

**A real-world comparison of treatment strategies
for metastatic pancreatic cancer:**

4-month FOLFIRINOX followed by maintenance therapy
versus 6-month FOLFIRINOX followed by observation

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Abstract

Introduction

Pancreatic adenocarcinoma is associated with one of the poorest prognoses in oncology. Although presenting high toxicity, the FOLFIRINOX chemotherapy regimen has resulted in considerable improvements in overall survival. The 2021 PANOPTIMOX-PRODIGE 35 Trial demonstrated the effectiveness in maintaining patient quality of life while preserving overall survival of a novel approach of 4 months of chemotherapy followed by 5-FU maintenance therapy as opposed to 6 months of chemotherapy followed by treatment pause. This study aims to compare the two strategies regarding overall survival and progression free survival in a real-world setting and to describe the treatment courses of the included patients.

Methods

This retrospective cohort identified 118 patients who received FOLFIRINOX between October 2020 and October 2025, of which 90 were included for statistical analysis. The primary endpoint was overall survival. Statistical analysis described differences in characteristics and outcomes between groups. The group receiving 5-FU maintenance was labeled maintenance group (MG) (n=24), the group receiving treatment pause was labeled pause group (PG) (n=15) and the group of patients that deviated from protocol was labeled deviation group (DG) (n=51).

Results

In the 90 included patients, the mean age was 66. 56% were male, and 44% were female. Treatment courses of patients were illustrated with a Sankey plot. Rates of hospitalization during 1st line treatment were 29% for MG, 47% for PG, and 71% for DG (p=0.003). mOS was 12.0 months, while PFS was 8 months. Group mOS was 22.6 in MG and 14.2 in PG (p=0.222). mOS was 22.5 months in resected patients and 11.5 months in non-resected patients (p=0.033). Median PFS was 11 months in MG and 9.1 months in PG (p=0.999). Cox regression on survival showed PG had a HR of 0.697 and MG had a HR of 0.259 when compared to DG, the latter difference being significant (p=0.260, p<0.001).

Discussion

This study's findings support the conclusion of the 2021 PANOPTIMOX-PRODIGE 35 Trial that 5-FU maintenance in PDAC may yield similar OS when compared to treatment pause. However, intention-to-treat analysis was not possible, which limits comparability. Confounding may skew results as patients may be selected for certain treatment strategies depending on prognostic factors. In this real-world setting, lacking adherence to protocol caused low sample sizes in MG and PG while DG made up over half the cohort, underlining the difficult treatment course for PDAC patients.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is characterized by one of the worst prognoses in all of oncology due to its subtle symptomatology and aggressive biology [1]. PDAC often presents at a late stage, and at time of diagnosis, locally advanced or disseminated disease represents approximately 80% of cases and consequently the 5-year survival is reported at around 11%, while this figure falls to around 3% when looking at metastatic disease alone [2, 3]. Curative intended treatment consists of resection and chemotherapy, however, even in resected patients, recurrence occurs in up to 75% of cases [4, 5]. Males account for around 52% of patients while 48% are female, and the mean age at diagnosis is around 70 [6].

The course for PDAC-patients begins at diagnosis which is most often obtained through 3-phase pancreas CT protocol while CT- or ultrasound-guided biopsy is often secured for histologic verification and molecular profiling. TNM-stage as well as initial treatment course is determined through a multidisciplinary team conference [7]. Patients in good overall health presenting with localized disease are offered resection [8, 9]. In borderline resectable cases, patients may receive neo-adjuvant therapy for tumor downstaging in order to potentially enable later resection which is achieved in around 60% of downstaging attempts [10, 11]. Patients with tumors that are deemed unresectable or with disseminated disease are referred to palliative oncologic treatment, while patients in poor overall health are not candidates for chemotherapy and may instead be referred to supportive care [10].

