ARTIGO ORIGINAL

# FOLFIRINOX for advanced pancreatic adenocarcinoma in Brazil: a single-institution experience

## FOLFIRINOX para adenocarcinoma de pâncreas avançado: experiência institucional

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## ABSTRACT

**Objective:** Data is lacking about FOLFIRINOX use for advanced pancreatic ductal adenocarcinoma in emerging countries. The objective of this study was to report outcomes of efficacy and safety in the setting of a South American institution. **Methods:** Patients treated with FOLFIRINOX for metastatic or locally advanced pancreatic cancer at Instituto do Câncer do Estado de São Paulo (Brazil), between November 2012 and January 2016 were retrospectively reviewed. Baseline characteristics, safety, response and overall survival were analyzed. **Results:** Sixty-one patients were enrolled (metastatic disease: 31). Median age was 61 years (range 37-74), and 88.5% had ECOG 0 or 1; 90.2% had T3 or T4 tumors and 36.1% had node-positive disease. FOLFIRINOX was given as the first-line treatment in 88.5% of patients, and was discontinued due to disease progression (55.7%), limiting toxicity (31.1%) or maximum benefit (13.1%). Median number of cycles was 10 (range 1-32). Dose reductions occurred in 81.9%. Grade 3 or 4 toxicity were found in 60.6% and were mainly hematological (36%), neuropathy (19.6%), fatigue (8.2%) and diarrhea (14.7%). Two patients had febrile neutropenia. Hospitalization during treatment occurred in 31.1% of cases, with three potential treatment-related deaths. Median overall survival was 16.26 in the full cohort; 13.6 in patients with metastatic disease, and 18.7 months in locally advanced disease. The response rate was 39.3% (32.2% in metastatic disease and 43.3% in locally advanced disease). **Conclusion:** Despite the high prevalence of grade 3 or 4 toxicities, FOLFIRINOX showed efficacy for the treatment of patients with advanced pancreatic adenocarcinoma, and is an excellent treatment option in emerging countries.

**Keywords:** Pancreatic neoplasms/drug therapy; FOLFIRINOX; Cohort studies; Brazil

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## RESUMO

**Objetivo:** São escassos os dados sobre uso de FOLFIRINOX para adenocarcinoma de pâncreas avançado em países emergentes. O objetivo desse estudo foi reportar os desfechos de eficácia e segurança do uso de FOLFIRINOX para adenocarcinoma de pâncreas avançado em uma instituição terciária Sul-Americana. **Métodos:** Pacientes tratados com FOLFIRINOX para adenocarcinoma de pâncreas avançado ou metastático no Instituto do Câncer do Estado de São Paulo (Brasil), entre Novembro de 2012 e Janeiro de 2016, foram retrospectivamente analisados. As características dos pacientes, dados de segurança, resposta e sobrevida global foram analisadas. **Resultados:** Sessenta e um pacientes foram avaliados (31 com doença metastática). Idade mediana foi de 61 anos (amplitude: 37 a 74 anos) e 88,5% eram ECOG 0 ou 1; 90,2% tinham tumores T3 ou T4, sendo 36,1% doença linfonodo-positiva. FOLFIRINOX foi administrado como primeira linha de tratamento em 88,5% dos pacientes avaliados e interrompido por progressão de doença (55,7%), toxicidade limitante (31,1%), ou benefício máximo (13,1%). O número mediano de ciclos foi 10 (amplitude: 1-32). Reduções de dose ocorreram em 81,9% dos pacientes. Toxicidades grau 3 ou 4 foram encontradas em 60,6% dos pacientes, sendo principalmente toxicidade hematológica (36%), neuropatia (19,6%), fadiga (8,2%), e diarreia (14,7%). Dois pacientes tiveram neutropenia febril. Hospitalização durante o tratamento ocorreu em 31,1% dos casos, tendo ocorrido 3 mortes potencialmente relacionadas ao tratamento. A sobrevida mediana foi de 16,26 meses na coorte completa, tendo sido de 13,6 meses nos pacientes com doença metastática e 18,7 meses na doença localmente avançada. A taxa de resposta foi de 39,3% (32,2% na doença metastática e 43,3% na doença localmente avançada). **Conclusão:** Apesar da alta prevalência de toxicidades grau 3 ou 4, FOLFIRINOX mostrou eficácia no tratamento de pacientes com adenocarcinoma de pâncreas avançado, sendo opção de tratamento em países emergentes.


