreatment serum CA19-9 **(A)** and CEA **(B)** levels of patients in NACT group and Control group had no statistical difference (p>0.05). Serum CA19-9 **(A)** and CEA **(B)** levels of patients in the NACT group were significantly decreased after neoadjuvant chemotherapy (p<0.05). 1 day preoperative serum CA19-9 CA19-9 **(A)** and CEA **(B)** levels of patients in the NACT group were significantly lower than those of the control group (p<0.001). Serum CA19-9 **(A)** and CEA **(B)** levels of patients in both groups were significantly decreased after surgery (p<0.05). 7 days postoperative serum CA19-9 **(A)** and CEA **(B)** levels of patients in NACT group were significantly lower than those of the control group (p=0.039, p=0.038). The difference between 1 month postoperative serum CA19-9 **(A)** and CEA **(B)** levels of patients in the NACT group and control group had no statistical significance (p>0.05).

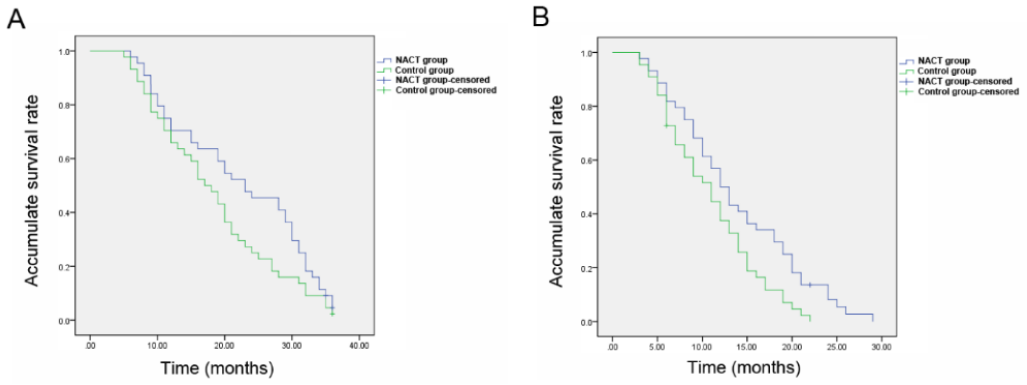

Figure 2. Kaplan-Meier survival curves of patients in the NACT group and control group. The overall survival rate **(A)** and progression-free survival rate **(B)** of patients in theNACT group were significantly higher than those of the control group (p=0.041, p=0.015).

Discussion

Due to the special biological characteristics and anatomic position of pancreatic cancer, its resectable rate is the lowest (about 18%) among digestive system tumors [14]. The prognosis of pancreatic cancer is extremely poor, and the median survival time is only 6.8 months [15]. It is difficult to realize R_0 resection even through surgery, so the NACT of pancreatic cancer has attracted the attention of clinicians. However, the value of NACT remains controversial due to the lack of large-sample and prospective clinical research. The results of a meta-analysis indicated that after NACT, tumor down-staging can be realized in about 1/3 of patients with local by advanced pancreatic cancer, the patients without an opportunity of surgical resection previously can be surgically treated, and some can even achieve R_0 resection [16]. There is a study showing that FOLFIRINOX regimen can effectively improve the target metastasis rate and median survival time of patients with metastatic pancreatic cancer, but the incidence rate of adverse reactions in grade 3 and above is higher [17]. After the dose of irinotecan is reduced from 180 mg/m^2 to 165 mg/m^2, the incidence rates of adverse reactions (grade 3-4 diarrhea and neutropenia) will significantly decline, and the median survival time can still be up to 8 months [18]. Some authors have also pointed out that after the infusion of 400 mg/m^2 fluorouracil is terminated, the incidence rate of neutropenia declines to 3%, and the survival time of patients with metastatic pancreatic cancer is prolonged to about 9 months [19]. According to the NCCN guidelines in 2015, FOLFIRINOX regimen can serve as anNACT regimen for resectable locally advanced pancreatic cancer patients with good physical conditions, but it is also recommended that the regimen be conducted in large medical centers and corresponding clinical trials be carried out[20].

The results of a recent prospective randomized controlled trial revealed that 15 out of 22 pancreatic cancer patients underwent surgery after receiving the FOLFIRINOX, the surgical margins were negative in 14 cases, and the median survival time was 21.7 months currently [10]. In the study of Ferrone et al [21] R_0 resection was realized in 37 out of 40 patients with locally advanced pancreatic cancer after receiving the FOLFIRINOX regimen and there was a lower lymph node positive rate and less nerve invasion. In the study of Khushman et al [22] 51 patients with locally advanced pancreatic cancer underwent surgery after full-dose or decreased-dose FIRFINOX-based concurrent radiochemotherapy, which showed that the median survival time was 35.4 months and the R_0 resection rate is 20%.Bai et al [23] proposed that reducing the dosage of irinotecan and oxaliplatin to 135 mg/m^2 and 68 mg/m^2, respectively, and terminating fluorouracil infusion can be used as an NACT regimen for locally advanced pancreatic cancer, for it is well tolerated by patients, and the R_0 resection rate and 1-year survival rate can reach 50.0% and 57.9%, respectively. In this study, in order to further improve the safety of NACT, the dosage of oxaliplatin was reduced to 64 mg/m^2. The R_0 resection rate in the NACT group [60.5% (23/38)] was obviously higher than that in the control group (p=0.045), and the patients had good tolerance. NACT group had significantly less intraoperative blood loss and significantly shorter average postoperative hospital stay than the control group (p=0.003, p=0.043). The total down-staging rate reached 36.8% after NACT. According to the follow-up results, the median OS was 22.6 months and 19.2 months, and the median PFS was 13.4 months and 11.5 months, respectively, in the NACT and control group. The results of log-rank test revealed that both OS and PFS in the NACT group were remarkably superior to those in the control group (p=0.041, p=0.015).