Over the past decades, a wide array of palliative treatment regimens has been proposed for metastatic PDAC (mPDAC) but limited gains in survival must be weighed against the heavy impact on quality of life (QOL) [12]. Today, the palliative first-line treatment in fit patients primarily consists of the FOLFIRINOX-regimen (oxaliplatin, irinotecan, 5-fluorouracil, and leucovorin) while nab-paclitaxel and gemcitabine-based regimens are often reserved for fragile patients or second line treatment [13, 14]. The FOLFIRINOX regimen yields response rates of approximately 32% while nab-paclitaxel and gemcitabine-based regimens significantly lag behind in this regard [13]. Furthermore, FOLFIRINOX chemotherapy is an especially strenuous regimen as toxicities such as neuropathy and thrombocytopenia are widespread limiting dose intensity and administered cycles, however, this multidrug approach has been shown to increase QOL in PDAC patients – a group otherwise characterized by low QOL even compared to other malignancies [15]. Many attempts have been made to reduce toxicity in order to further improve drug tolerance and QOL in PDAC while preserving therapeutic impact [16].

In cases of disease control, patients conventionally receive treatment pause after 6 months of FOLFIRINOX due to the severity of toxicities and adverse events linked to indefinite oncological palliative treatment. However, the 2021 landmark RCT PANOPTIMOX-PRODIGE 35 Trial showed that 4-month FOLFIRINOX induction therapy followed by de-escalation to 5-fluorouracil plus leucovorin (5-FU/LV) until disease progression (DP) maintained similar overall survival while preserving QOL for longer than the previous standard of 6-month induction therapy followed by observation [17]. This granted obvious advantages in the palliative setting, as prolonging survival often comes at a cost in QOL, limiting personal gain for PC patients [15]. It has yet to be determined, however, how this novel strategy performs in a real-world clinical setting where patients are often in poorer overall health than in clinical trial cohorts.

This study aims to assess the course of palliative FOLFIRINOX treatment in pancreatic cancer as well as to evaluate whether the novel strategy of 4-month FOLFIRINOX induction followed by de-escalation to 5-FU/LV until progression is non-inferior regarding real-world OS compared to the previous standard of 6-month induction followed by a treatment pause in patients with mPDAC.

Methods

This registry study included patients receiving palliative treatment for metastatic pancreatic cancer at the department of oncology at Aalborg University Hospital between October 2020 and October 2025. Patients were divided into groups according to regimen. Thus, patients receiving 4-month induction chemotherapy followed by de-escalation were addressed as the maintenance group (MG) while the patient group receiving 6-month induction chemotherapy followed by observation will be addressed as the pause group (PG). Patients who received neither treatment pause nor 5-FU maintenance were labeled the deviation group (DG). Patient data was accessed through electronic records and was collected using REDCap electronic data capture tools hosted at Aalborg University Hospital [18]. Inclusion criteria were administration of FOLFIRINOX between October 1st of 2020 and the 7th of October 2025. Exclusion criteria were concurrent cancer diagnoses except CLL and non-melanoma skin cancer, diagnosis abroad, not receiving FOLFIRINOX as first line therapy, not receiving palliative treatment, and receiving both maintenance and pause treatment regimens.

Gathered patient data included age at diagnosis, height, weight, gender, ECOG performance status before chemotherapy administration, cTNM staging, tumor resection as well as date and radicality, chemotherapy regimen (maintenance, pause or other), whether or not 1st line treatment was intended to be neoadjuvant, date of chemotherapy start, hospital admission during 1st line treatment, dose reduction of 1st line treatment, whether 2nd line treatment was given as well as the type and date of administration, whether 3rd line treatment was given and the date of administration, disease progression, date of progression, death and date of death. Treatment pause and maintenance therapy was noted regardless of induction duration. The date of progression was set as the first mention of either confirmed progression, or the date of first suspicion of progression if progression was later confirmed. Therapy was marked as intended neoadjuvant when electronic records note that the intention was downstaging for resection. Hospitalization during 1st line was defined as any hospital admission spanning at least one night during 1st line treatment or up to 14 days after the last administered dose.

Statistics

Data was exported from REDCap and analyzed statistically in R Statistical Software (v4.5.2; R Core Team 2025) using the *gtsummary* package (v2.3.0) for visualization of patient characteristics and the *ggsankey* package (v1.0) for creation of a Sankey plot. Chi-squared, T-test, Kaplan-Meier, log-rank, and Cox-regression analyses were performed using IBM® SPSS® Statistics (version 28). A forest plot was created with Google Colab.