**Descritores:** Neoplasias pancreáticas/tratamento farmacológico; FOLFIRINOX; Estudos de coortes; Brasil

## INTRODUCTION

Pancreatic ductal adenocarcinoma (PDA) is the fourth most lethal in cancer worldwide, with 41,780 deaths estimated for 2016 in the United States alone. The 5-year survival for this disease is around 8%. Metastatic disease, which accounts to more than half of patients with PDA, presents with even lower survival rates (2.6%).[1,2] In Brazil, 8,070 deaths for pancreatic cancer were registered in 2013.[3]

Relevant improvements were recently achieved in first-line treatment of metastatic pancreatic cancer patients with the publication of two phase III studies showing superiority of FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin),[4] as well as the association of gemcitabine with nab-paclitaxel over gemcitabine alone, considered the standard of care up to that time.[5] In PRODIGE 4/ACCORD 11 trial, FOLFIRINOX was shown to increase median overall survival, progression free survival and objective response rate over gemcitabine, at the expense of a worse toxicity profile. Notwithstanding the significant gains, only a minority of patients with advanced or metastatic PDA fulfills the restrictive criteria of ACCORD 11.[6] The data from MPACT (gemcitabine plus nab-paclitaxel versus gemcitabine) is similar.[7]

During the past few years, many distinct centers have reported their experience with the use of FOLFIRINOX or modified FOLFIRINOX regimens in real-life experience for advanced PDA, with heterogeneous results regarding efficacy and toxicity.[8–19] Indeed, a meta-analysis of 13 studies (11 of them retrospective studies and none of them conducted in developing countries) confirmed the survival improvement

after FOLFIRINOX treatment when compared to gemcitabine in patients with locally advanced pancreatic cancer (LAPC). In this way, reports of FOLFIRINOX administration for advanced PDA in low to mid-income countries and South America are still lacking in the literature and may pose a relevant piece of evidences in everyday clinical decision-making.

**Objectives:** The aim of this study was to report outcomes of efficacy and safety in the setting of a Brazilian large cancer tertiary institution.

## METHODS

### Patients

Data from consecutive patients with histologically proven locally advanced or metastatic pancreatic ductal adenocarcinoma who have received FOLFIRINOX (oxaliplatin 85 mg/m$^2$, irinotecan 180 mg/m$^2$, folinic acid 400 mg/m2, 5-fluorouracil as a bolus of 400 mg/m$^2$ and 2,400 mg/m2 infused in 46 hours - repeated each 2 weeks until maximum benefit, disease progression or unacceptable toxicity at physician's discretion), as described[4], as first, second or third-line treatment regimen were retrospectively assessed after a chart review using the local database of Instituto do Câncer do Estado de São Paulo, Brazil. Only patients who completed at least one full cycle of FOLFIRINOX were included. Histologies other than adenocarcinoma and presence of other active or previous primary neoplasia (except non-melanoma skin cancer) were exclusion criteria for this analysis. Approval by the local Research and Ethics Committee was obtained previously to gathering or analyzing any data (Protocol number: 210/14).

### Assessment and outcomes

We assessed and recorded data on age, gender, date of relapse, use of adjuvant chemotherapy or radiotherapy, location of primary tumor, clinical and radiological staging according to the 7th AJCC, histological grade and differentiation, surgical procedures previously performed, presence of biliary derivations or stents, and Eastern Clinical Oncology Group performance status (ECOG-PS) at time of diagnosis. Data on outcomes after the FOLFIRINOX regimen was collected as well: date of progression or death, number of received cycles, reason of discontinuation, and best response after FOLFIRINOX as defined by RECIST 1.1.[20] CT scans were analyzed by two independent radiologists. The primary endpoint was overall survival; secondary outcomes were safety and response rate after FOLFIRINOX treatment. Adverse events were graded by Common Toxicity Criteria Adverse Events (CTCAE v. 4.0).

### Statistics

Patient characteristics and outcomes were reported with descriptive statistics. Overall survival (OS) was calculated as the date of first dose of FOLFIRINOX to the date of death or last follow-up. Kaplan-Meier estimates were calculated and plotted for OS. Log-rank test and Cox proportional hazard model were used when appropriate to compare time-to-event outcomes. $P < 0.05$ was considered to set statistical significance. All analyses were performed using IBM SPSS version 21.

