ORIGINAL RESEARCH

Enhanced Survival Outcomes with FOLFIRINOX in Initial Metastatic Pancreatic Cancer: Single-Center Study

Emir Sokolovic[1], Amil Druzic[1*], Una Stojanovic[1], Elma Kapisazovic[1], Emina Borovac-Gurda[1], Jasmina Redzepagic[4], Amina Aljic[3], Mattar Layan[3], Sejla Ceric[5], Berisa Hasanbegovic[1], Anes Pasic[2], Semir Beslija[1]

[1]Clinic of Oncology, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[2]Clinic of Oncology, Clinical Center University of Maribor, Maribor, Republic of Slovenia
[3]Faculty of Medicine, University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[4]Clinic of Pathology, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[5]Clinic for Nuclear Medicine, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

Corresponding Author: Amil Druzic, MD. Clinic of Oncology, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina; E-mail: amil.druzic@gmail.com; Phone: +387 66260904 ; ORCID ID: 0009-0008-5198-6902.

Pages: 75 - 81 / Published online: 27 December 2024

Cite this article: Sokolovic E, Druzic A, Stojanovic U, Kapisazovic E, Borovac-Gurda E, Redzepagic J, et al. Enhanced Survival Outcomes with FOLFIRINOX in Initial Metastatic Pancreatic Cancer: Single-Center Study. Sar Med J. 2024; 1(2): Online ahead of print. DOI: 10.70119/0020-24

Original submission: 15 October 2024; **Revised submission:** 17 November 2024; **Accepted:** 29 November 2024

Abstract

Introduction. The aim of this article is to evaluate the efficacy and outcomes of FOLFIRINOX as a first-line treatment for initial metastatic pancreatic cancer patients at the Clinical Center University of Sarajevo.

Methods. The research presents a retrospective analysis was conducted on 33 patients treated with FOLFIRINOX, between January 2021 and January 2023. Baseline characteristics, tumor markers (CEA, CA 19-9, CA 125), neutrophil-to-lymphocyte ratio (NLR), neutrophil-to-platelet ratio (NPR) and initial metastatic site were evaluated using Cox regression analysis in order to identify predictive and prognostic factors for progression-free survival (PFS) and overall survival (OS).

Results. The median age of patients was 64 (range 38-76). There were 18 males and 15 females. The median OS was 21.7 months (95% CI, 10.5-32.9) and the median PFS was 10.0 months (95% CI, 8.2-11.8). A statistically significant negative correlation was found between NLR and OS (r=-0.464, p=0.045). Patients with initial liver metastasis had a numerically worse median OS (16.3 months, 95% CI, 5.1-27.5), compared to those with non-liver metastasis (OS not reached, p=0.058). Tumor markers, NLR, NPR, and initial metastatic site were not independent predictors of PFS and OS.

Conclusion. FOLFIRINOX demonstrates significant efficacy in treating metastatic pancreatic cancer in a real-world setting. Personalized approaches, including genetic profiling and microbiome analysis, along with AI integration, offer promising avenues to enhance treatment outcomes and quality of life for patients.

Keywords: metastatic pancreatic cancer, enhanced outcomes, overall survival, progression-free survival.

INTRODUCTION

Pancreatic cancer is acknowledged as one of the most formidable challenges in oncology, characterized by its aggressive progression and poor prognosis. The disease is among the poorest in terms of prognosis and the disease ranks as the sixth leading cause of cancer mortality in both sexes combined (1).

Taking into account the advances in medical research, the five-year survival rate has recently improved by approximately 13% – a moderate but significant increase which reflects improvements in treatment and early detection methods (2). However, for patients with unresectable pancreatic cancer, the five-year survival rate remains below 5%, implying the particularly dire prognosis for those whose cancer cannot be surgically removed (2). In the United States, the projected figures for 2024 indicate 66,440 new cases and 51,750 deaths, emphasizing the deadly nature of this disease (2). In Bosnia and Herzegovina, the situation mirrors the global challenge, with estimated 502 new cases and 489 deaths reported in 2022, suggesting a high fatality rate that nearly matches the incidence (3).

Considering the recent advancements in treatment, FOLFIRINOX has emerged as a crucial therapy for metastatic pancreatic cancer. Introduced in the early 2010s, FOLFIRINOX presents a combination regimen of fluorouracil, leucovorin, irinotecan and oxaliplatin. The ACCORD trial, published in 2011, demonstrated that FOLFIRINOX significantly extended median overall survival to 11.1 months, compared to 6.8 months for patients treated with gemcitabine, marking a valuable improvement in the management of this disease (4). Despite its intense side effects and the necessity for careful patient selection, FOLFIRINOX is a good example of the shift in the approach towards aggressive combination therapies that target multiple aspects of tumor growth and survival, with the aim of extending lifespan and improving the quality of life for patients suffering from this devastating disease.