Patient data was analyzed through descriptive statistics. Significant differences between groups in table 1 were tested for, and the p-value was noted. Group characteristics were compared using Kruskal-Wallis tests for continuous variables and chi-squared or Fisher's exact tests for categorical variables, as appropriate for the data distribution and sample sizes. The treatment course of the included patients was illustrated with a Sankey plot. Primary and secondary endpoints were survival and progression-free survival (PFS), which was compared between groups with Kaplan-Meier plots and significance was determined through log-rank value. Correlation between treatment strategy and hospitalization was determined through chi-squared analysis. Cox regression was used to

assess variables' impact on survival, and hazard ratios and their CIs were illustrated with a forest plot. Statistical significance was defined as $p < 0.05$.

Results

The study assessed 118 patients of which 28 were excluded due to reasons listed in Figure 1. The 90 included patients were divided according to post-induction regimen into the MG with 24 patients, PG with 15 patients, and DG with 51 patients.

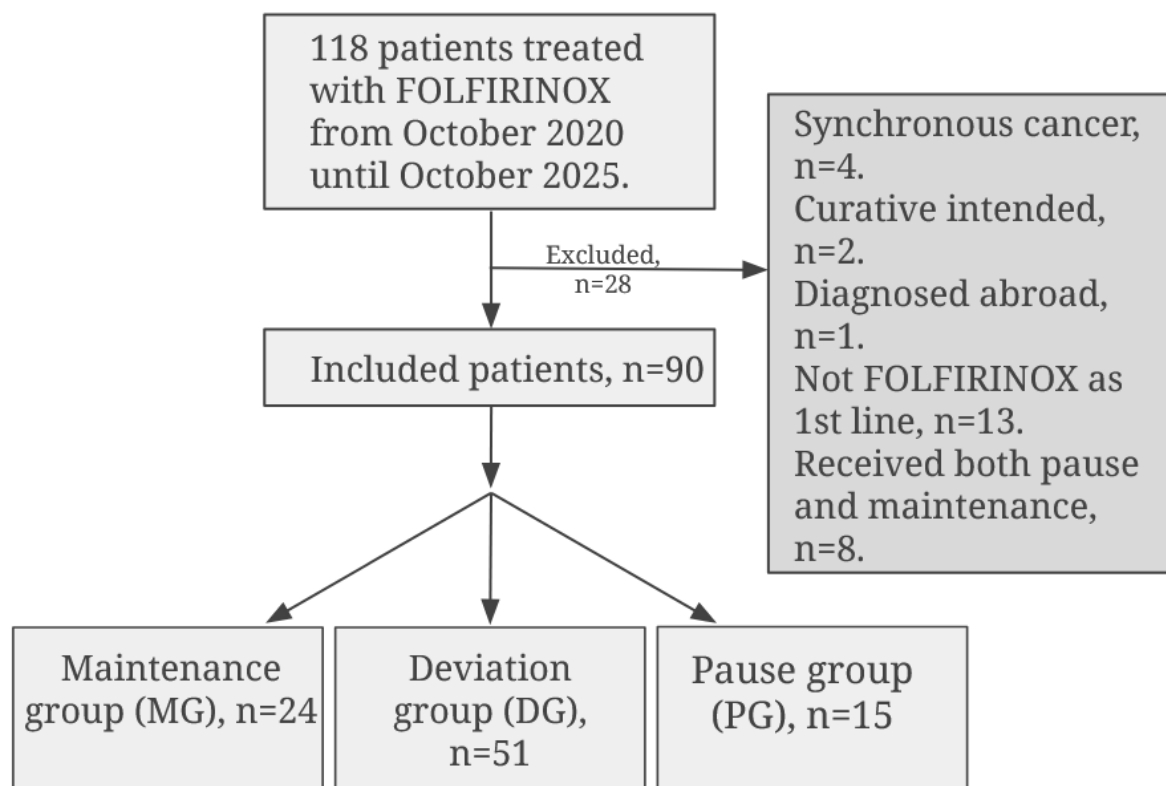


Figure 1: Patient inclusion and exclusion. 118 cases of palliative FOLFIRINOX treatment were identified, of which 28 cases were excluded. 90 patients were included and distributed into groups according to post-induction regimen.