## RESULTS

### Patient demographics

From November 2012 to January 2016, 61 consecutive patients with LAPC or metastatic PDA who received at least 1 cycle of FOLFIRINOX were identified. Database was closed in July 2016. Patient demographics and tumor characteristics are summarized in table 1. Median age at the beginning of cycle 1 was 61 years (range 37-74) and there was no predominance between the genders. Most patients presented with ECOG-PS 0 (31.1%) or 1 (57.4%). However, we found 9.8% and 1.6% with ECOG-PS 3 or 4, respectively. Many patients were submitted to surgical bypass (39.2%) or biliary stents (32.8%) previous to the treatment.

At the time of analysis, thirty-two patients had metastatic disease and 31 had locally advanced

unresectable disease. Metastatic sites were liver (25 pts - 40.9%), lung (6 pts - 9.8%), peritoneum (21 pts - 34.4%), brain (1 pt - 1.6%) and bones (3 pts - 4.9%). Three patients (4.9%) had histological diagnosis of mucinous adenocarcinoma of the pancreas. Approximately two-thirds (45 pts - 73.8%) of primary tumors were located in the head of pancreas. We found a predominance of T3 and T4 staging (16.4% and 73.8%, respectively). Two patients had T1 and 4 patients had T2 disease. N-positive disease was detected in 22 patients (36.1%). Seven patients (11.1%) had been previously submitted to upfront resection of primary tumor, 6 of them had R0 resections and 4 received adjuvant gemcitabine. No patient received radiotherapy in adjuvant or neoadjuvant setting. Fifty patients had CA19.9 expression (baseline median level = 1277 U/mL); CA 19.9 levels were missing in two patients.

**Treatment with FOLFIRINOX**

As depicted in table 2, the majority of patients had received FOLFIRINOX as first-line treatment (54 pts - 88.5%). Six were treated in second-line (9.8%) and 1 in third-line (1.6%). Median number of completed cycles was 10 (range 1-32). Sixty-four percent (39 pts) received more than 6 cycles; and 13 patients (21.3%) received 1 to 3 cycles. Reasons for discontinuation were disease progression (34 pts - 55.7%), limiting toxicity (19 pts - 31.1%) and maximum benefit (8 pts - 13.1%). Second-line gemcitabine was administered in 23 patients (37.7% of full cohort, and 42.5% when considered only patients who received FOLFIRINOX as the first-line treatment).

**Dose reductions, safety and toxicities**

Dose-reductions were made in the first-cycle in 18 patients (29.5%). Reduction in 1 or more drugs considering all cycles occurred in 50 patients (81.9%). Omission of 5-FU bolus was the most common modification (38 pts - 62.2%), followed by reductions in oxaliplatin (34 pts - 55.7%), reductions in irinotecan (30 pts - 49.1%) and in infusional 5-FU (15 pts - 24.5%). Hospitalization during treatment with FOLFIRINOX occurred 23 times in 19 patients (31.1%; 0.03 hospitalizations/cycle) (Table 2). When considering only patients with ECOG 0 or 1, hospitalizations occurred 20 times in 17 patients (31.4%; 0.03 hospitalizations/cycle). When considering the group of patients that started FOLFIRINOX with up-front dose reductions, 26.6% interrupted chemotherapy due to limiting toxicities, against 28.2% in the group that started with full-dose regimen.

Grade ≥ 3 side effects were reported in 37 patients (60.6%) at any time of treatment (Table 3). Most common grade ≥ 3 side-effects were: hematological (22 pts - 36%), neuropathy (12 pts - 19.6%) diarrhea (9 pts - 14.7%), fatigue (5 pts - 8.2%) and nausea/vomiting (4 pts - 6.5%). Neutropenia grade ≥ 3 occurred in 15 patients (24.6%), and febrile neutropenia in 2 patients (3.2%). Only three patients received filgrastim as preventive measure to neutropenia after FOLFIRINOX. Potential treatment-related deaths were reported in 3 cases (two due to severe colitis and one due to febrile neutropenia).