Besides the recent promising increase in survival rates, there is also an ongoing need for advancements in both therapeutic approaches as well as diagnostic techniques, in order to change the overall dismal survival statistics. The American Society of Clinical Oncology (ASCO) guidelines emphasize the importance of early testing for actionable genomic alterations in patients who are likely to become candidates for additional treatment after the first-line therapy. This includes testing for microsatellite instability, mismatch repair deficiency, BRCA mutations and NTRK gene fusions (5).

Pancreatic Ductal Adenocarcinoma (PDAC) patients with somatic/germline mutations in the DNA Damage Repair (DDR) pathway, such as BRCA1, BRCA2 and PALB2, may benefit from platinum-based therapies and PARP inhibitors such as Olaparib. Similarly, KRAS mutations, prevalent in about 95% of PDAC cases, are being targeted with the new therapeutics like Sotorasib and Adagrasib, which have shown promising results in many clinical trials. Besides that, immunotherapy is showing up as a potential treatment for a subset of PDAC patients with mismatch repair deficiency (dMMR) and/or high microsatellite instability (MSI-H), within which medications like Pembrolizumab demonstrate particular efficacy. These advancements underscore the importance of personalized medicine in the future management of pancreatic cancer, setting the ground for better outcomes through targeted and immune-based therapies (6).

An additional advantage of early testing for actionable genomic alterations is the opportunity it provides for patients to qualify for clinical trials specifically targeting these genetic changes.

METHODS

Patients and Study Design

This retrospective cohort study was conducted at the Clinic of Oncology, Clinical Center University of Sarajevo. We included patients diagnosed with initially metastatic pancreatic cancer who were treated from January 2021 to January 2023. The stu-

dy aimed to evaluate the efficacy of FOLFIRINOX as a first-line treatment and to identify potential predictive and prognostic biomarkers.

Methods

Within the study, 33 patients with a confirmed diagnosis of initially metastatic pancreatic cancer were included. Eligibility for inclusion required patients to be treated with FOLFIRINOX as their first-line treatment. We excluded patients deemed unfit for FOLFIRINOX based on predefined clinical criteria including performance status and organ function tests. The criteria for being deemed unfit were rigorous and aligned with the latest oncological guidelines.

Data were collected retrospectively from electronic medical records and patient files, thoroughly maintained by the Clinic of Oncology. We extracted demographic information, clinical history, treatment details and follow-up outcomes. The primary collected variables included:

The primary analyzed outcomes were overall survival and progression-free survival, defined from the start of the treatment to the date of the last follow-up or death.

We evaluated several potential predictive and prognostic factors including:

- Tumor Markers: Carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA 19-9) and cancer antigen 125 (CA 125).
- Inflammatory Markers: Neutrophil-to-lymphocyte ratio (NLR) and neutrophil-to-platelet ratio (NPR).
- Metastatic Site: Initial sites of metastasis were recorded and classified.

Statistical Methods

- analysis was performed using SPSS software (Version 25, IBM Corp., Armonk, NY, USA). Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis was conducted using Cox proportional hazards regression models to identify independent predictors of survival. A two-sided p-value of less than 0.05 was considered statistically significant.

RESULTS

This study analyzed the outcomes of 33 patients with initially metastatic pancreatic cancer treated with FOLFIRINOX as a first-line treatment at the Clinic of Oncology, Clinical Center University of Sarajevo, from January 2021 to January 2023.

The median age of the patients was 64, ranging from 38 to 76 years, with a distribution of 18 males and 15 females. We have not identified a statistically significant difference in progression-free survival and overall survival between gender groups.

The median overall survival (OS) for the cohort was 21.7 months, with a 95% confidence interval (CI) of 10.5 to 32.9 months.

The median progression-free survival (PFS) was 10.0 months, with a 95% CI of 8.2 to 11.8 months.

A statistically significant negative correlation was found between the NLR and overall survival of patients (correlation coefficient r = -0.464, p = 0.045).

Patients presenting with initial liver metastasis exhibited a worse median OS of 16.3 months (95% CI: 5.1 to 27.5 months), compared to those with non-liver metastatic sites, where the median OS was not reached. The difference approached statistical significance (log-rank p-value = 0.058). The impact of metastatic sites on survival outcomes is illustrated in Figure 1.