Baseline characteristics of the 90 included patients are presented in Table 1. The median age at diagnosis for the entire cohort was 66 years and the gender distribution was 44% female and 56% male. Median follow-up was 32 months. Only characteristics regarding hospitalization during 1st line and duration of follow-up were significantly different between the three groups ($p=0.003$, $p<0.001$).

Characteristic	Post-induction regimen				p-value ²
	Overall N = 90 ¹	Maintenance N = 24 ¹	Deviation N = 51 ¹	Pause N = 15 ¹	
Age at diagnosis, years	66 (58, 71)	67 (63, 72)	65 (58, 68)	64 (55, 74)	0.3
Sex					0.8
Female	40 (44%)	10 (42%)	24 (47%)	6 (40%)	
Male	50 (56%)	14 (58%)	27 (53%)	9 (60%)	
BMI	25.0 (22.7, 27.6)	23.1 (20.6, 25.9)	25.2 (23.0, 27.4)	25.6 (23.7, 28.1)	0.2
Performance status at induction					0.4
0	46 (51%)	11 (46%)	24 (47%)	11 (73%)	
1	37 (41%)	11 (46%)	23 (45%)	3 (20%)	
2	7 (7.8%)	2 (8.3%)	4 (7.8%)	1 (6.7%)	
Intended neoadjuvant	38 (42%)	8 (33%)	21 (41%)	9 (60%)	0.3
Resected	12 (13%)	0 (0%)	10 (20%)	2 (13%)	0.052
Hospitalization during 1st line	50 (56%)	7 (29%)	36 (71%)	7 (47%)	0.003
Follow-up, months	32 (20, 49)	22 (13, 33)	34 (21, 46)	59 (34, 65)	<0.001

¹ Median (Q1, Q3); n (%)

² Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 1: Baseline characteristics regarding age, sex, BMI, ECOG performance status, intended regimen, resection, hospitalization and follow-up for the entire cohort as well as individual groups.

Figure 2 represents the treatment course of included patients. Event nodes include intended initial strategy, resection, post-induction regimen and whether the patient received 2nd line therapy.