**Clinical outcomes**

Median OS was 16.26 months (95% CI: 14.58-17.94). In patients with metastatic disease and LAPC, median OS was 13.60 months (95% CI: 8.02-19.17) and 18.70 months (95% CI: 15.25-22.14), respectively. These differences were statistically significant (log-rank test; P = 0.041; HR = 0.556 - 95% CI = 0.31-0.98). Partial responses were found in 24 patients (39.3%) and stable disease in 20 patients (32.8%). No complete responses were detected. One patient with LAPC was submitted to R0 tumor resection after a partial response to 6 cycles of FOLFIRINOX (Table 4).

**CA19.9**

Fifty patients had elevated CA19.9, and median level was 1277 U/mL; CA 19.9 levels were missing in two patients. Twenty-seven patients had >50% decreases in CA 19.9 levels after FOLFIRINOX treatment and there was a trend to increased OS (HR=0.77; 95% CI = 0.40-1.45) in this group (median OS: 19.10 months) when compared with the group who had less than 50% decrease or increase in CA19.9 (median OS: 16.26 months).

**Table 1. Patients demographics and tumor characteristics**

| Characteristic | Result |
|---|---|
| Total | 61 |
| Age - median (range) | 61 (37-74) |
| Sex | |
| Male - n (%) | 30 (49.2) |
| Female - n (%) | 31 (50.8) |
| ECOG-PS- n (%) | |
| 0 | 19 (31.1) |
| 1 | 35 (57.4) |
| 2 | 6 (9.8) |
| 3 | 1 (1.6) |
| Surgical bypass previous to treatment - n (%) | 24 (39.2) |
| Biliary stent previous to treatment - n (%) | 20 (32.8) |
| Status at diagnosis - n (%) | |
| Localized | 8 (13.1) |
| LAPC | 24 (39.3) |
| Metastatic | 29 (47.5) |
| Status at FOLFIRINOX start - n (%) | |
| Metastatic | 31 (50.8) |
| LAPC | 30 (49.2) |
| Location of primary tumor - n (%) | |
| Head | 45 (73.8) |
| Body or tail | 16 (26.2) |
| Tumor staging - n (%) | |
| T1 | 2 (3.3) |
| T2 | 4 (6.6) |
| T3 | 10 (16.4) |
| T4 | 45 (73.8) |
| Tx | 1 (1.6) |
| Node staging - n (%) | |
| N0 | 36 (59) |
| N1 | 22 (36.1) |
| Nx | 3 (4.9) |
| CA19.9 - median | 1277 |

LAPC: locally advanced pancreatic cancer

**Table 2. Characteristics related to FOLFIRINOX treatment**

| Characteristic | Result |
|---|---|
| Number of cycles - median (range) | 10 (1-32) |
| Number of cycles - n (%) | |
| >6 cycles | 39 (64) |
| 4-6 cycles | 9 (14.7) |
| 1-3 cycles | 13 (21.3) |
| Line of treatment - n (%) | |
| First | 54 (88.5) |
| Second | 6 (9.8) |
| Third | 1 (1.6) |
| Reason for discontinuation - n (%) | |
| Maximum benefit | 8 (13.1) |
| Disease progression | 34 (55.7) |
| Limiting toxicity | 19 (31.1) |
| Dose reduction - n (%) | |
| Reduction in the first cycle | 18 (29.5) |
| Reduction in 1 or more drugs | 50 (81.9) |
| Reduction in oxaliplatin | 34 (55.7) |
| Omission of 5-FU bolus | 38 (62.2) |
| Reduction in irinotecan | 30 (49.1) |
| Reduction in infusional 5-FU | 15 (24.5) |
| Hospitalization | 19 (31.1) |
| Use of filgrastim | 3 (4.9) |
| Second-line gemcitabine | 23 (37.7) |

**Table 3. Patients presenting grade ≥3 FOLFIRINOX-related toxicities**

| Toxicity | Result n (%) |
|---|---|
| Grade ≥ 3 toxicity | 37 (60.6) |
| Hematological | 22 (36) |
| Neutropenia | 15 (24.6) |
| Febrile neutropenia | 2 (3.2) |
| Diarrhea | 9 (14.7) |
| Neuropathy | 12 (19.6) |
| Fatigue | 5 (8.2) |
| Acute myocardial infarction | 1 (1.6) |
| Nausea/vomiting | 4 (6.5) |
| Potential treatment-related deaths | 3 (4.9) |