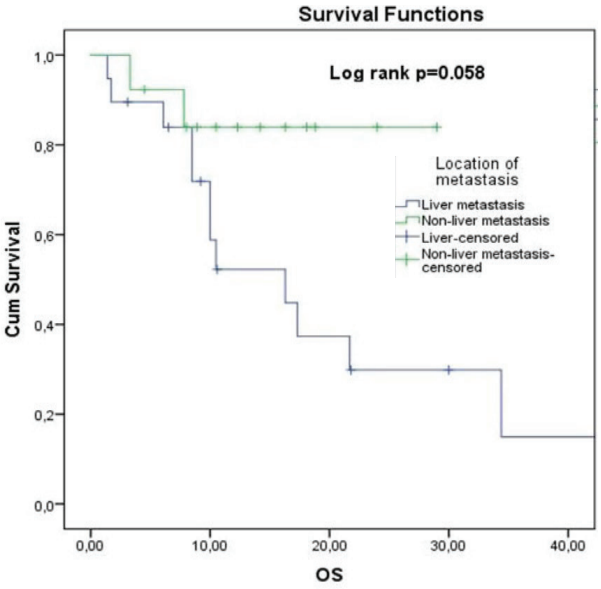

Figure 1 Kaplan-Meier survival analysis of patients divided in two groups based on the location of metastatic disease.

Metastatic sites were located predominantly in the liver (52.6%), followed by the lungs (23.6%), retroperitoneal lymph nodes (13.1%), peritoneum (5.3%), stomach (2.7%) and bones (2.7%). The detailed distribution of metastatic sites among patients is presented in Table 1.

Table 1 Frequency and percentage distribution of metastatic sites among the patients.

Location of Metastasis	Frequency (n)	Percent (%)
Liver	20	52.6
Lungs	9	23.6
Retroperitoneal lymph nodes	5	13.1
Peritoneum	2	5.3
Stomach	1	2.7
Bones	1	2.7
Total	38	100

Survival analysis was performed, dividing the patients into two groups based on the location of metastatic disease. The survival curves highlighted the differential impact of metastatic sites on survival outcomes and are shown in Figure 1.

The study assessed tumor markers (CEA, CA 19-9, CA 125), NLR, neutrophil-to-platelet ratio (NPR) and the initial site of metastasis for their potential as predictive and prognostic markers. However, none of the noted parameters were identified as independent predictive or prognostic markers for PFS and OS.

DISCUSSION

Patients with initially metastatic pancreatic cancer who were treated with FOLFIRINOX at our site achieved better PFS and OS results compared to the clinical studies that established this regimen. Within our study, the median overall survival (OS) was 21.7 months, and the median progression-free survival (PFS) was 10.0 months, significantly higher than the 11.1 months OS and 6.8 months PFS reported in the ACCORD trial (4). This difference in outcomes may be attributed to several factors, including advancements in supportive care.

Considering the timeline of the ACCORD trial, it should be pointed out that since then, there have been significant improvements in supportive care which help patients to better manage the intense side effects associated with the FOLFIRINOX regimen. Enhanced supportive care can lead to improved tolerability, allowing patients to maintain optimal dosing and treatment schedules, which can be crucial in achieving the best outcomes (1, 7).

When it comes to the patient selection process and the management in general, our study likely benefited from implementing refined criteria for selecting patients, but also from the advancements made in the initial diagnostic management of pancreatic cancer. This includes more precise diagnostic tools and closer monitoring, which can contribute to better overall outcomes (2, 4, 8). Besides that, this aspect aligns with the findings from other studies as well, such as Yoon et al., which also reported better survival rates due to enhanced supportive care and closer patient monitoring (8).

It is interesting to note that variations in healthcare practices, accessibility to advanced care, and demographic differences can also significantly influence treatment outcomes. Studies indicate that regional differences impact survival rates and treatment effectiveness, suggesting that local healthcare infrastructure and practices play critical roles in the success of complex treatments like FOLFIRINOX (9).

Even though the previously noted findings indicate that FOLFIRINOX really does offer improved survival benefits, we need to take into consideration that this regimen is at the same time associated with higher toxicity and cost. Economic evaluations suggest that while remaining more expensive, the cost-effectiveness of FOLFIRINOX may be justified by the significant survival benefit that it brings (7, 10). Moreover, quality of life considerations are paramount, as treatment intensity must be balanced against potential quality of life deterioration. Gourgou-Bourgade et al. highlighted that FOLFIRINOX significantly reduces quality of life impairment compared with gemcitabine, despite its higher toxicity profile (7).