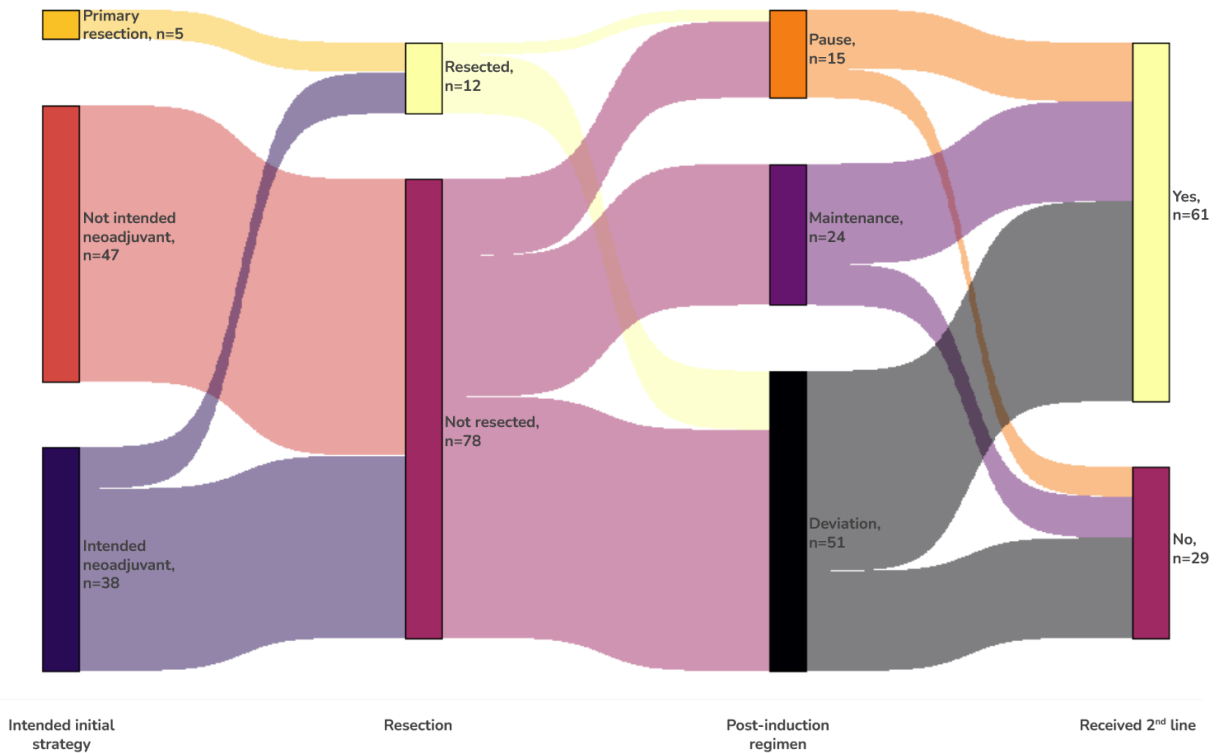


Figure 2: Sankey diagram visualizing the treatment course of palliative pancreatic cancer.

Oncological outcomes

The 1-year survival was 51%. Survival is illustrated in the following Kaplan-Meier plot. Median overall survival (mOS) was 12.0 months. The 1-year progression-free survival was 35%. Median PFS (mPFS) was 8.0 months. mOS in non-resected patients was 11.5 months, while mOS was 22.5 months in the resected patients ($p=0.033$). mPFS in non-resected patients was 7.4 months, while mPFS was 14.2 months in resected patients ($p=0.082$). Among non-resected patients, mPFS was 11 months in MG and 8.3 months in PG ($p=0.393$). There was no significant correlation between survival time and treatment strategy ($p=0.222$). mOS in months was 22.6 in MG and 14.2 in PG. Among cM1 patients, mOS was 17.6 months in MG and 10.2 months in PG ($p=0.002$). PFS was not significantly different between MG and PG ($p=0.999$). mPFS in months was 11.0 for MG and 9.1 for PG. mOS in cM0 patients was 15.8, while mOS for cM1 patients was 10.6 months ($p=0.109$).