**Table 4. Clinical outcomes after FOLFIRINOX treatment**

| | Full cohort | Metastatic disease N = 31 | LAPC N = 30 |
|---|---|---|---|
| OS - median (95% CI) | 16.2 (14.5-17.9) | 13.60 (8.0-19.1) | 18.7 (15.2-22.1) |
| Response (%) | | | |
| PR | 24 (39.3) | 10 (32.2) | 13 (43.3) |
| CR | 0 | 0 | 0 |
| SD | 20 (32.8) | 7 (22.5) | 12 (38.7) |

**Table 5. Real-world experiences with FOLFIRINOX regimen for advanced pancreatic cancer**

| Study | Year | N | OS (median in months) | Response rate (%) | Serious AEs* (%) |
|---|---|---|---|---|---|
| Mota et al. | 2017 | 61 | Full cohort: 16.26; Metastatic:13.6; LAPC: 18.70 | Full cohort: 39.3; Metastatic: 32.2; LAPC: 43.3 | 60.6 |
| Rombouts et al.[26] | 2016 | 50 | Metastatic: 9.0; LAPC: 14.80 | Full cohort: 25; Metastatic: 32; LAPC: 12 | 52 |
| Chllamma et al. [10] | 2016 | 102 | Metastatic: 12.9; LAPC: 23 | 13 | N/R (43.1% of grade3/4 hematological AEs) |
| Ghorani et al. Δ[13] | 2015 | 18 | 8.9 | 46.7 | N/R |
| Zahir et al.[14] | 2015 | 101 | 10.5 | N/R | N/R |
| Takeda et al. #[12] | 2015 | 10 | N/R | 10 | N/R |
| Moorcraft et al.[15] | 2014 | 49 | 12.9 | 41 | N/R (29% of grade 3/4 neutropenia) |
| Kraemer et al.[16] | 2014 | 16 | 8.45 | 50 | N/R |
| Hohla et al.[17] | 2014 | 49 | 13 | 55.1 | N/R |
| Amireault et al.[9] | 2014 | 46 | 12.6 | N/R | N/R (3 treatment-related deaths) |
| Mahseth et al. †[18] | 2013 | 60 | 16.4 | 30 | 40 |
| Gunturu et al.[11] | 2013 | 35 | not reached | 48 | 2.9 |
| Peddi et al.[8] | 2012 | 61 | 13.5 | 25 | N/R (19.7% of hematological AEs) |

* G3, G4 or G5 AEs; # Only Japanese patients; used a modified (m)FOLFIRINOX scheme as follows: oxaliplatin at 85 mg/m2, leucovorin at 200 mg/m2 and irinotecan at 150 mg/m2, followed by continuous infusion of 5-FU over 46 hours at 2,400mg/m2; N/R means not reported; @ This study did not report the rate of all G3 and 4 AEs, however the reported rate of G3 and 4 hematologic AEs was 43.1 %; Δ used a modified (m)FOLFIRINOX scheme as follows: oxaliplatin at 85 mg/m2, leucovorin at 400 mg/m2 and irinotecan at 135 mg/m2, followed by continuous infusion of 5-FU over 46 hours at 2,400mg/m2, with routine filgrastim; † used a mFOLFIRINOX regimen: oxaliplatin 85 mg/m2, leucovorin 400 mg/m2, irinotecan 180 mg/m2 and 5-FU 2400 mg/m2 over 46 hours with routine pegfilgrastim at D+3

## DISCUSSION

The present study retrospectively reviewed patients with LAPC or metastatic PDA treated with FOLFIRINOX at Instituto do Câncer do Estado de São Paulo, a large public Cancer Center in Brazil. Median OS was 16.26 months (13.6 months in metastatic and 18.7 in LAPC disease). As detailed in table 5, our results are consistent with others, acknowledging all caveats surrounding cross-studies comparisons. The median OS in the pioneer PRODIGE study was 11.1 months in the FOLFIRINOX group. The fact that PRODIGE included only patients with metastatic PDA may be among the factors that would explain our study with slightly higher median OS detected.[4]

Despite baseline CA19.9 and a decrease in CA19.9 levels having been shown to correlate with response after FOLFIRINOX treatment,[10,17,21] we only detected a non-significant trend in increased OS after a 50% decrease in CA19.9 levels, perhaps due to the small sample size.