The modified FOLFIRINOX regimen in this study had a short treatment cycle, and its expenses were lower than that of the gemcitabine combined with albumin-bound paclitaxel, which is easy to be popularized in the clinic. However, as a retrospective study, this study had certain limitations. For example, the sample size was small, and it was difficult to determine the exact number of cycles of modified FOLFIRINOX NACT before surgery. The evaluation criteria for whether the tumor is resectable after NACT, whether the combined or sequential radiotherapy is needed for patients with tumor invasion in local vessels after NACT, and the chemotherapy regimen adopted as adjuvant therapy after surgery should be further determined. In the future, the conclusion in this study needs to be confirmed by more rigorous prospective multicenter randomized studies with a larger sample size.

Conclusions

Modified FOLFIRINOX NACT is safe and feasible in the treatment of resectable pancreatic cancer, and the adverse reactions are tolerable, which can effectively reduce the tumor stage, raise the R0 resection rate, and greatly improve the patient's survival and disease progression.

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Conflict of interests

The authors declare no conflict of interests.

References

1. Chen W, Zheng R, Baade PD et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115-32.
2. Dimitrokallis N, Karachaliou GS, Moris D. New NCCN Guidelines for Locally Advanced Pancreatic Cancer: New Horizons in Extending Resectability. JBUON2020;25:2125-6.
3. Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol 2016;22:9694-705.
4. Versteijne E, Vogel JA, Besselink MG et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg 2018;105:946-58.
5. Heinrich S, Lang H. Neoadjuvant Therapy of Pancreatic Cancer: Definitions and Benefits. Int J Mol Sci 2017;18:1622.
6. Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
7. Li X, Ma T, Zhang Q et al. Modified-FOLFIRINOX in metastatic pancreatic cancer: A prospective study in Chinese population. Cancer Lett 2017;406:22-6.
8. Frigerio I, Regi P, Giardino A et al. Downstaging in Stage IV Pancreatic Cancer: A New Population Eligible for Surgery? Ann Surg Oncol 2017;24:2397-403.
9. Shaib WL, Hawk N, Cassidy RJ et al. A Phase 1 Study of Stereotactic Body Radiation Therapy Dose Escalation for Borderline Resectable Pancreatic Cancer After Modified FOLFIRINOX (NCT01446458). Int J Radiat Oncol Biol Phys 2016;96:296-303.
10. Katz MH, Shi Q, Ahmad SA et al. Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer: Alliance for Clinical Trials in Oncology Trial A021101. JAMA Surg 2016;151:e161137.
11. Stein SM, James ES, Deng Y et al. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. Br J Cancer 2016;114:737-43.
12. Nanda RH, El-Rayes B, Maithel SK, Landry J. Neoadjuvant modified FOLFIRINOX and chemoradiation therapy for locally advanced pancreatic cancer improves resectability. J Surg Oncol 2015;111:1028-34.
13. Chatterjee D, Katz MH, Foo WC et al. Prognostic Significance of New AJCC Tumor Stage in Patients With Pancreatic Ductal Adenocarcinoma Treated With Neoadjuvant Therapy. Am J Surg Pathol 2017;41:1097-104.
14. Ohgi K, Yamamoto Y, Sugiura T et al. Is Pancreatic Head Cancer with Portal Venous Involvement Really Borderline Resectable? Appraisal of an Upfront Surgery Series. Ann Surg Oncol 2017;24:2752-61.
15. Sakin A, Sahin S, Sakin A et al. Assessment of pretreatment albumin-bilirubin grade in pancreatic cancer patients with liver metastasis. JBUON 2020;25:1941-6.
16. Assifi MM, Lu X, Eibl G, Reber HA, Li G, Hines OJ. Neoadjuvant therapy in pancreatic adenocarcinoma: a meta-analysis of phase II trials. Surgery 2011;150:466-73.
17. Vaccaro V, Sperduti I, Milella M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;365:768-9.
18. Blazer M, Wu C, Goldberg RM et al. Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. Ann Surg Oncol 2015;22:1153-9.
19. Mahaseth H, Brutcher E, Kauh J et al. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. Pancreas 2013;42:1311-5.
20. Nitsche U, Wenzel P, Siveke JT et al. Resectability After First-Line FOLFIRINOX in Initially Unresectable Locally Advanced Pancreatic Cancer: A Single-Center Experience. Ann Surg Oncol 2015;22 (Suppl 3):S1212-20.
21. Ferrone CR, Marchegiani G, Hong TS et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 2015;261:12-7.
22. Khushman M, Dempsey N, Maldonado JC et al. Full dose neoadjuvant FOLFIRINOX is associated with prolonged survival in patients with locally advanced pancreatic adenocarcinoma. Pancreatology 2015;15:667-73.
23. Bai X, Su R, Ma T et al. [Modified FOLFIRINOX for advanced pancreatic cancer: a tertiary center experience from China]. Zhonghua Wai Ke Za Zhi 2016;54:270-5.