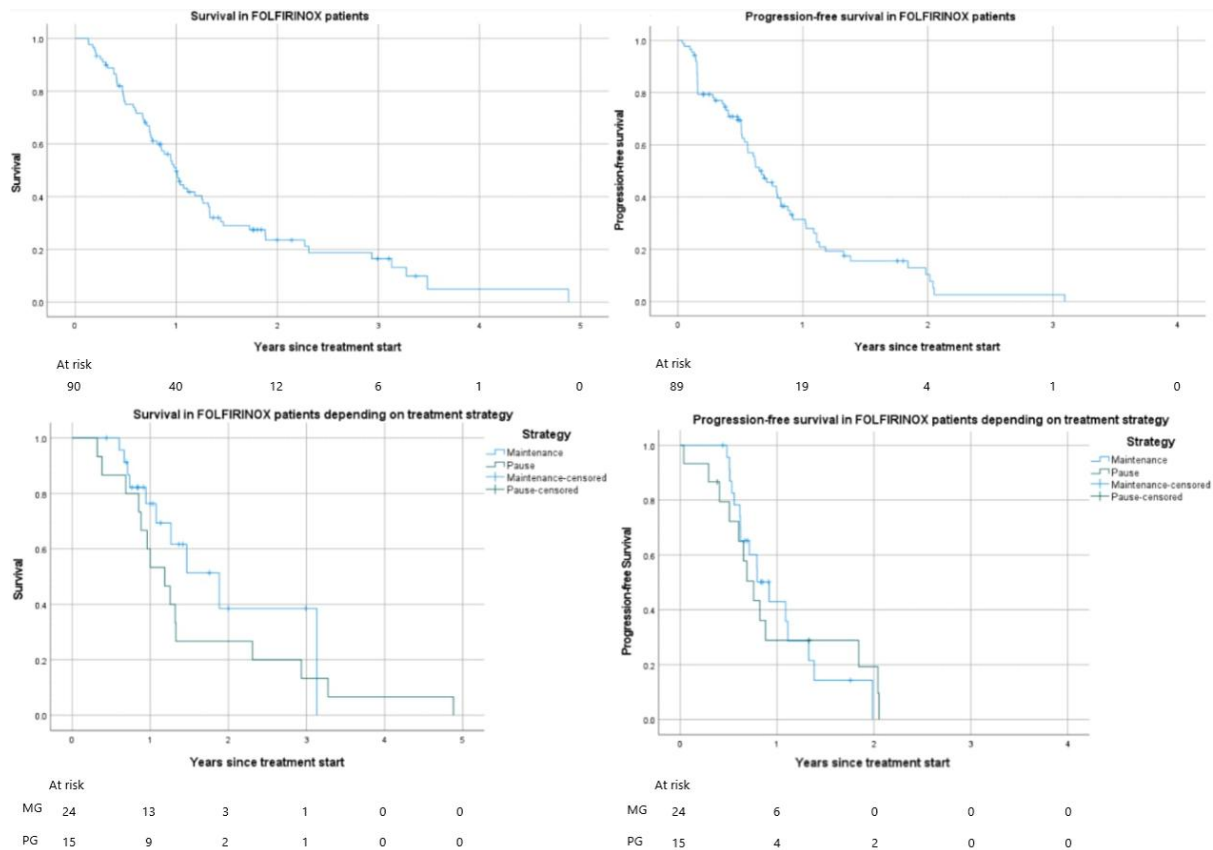


Figure 3: Kaplan Meier plots describing cohort overall survival (top left) and progression-free survival (top right) as well as overall survival (bottom left) and progression-free survival (bottom right) between the maintenance and pause groups.

Cox regression on survival showed that PG and MG were associated with decreased HR of 0.697 and 0.259 respectively when compared to DG ($p=0.26$, $p<0.001$). Resected patients showed lower HR than non-resected patients ($p=0.014$). Performance status was not associated with significantly different HR, although trends suggest HR increases with increasing PS ($p=0.333$). HR is illustrated in the forest plot below.

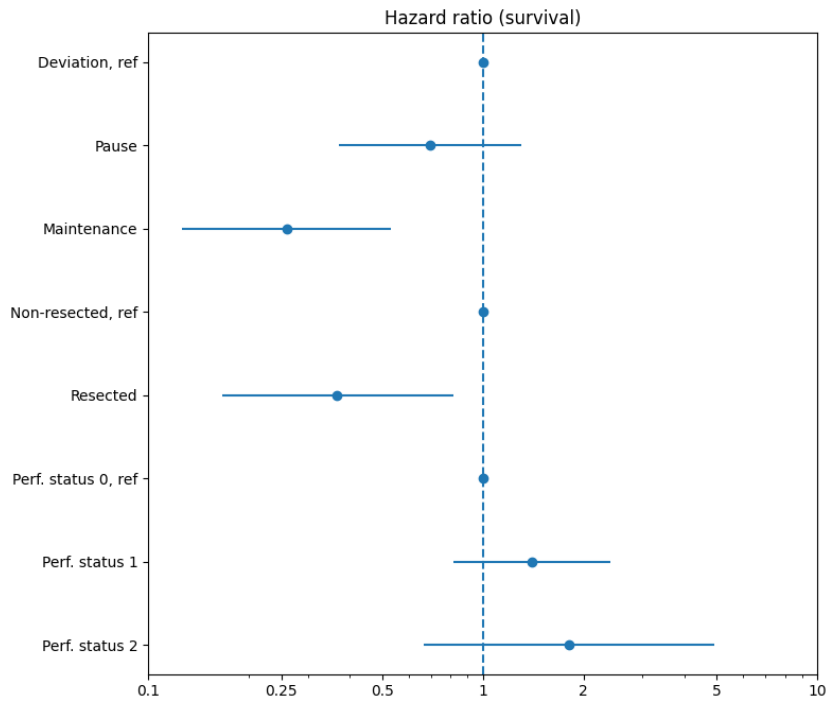


Figure 4: Forest plot illustrating hazard ratios for covariables including treatment strategy, resection and ECOG performance status (PS).