Significant differences in outcomes between patients with LAPC and metastatic disease (median OS: 13.6 vs 18.7 months; HR = 0.55; p = 0.041) were detected in our cohort. Accordingly, a Canadian retrospective study (median OS: 14 months in metastatic disease and 18.4 months in LAPC) [22] and the Royal Marsdem experience showed similar results (median OS: 10.4 months in metastatic disease and 18.4 months in LAPC).[15] These similarities in outcomes between our study and others are of particular relevance, specially considering ours was conducted in an emerging country. On the other side, a Pakistani study assessed patients with metastatic PDA who have received FOLFIRINOX and found a median OS of 10.5 months and median PFS of 7.3 months.[23]

The majority of patients received FOLFIRINOX as first-line treatment; but almost 10% received FOLFIRINOX as second-line treatment. In this cohort, dose reductions were common and occurred in 29.5% in the first cycle and in 81.9% considering all cycles. Small single-center experiences detected similar outcomes and acceptable toxicities after removing the 5-FU bolus [18] or reducing irinotecan dose to 135 mg/m2[13] in the original FOLFIRINOX scheme. A phase 2 study evaluated a modified FOLFIRINOX regimen (25% reduction in 5-FU bolus and irinotecan) and showed similar survival outcomes with reduced adverse events comparing to the historical controls.[24] In the present study, hospitalization during treatment with FOLFIRINOX occurred in 31.1% of patients; the main cause was sepsis/infection, and this is in consonance with other reports.[8–10] No catheter complications were detected.

Serious adverse events (grade ≥ 3) occurred in 60.4% of patients and led to limiting toxicity as the reason for discontinuing FOLFIRINOX in 31.1% of analyzed patients. Major toxicities were neutropenia, diarrhea, neuropathy and fatigue. Importantly, we detected 3 potential treatment-related deaths. The rate of grade 3 or more adverse events was apparently higher than other previous reports.[10,13] For example, in the Royal Marsdem cohort, limiting toxicity was considered a reason for discontinuation in only 4%.[15] Filgrastim was administered in only 4.9% of patients. This is a provocative finding, if we consider that our cohort had 24.6% grade 3 or 4 neutropenia and only 2 patients with febrile neutropenia. In the PRODIGE study, which led the approval of FOLFIRINOX for advanced PDA, 42.5% of patients received filgrastim and febrile neutropenia occurred in 5.4% of them.[4] Furthermore, a small retrospective study showed the incidence of G3/4 neutropenia as 33% of patients receiving FOLFIRINOX and prophylactic G-CSF.[25] The increased flexibility to dose reduce or interrupt chemotherapy in the real-world scenario may have contributed to these potential differences.

Our study has several limitations. First, the retrospective assessment may produce biases, such as patient selection and inaccuracies in data collections. Because there were no standardized methods for dose reductions and FOLFIRINOX interruption, these were made at physician's discretion.

## CONCLUSIONS

In summary, the present retrospective study provided relevant insights into the safety and clinical outcomes of FOLFIRINOX treated in an emerging country in South America. Considering the limitations of a retrospective analysis, this study supports the efficacy of FOLFIRINOX without routine filgrastim against advanced PDA in good-performance status patients, despite high rates of hospitalization, dose reductions and toxicities. These findings may increase the notion that FOLFIRINOX should be offered to fit patients in centers where emergency care is promptly available.

**Author´s Contributions**

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## REFERENCES

1. SEER Cancer Statistics Factsheets: Pancreas Cancer. National Cancer Institute. Bethesda, MD. 2016.

2. Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2013. Ann Oncol. 2013;24(3):792–800.

3. Instituto Nacional de Cancer (INCA). Sistema de Informação de Mortalidade/Brazil. 2013.

4. 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.

5. 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.

6. Ho MY, Kennecke HF, Renouf DJ, Cheung WY, Lim HJ, Gill S. Defining Eligibility of FOLFIRINOX for First-Line Metastatic Pancreatic Adenocarcinoma (MPC) in the Province of British Columbia: A Population-based Retrospective Study. Am J Clin Oncol. 2017;40(6):552-554.

7. Peixoto RD, Ho M, Renouf DJ, Lim HJ, Gill S, Ruan JY, et al. Eligibility of Metastatic Pancreatic Cancer Patients for First-Line Palliative Intent nab-Paclitaxel Plus Gemcitabine Versus FOLFIRINOX. Am J Clin Oncol. 2015 Am J Clin Oncol. 2017;40(5):507-511.