The recent NAPOLI-3 clinical trial demonstrated an improvement in median survival to 11.1 months (95% CI 10.0–12.1) for patients treated with the NALIRIFOX regimen (liposomal irinotecan, oxaliplatin, leucovorin, and fluorouracil), compared to 9.2 months (95% CI 8.3–10.6) for those receiving nab-paclitaxel-gemcitabine. These findings position NALIRIFOX as a promising new first-line treatment option for patients with metastatic pancreatic cancer.

Aside from the quality of life considerations and survival benefits of FOLFIRINOX, we found that survival outcomes can be impacted by liver metastasis as well. Precisely, our findings indicated that patients with initial liver metastasis had a worse median OS compared to those with non-liver metastases. This observation aligns with existing research indicating that liver metastases in pancreatic cancer are associated with weaker prognosis. The general physiological role of the liver in drug metabolism and the aggressive nature of liver-invading tumors likely contribute to worse outcomes. Studies have shown that liver metastases are often linked with higher tumor burden and more aggressive disease, impacting the effectiveness of systemic treatments and overall patient survival (6, 11).

Genetic profiling can change treatment outcomes through identification of patients who are more likely to respond to different chemotherapy regimens based on their genomic information, thus highlighting the potential benefits of integrating precision medicine into treatment protocols for metastatic pancreatic cancer (5). For instance, the presence of certain DNA repair gene mutations may make cancer cells more susceptible to the DNA-damaging agents in FOLFIRINOX. Further research into these predictive biomarkers could refine patient selection criteria, potentially leading to even better clinical outcomes and more personalized treatment approaches (12).

When we bring up patient profiling, it is important to highlight that the use of artificial intelligence (AI) in healthcare is transforming the development of that process and the customization of treatment plans in general. AI can analyze extensive datasets, including genetic profiles, clinical histories and treatment responses, to identify patterns that predict which patients are most likely to benefit from specific chemotherapy regimens. These AI algorithms provide clinicians with data-driven insights, enhancing the precision of treatment plans and optimizing patient outcomes (13, 14). Future research should investigate the incorporation of AI tools in routine clinical practice in order to further refine patient selection and personalize treatment strategies, particularly in pancreatic cancer.

The composition of the gut microbiome can influence the body's response to chemotherapy and also modulate the immune response against tumors. Studies indicate that certain bacterial populations can enhance the effectiveness of chemotherapy, while others may contribute to resistance or increased toxicity. Including microbiome analysis into patient profiling could lead to even more personalized treatment modalities aimed at improving outcomes and reducing side effects (15). Chrysostomou et al. highlighted that gut microbiota modulation could impact the efficacy and toxicity of cancer chemotherapy and immunotherapy, suggesting that microbiome-targeted in-

terventions might be a valuable addition to cancer treatment protocols (15).

Innovative targeted therapies, based on genomic results, could potentially improve survival and quality of life in PDAC (Pancreatic Ductal Adenocarcinoma) patients. PDAC patients with somatic/germline mutations in the DNA Damage Repair (DDR) pathway, such as BRCA1, BRCA2, and PALB2, may benefit from platinum-based therapies and PARP inhibitors like Olaparib (5). Similarly, KRAS mutations, prevalent in about 95% of PDAC cases, are being targeted with new therapeutics like Sotorasib and Adagrasib, which have shown promising results in clinical trials (6). Besides that, immunotherapy is also showing up as a potential treatment for a subset of PDAC patients with mismatch repair deficiency (dMMR) and/or high microsatellite instability (MSI-H), within which medications like Pembrolizumab demonstrate particular efficacy (5, 7). These advancements emphasize the importance of personalized medicine in the future management of pancreatic cancer, making space for better outcomes through targeted and immune-based therapies (8).

Although the study provides valuable insights, several limitations must be acknowledged. First, the relatively small sample size of 33 patients may reduce the statistical power of our analysis and limit the generalizability of our findings to broader patient populations. The retrospective design of the study introduces inherent limitations, including the potential for selection bias and incomplete data collection. Moreover, the biomarker analysis in this study was limited to tumor and inflammatory markers (CEA, CA 19-9, CA 125, NLR, NPR). While these markers have been associated with prognostic outcomes in other studies, our analysis did not include genomic or molecular profiling, which could offer more precise predictive insights, especially in the context of emerging targeted therapies and personalized medicine.