Rates of hospitalization during 1st line therapy between the arms were 29% in MG, 47% in PG and 71% in DG. The differences were significant ($p=0.003$). However, when DG was filtered out, differences were not significant ($p=0.268$).

Discussion

Outcomes

This study found a 1-year survival of 51% and a median overall survival (mOS) of 12.0 months. This is relatively long compared to similar studies, such as a Danish nationwide unselected real-world register study which found mOS of 10.0 months and the PANOPTIMOX-PRODIGE 35 Trial which found mOS 10.1 and 11.2 for their PG and MG respectively [6, 17]. This study's 1-year PFS was 35% while median PFS was 11 and 9.1 months for MG and PG respectively. The PANOPTIMOX-PRODIGE 35 Trial found 5.7 and 6.3 in the corresponding groups. Therefore, this study seems to indicate more favorable outcomes than existing literature. The difference may in part be due to differences in study design, as the present study included resected patients. If resected patients are excluded the mOS was 11.5 months and the median PFS was 11 months in MG and 8.3 months in PG. Furthermore, the PANOPTIMOX-PRODIGE 35 Trial followed an intention-to-treat strategy, where patient data is analyzed according to their random allocation into groups and not necessarily the received regimen. In the present study, however, patients that did not tolerate treatment were analyzed as DG. Intention-to-treat analysis was not possible in the present study, as intended regimen was rarely noted in patient records, and treatment was most often given on an ad-hoc basis.

Treatment strategy was found to be significantly correlated with OS. When DG was filtered out, however, there was no significant difference between MG and PG. The reason for DG's poor survival outcome may be due to confounding as patients experiencing poor health and adverse events may be ineligible for the maintenance or pause protocol and thus deviating from either regimen. This is supported by the finding that patients in DG are significantly more often hospitalized during 1st line treatment than the other groups ($p=0.003$). Insignificant trends also indicate some confounding in the selection of post-induction regimen as PG experienced higher rates of hospitalization compared to MG ($p=0.268$).

The fact that 51 patients out of 90 did not follow either the maintenance or pause treatment protocol illustrates the difficulties of implementing oncologic treatment protocols in PDAC. This indicates that FOLFIRINOX regimens in PDAC may be too ambitious, and even in this cohort selected for palliative FOLFIRINOX treatment, specific FOLFIRINOX regimens were not feasible for a majority of patients.

Cox regression showed that MG was associated with lower hazard ratio (HR) than MG. This may be due to treatment pause being favored for patients who have experienced serious side effects or general decrease in overall health, as oncologists may view this course of action to be less taxing. Contrary to this, maintenance therapy may simply be more tolerable, as suggested by the non-significant trends of lower rates of hospitalization during 1st line ($p=0.268$). Due to limitations in the design of this retrospective study, it is not possible to conclude which, if any, of these explanations are true. In the PANOPTIMOX-PRODIGE 35 trial patients were simply randomized into treatment strategies, eliminating this potential selection bias. Furthermore, low sample size limits the confidence of the results. The PANOPTIMOX-PRODIGE 35 Trial also found that maintenance therapy yielded greater mOS compared to treatment pause by 1.1 months, although the trial did not assess if the difference was statistically significant. As expected, HR was also shown to increase with rising PS, although not significantly.

While there are fundamental dissimilarities between the present study and the PANOPTIMIX-PRODIGE 35 trial, our results support the conclusion that FOLFIRINOX followed by 5-FU maintenance yields non-inferior survival and PFS compared to FOLFIRINOX followed by treatment pause – even in a real-world clinical setting. Furthermore, our results suggest the former may be more tolerable with MG being less often hospitalized during 1st line than PG, although confounding may skew results.

Survival analyses suggest that resection is associated with significantly increased survival, indicating that this is a preferable treatment option despite the risk of complications and long recovery. However, confounding may skew this result as resection necessitates a certain standard of health and limited tumor burden guaranteeing resected patients a better starting point. Furthermore, the design of this study also dictates guaranteed time bias for resected patients as resection is a curative intended treatment and this study included only patients undergoing palliative FOLFIRINOX treatment. This means that included patients who have undergone resection have all at some point been “curable” and thereby having a more favorable prognosis.