8. Peddi PF, Lubner S, McWilliams R, Tan BR, Picus J, Sorscher SM, et al. Multi-institutional experience with FOLFIRINOX in pancreatic adenocarcinoma. Journal of Oncology Practice. 2012;13(5):497–501.

9. Amireault C, Beaudet J, Gaudet G, Raymond N, Ayoub J-PM, Letourneau R, et al. FOLFIRINOX in the real-world setting: The multicentric experience of six Canadian institutions. J Clin Oncol. 2014;3(Suppl 3):abstr 367.

10. Chllamma MK, Cook N, Dhani NC, Giby K, Dodd A, Wang L, et al. FOLFIRINOX for advanced pancreatic cancer: the Princess Margaret Cancer Centre experience. Br J Cancer. 2016;115(6):694–54.

11. Gunturu KS, Yao X, Cong X, Thumar JR, Hochster HS, Stein SM, et al. FOLFIRINOX for locally advanced and metastatic pancreatic cancer: Single institution retrospective review of efficacy and toxicity. Med Oncol. 2013;30(1):361.

12. Takeda Y, Katsura Y, Ohmura Y, Morimoto Y, Ishida T, Motoyama Y, et al. FOLFIRINOX Combination Chemotherapy in Patients with Metastatic or Recurrent Pancreatic Cancer--A Single Institution Experience. Gan To Kagaku Ryoho. 2015;42(12):2360–3.

13. Ghorani E, Wong HH, Hewitt C, Calder J, Corrie P, Basu B. Safety and Efficacy of Modified FOLFIRINOX for Advanced Pancreatic Adenocarcinoma: A UK Single-Centre Experience. Oncol. 2015;89(5):281–7.

14. Zahir MN, Jabbar AA. Metastatic Pancreatic Carcinoma and Experience with FOLFIRINOX - a Cross Sectional Analysis From a Developing Country. Asian Pac J Cancer Prev. 2015;16(14):6001–6.

15. Moorcraft SY, Khan K, Peckitt C, Watkins D, Rao S, Cunningham D, et al. FOLFIRINOX for locally advanced or metastatic pancreatic ductal adenocarcinoma: The royal marsden experience. Clin Colorectal Cancer. 2014;13(4):232–8.

16. Kræmer PC, Schmidt HH, Ladekarl M. Danish experiences with FOLFIRINOX as first-line therapy in patients with inoperable pancreatic cancer. Dan Med J. 2014;61(4):A4819.

17. Hohla F, Hopfinger G, Romeder F, Rinnerthaler G, Bezan A, Stättner 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.

18. Mahaseth H, Brutcher E, Kauh J, Hawk N, Kim S, Chen Z, et al. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. Pancreas. 2013;42(8):1311–5.

19. Petrelli F, Coinu A, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, et al. FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta-analytical review of published studies. Pancreas. 2015 May;44(4):515–21.

20. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47.

21. Pelzer U, Hilbig A, Sinn M, Stieler J, Bahra M, Dörken B, et al. Value of Carbohydrate Antigen 19-9 in Predicting Response and Therapy Control in Patients with Metastatic Pancreatic Cancer Undergoing First-Line Therapy. Front Oncol. 2013;3:155.

22. Amireault C, Ayoub J-PM, Beaudet J, Gaudet G, Letourneau R, Loungnarath R, et al. FOLFIRINOX in the real world setting: The multicentric experience of six Canadian institutions. J Clin Oncol. 2014;(Suppl): abstr 367.

23. Zahir MN, Jabbar AA. Metastatic Pancreatic Carcinoma and Experience with FOLFIRINOX - a Cross Sectional Analysis From a Developing Country. Asian Pac J Cancer Prev. 2015;16(14):6001–6.

24. Stein SM, James ES, Deng Y, Cong X, Kortmansky JS, Li J, et al. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. Br J Cancer. 2016;114(7):737–43.

25. Terazawa T, Goto M, Miyamoto T, Asaishi K, Shimamoto F, Kuwakado S, et al. Efficacy of Prophylactic G-CSF in Patients Receiving FOLFIRINOX: A Preliminary Retrospective Study. Intern Med. 2015;54(23):2969–73.