As this study was conducted at a single institution, the results may not be broadly applicable to other healthcare settings or regions with different treatment protocols and patient populations.

In summary, while this study contributes to the growing body of evidence supporting the use of FOLFIRINOX in metastatic pancreatic cancer, these limitations should be considered when interpreting the results. Further research with larger, multicenter cohorts, prospective designs, and comprehensive biomarker and quality of life assessments is warranted to refine treatment strategies and optimize outcomes for this patient population. The limitations of our research pertain to the small sample size of patients and the lack of information on the molecular profile of patients.

CONCLUSION

The results of our study correlate with the outcomes of therapy with FOLFIRINOX in pivotal clinical trials and confirm the efficacy and safety of this combination in a real-world setting.

Acknowledgement: None.

Declaration of Patient Consent: Written, informed consent was obtained from all volunteers in the study.

Authors' Contributions: ES, AD, US, EK, EB-G, JR, AA, LM, SC, BH, AP and SB gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author had role in article drafting and in process of revision. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial Support and Sponsorship: None.

Conflict of Interest: None.

REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram, I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-63. doi: 10.3322/caac.21834.
2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12-49. doi: 10.3322/caac.21820.
3. Global Cancer Observatory, Bosnia and Herzegovina Cancer Fact Sheet 2022 [Internet]; [reviewed 2024 Sept 15]. Available from: https://gco.iarc.who.int/media/globocan/factsheets/populations/70-bosnia-herzegovina-fact-sheet.pdf.
4. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817-25. doi: 10.1056/NEJMoa1011923.
5. Sohal DPS, Kennedy EB, Cinar P, Conroy T, Copur MS, Crane CH, et al. Metastatic Pancreatic Cancer: ASCO Guideline Update. J Clin Oncol. 2020;38(27):3217-30. doi: 10.1200/JCO.20.01364.
6. Kolbeinsson HM, Chandana S, Wright GP, Chung M. Pancreatic Cancer: A Review of Current Treatment and Novel Therapies. J Invest Surg. 2023;36(1):2129884. doi: 10.1080/08941939.2022.2129884.
7. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouché O, Guimbaud R, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. J Clin Oncol. 2013;31(1):23-9. doi: 10.1200/JCO.2012.44.4869.
8. Schepis T, De Lucia SS, Pellegrino A, del Gaudio A, Maresca R, Coppola G, et al. State-of-the-Art and Upcoming Innovations in Pancreatic Cancer Care: A Step Forward to Precision Medicine. Cancers (Basel). 2023;15(13):3423. doi: 10.3390/cancers15133423.
9. Wainberg ZA, Melisi D, Macarulla T, Pazo Cid R, Chandana SR, De La Fouchardière C, et al. NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial. Lancet. 2023;402(10409):1272-81. doi: 10.1016/S0140-6736(23)01366-1.
10. Wang ZQ, Zhang F, Deng T, Zhang L, Feng F, Wang FH, et al. The efficacy and safety of modified FOLFIRINOX as first-line chemotherapy for Chinese patients with metastatic pancreatic cancer. Cancer Commun (Lond). 2019;39(1):26. doi: 10.1186/s40880-019-0367-7.
11. Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016;387(10018):545-57. doi: 10.1016/S0140-6736(15)00986-1.
12. Sohal DPS, Mangu PB, Khorana AA, Shah MA, Philip PA, O'Reilly EM, et al. Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016;34(23):2784-96. doi: 10.1200/JCO.2016.67.1412.
13. Liu X, Faes L, Kale AU, Wagner SK, Fu DJ, Bruynseels A, et al. A comparison of deep learning performance against health-care professionals in detecting diseases from medical imaging: a systematic review and meta-analysis. Lancet Digit Health. 2019;1(6):e271-e97. doi: 10.1016/S2589-7500(19)30123-2.
14. Esteva A, Robicquet A, Ramsundar B, Kuleshov V, DePristo M, Chou K, et al. A guide to deep learning in healthcare. Nat Med. 2019;25(1):24-9. doi: 10.1038/s41591-018-0316-z.
15. Chrysostomou D, Roberts LA, Marchesi JR, Kinross JM. Gut Microbiota Modulation of Efficacy and Toxicity of Cancer Chemotherapy and Immunotherapy. Gastroenterology. 2023;164(2):198-213. doi: 10.1053/j.gastro.2022.10.018.