Patient characteristics

This study’s cohort included 90 patients who underwent FOLFIRINOX as first line treatment for PDAC in a palliative setting, 24 of which received maintenance therapy while 15 received treatment pause. Surprisingly, 51 patients received neither post-induction regimen, probably primarily due to cases of uncontrolled disease.

The male to female distribution was found to be 56% to 44% which somewhat corresponds to the PANOPTIMOX-PRODIGE 35 Trial as well as a Danish nationwide unselected real-world register study which found males to female ratios of 61.5% to 38.5% and 53% to 47% of their cohorts, respectively [6, 17]. The median age was 66, which is a little lower than the PANOPTIMOX-PRODIGE 35 Trial at 70. Performance status at induction was not significantly different between MG, PG, and DG (p=0.4).

While 42% of patients initiated neoadjuvant chemotherapy, only 7.7% were resected after attempted downstaging and 5.6% received primary resection underlining the aggressive nature of PDAC. Furthermore, the rate of resection was highest in DG at around 20% versus 0% and 13% in MG and PG, respectively (p=0.052). The resected patients in DG may represent the patients who have completed curative intended treatment and later relapsed, thus potentially presenting with more complicated disease at the time of progression which could cause deviation from treatment pause or maintenance therapy. It is, however, not possible to identify these patients in the data of this study.

56% of included patients were hospitalized during 1st line treatment alone, underlining the intense difficulties facing PDAC patients. Follow-up time was significantly different between the three groups, with PG having a median follow-up of 59 months versus 22 and 34 months in MG and DG respectively (p=<0.001). This is most likely due to the fact that treatment pause was the dominating regimen before, and even for some time after, the introduction of maintenance therapy for PDAC, thus skewing the data toward longer follow-up in PG.

Figure 2 seeks to illustrate this complex course of palliative treatment in PDAC. Most patients who are treated with curative intended primary resection are never resected due to progression or inoperability and most of the resected patients end up deviating from specific treatment regimens altogether. Only about two thirds of patients underwent 2nd line treatment.

Strengths and limitations

This study highlights the challenges of replicating and comparing findings of RCTs in retrospective analysis of real-world data. Furthermore, in clinical trials, patients are selected for a certain standard of health to maximize feasibility of the treatment protocols. In the real world, many patients are given FOLFIRINOX despite a poor chance of tolerating the protocol in its entirety, which leads to heterogeneous treatment courses that are difficult to quantify and analyze.

Outcome comparability to the landmark PANOPTIMOX-PRODIGE 35 Trial is limited due to this RCT's intention-to-treat protocol, which could not be replicated in the present study due to the ad-hoc nature of the palliative treatment course in PDAC. Furthermore, sparse information on QOL in this study's cohort prevented comparison of this crucial aspect of palliative treatment.

The present study's design may have allowed for stronger conclusions, if dose intensity, adverse events, quality of life and completion of curative intended treatment was assessed. Furthermore, the sample size was quite low after dividing patients into subgroups, which decreases the likelihood of identifying subtle differences. Patients were also highly selected, as only patients who received FOLFIRINOX as 1st line palliative therapy were included. This reduces applicability to the general pancreatic cancer patient population.

Conclusion

This study supports the findings of the landmark PANOPTIMOX-PRODIGE 35 Trial in a real world setting as maintenance therapy has been shown to be non-inferior to treatment pause regarding OS and PFS. Hospitalization during 1st line treatment significantly correlates with deviation from either regimen and, in general, intended treatment course has been found to be rarely adhered to. Furthermore, maintenance therapy exhibited lower HR compared to treatment pause regarding survival, which may be subject to selection bias. The design of this study does, however, not allow for further investigation into the differences in overall health, side effects, and adverse events and the potential implications of these parameters on patient allocation into treatment groups. Further research is needed in order to verify the non-inferiority of maintenance therapy and shed light on potential biases in allocation of patients into treatment groups based on baseline factors. Furthermore, investigation into the consequences of regimen deviation and evidence-based regimen alternatives should be conducted to allow for better decision making.

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