



Evolving survival patterns in pancreatic adenocarcinoma: a 23-year retrospective observational analysis

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Background: Pancreatic adenocarcinoma (PA) remains one of the most lethal malignancies. However, treatment options have expanded. Since 2011, FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, and irinotecan) and nab-paclitaxel plus gemcitabine have demonstrated superior outcomes over gemcitabine for advanced disease and have become standard chemotherapy regimens. This study aimed to analyze 23-year survival trends in PA at a Brazilian cancer center, focusing on comparisons between the pre- and post-FOLFIRINOX eras.

Methods: This retrospective study analyzed patients diagnosed and treated at a large cancer center from 2000 to 2023, examining survival trends and changes in clinicopathological features and treatment across two 12-year periods: Period 1 (2000–2011), before FOLFIRINOX, and Period 2 (2012–2023), after FOLFIRINOX incorporation. The primary objective was to compare overall survival rates between the two time periods. The secondary objective was to evaluate changes in clinicopathological characteristics and treatment modalities.

Results: A total of 1,078 patients were included in this analysis, with 274 patients in Period 1 and 804 patients in Period 2. The proportion of female patients increased in Period 2 (43.8% in Period 1 vs. 50.9% in Period 2, $P=0.051$), and the median age at diagnosis rose from 62.5 to 66 years ($P<0.001$). Early-stage tumors (stages I–II) were more frequently diagnosed in Period 2 (16% vs. 29.8%, $P<0.001$). Chemotherapy use increased from 70.1% (192 patients) in Period 1 to 83.2% (669 patients) in Period 2 ($P<0.001$), while multimodal therapy (surgery + chemotherapy) rose from 11.3% to 16.7% ($P<0.001$). Median overall survival (mOS) improved from 7.29 months in Period 1 to 13.24 months in Period 2 ($P<0.001$), with the 5-year survival increasing from 5.2% to 14.3%. Among the early-stage patients, mOS increased from 19.7 to 34.4 months ($P=0.01$). No survival difference was observed for stage III disease (mOS: 16.7 vs. 14.8 months, $P=0.76$), while outcomes for stage IV improved (mOS: 4.76 vs. 9.99 months, $P<0.001$).

Conclusions: This 23-year analysis highlights the evolving treatment landscape and improved outcomes in PA with the introduction of more effective therapies.

Keywords: Pancreatic cancer; adenocarcinoma; survival; prognosis

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Introduction

Pancreatic adenocarcinoma (PA) is a highly lethal malignancy (1), with a rising incidence globally in recent years (2,3). Curative treatment is limited to patients with localized disease and typically involves surgery, combined with (neo)adjuvant chemotherapy and, in particular cases, radiotherapy (4,5). For patients with unresectable or metastatic disease, systemic chemotherapy remains the primary therapeutic option (6) and maintenance therapy with targeted therapy can be used in highly selected cases (7). Over the past two decades, surgical techniques have advanced toward less invasive methods, resulting in reduced morbidity and mortality (8,9).

Additionally, more effective chemotherapy (10-12) and radiotherapy (13) regimens have demonstrated improved outcomes. Notably, in 2011, a phase 3 randomized trial clearly demonstrated the superiority of FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, and irinotecan) over single-agent gemcitabine in overall survival (OS), progression-free survival, and objective response (10). In 2013, a second randomized phase 3 trial showed that nab-paclitaxel plus gemcitabine significantly improved survival compared to single agent gemcitabine (11). As a result, FOLFIRINOX and nab-paclitaxel plus gemcitabine became standard treatments for fit patients with advanced disease.

Highlight box

Key findings

- The introduction of more effective treatment regimens has led to improved survival rates in pancreatic adenocarcinoma (PA).
- The proportion of female patients diagnosed with PA has increased.
- Early-stage tumors are being diagnosed more frequently in recent years.

What is known and what is new?

- PA remains a highly aggressive malignancy with poor overall survival.
- This study highlights that Stage III disease continues to pose significant treatment challenges, with limited therapeutic advancements and a rising incidence among female patients.

What is the implication, and what should change now?

- Incorporation of new tools for early-stage diagnosis is crucial to increase survival rates.
- Future research should focus on factors contributing to higher incidence among female patients.
- Better multimodal strategies for stage III patients are an unmet need.

In this study, we aim to evaluate survival trends in patients diagnosed with PA and treated at a major cancer center in Brazil over the past 23 years, focusing on a comparison between the pre-FOLFIRINOX and post-FOLFIRINOX eras. We present this article in accordance with the STROBE reporting checklist (14) (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-2024-942/rc>).

Methods

We conducted a retrospective analysis of patients with histologically confirmed PA, diagnosed between 2000 and 2023 at a large cancer center in Brazil. The study included patients aged 18 years or older, all of whom received treatment at our institution. All cases with stages I–IV disease [according to the American Joint Committee on Cancer (AJCC) 7th edition] were considered, and patients with histologies other than adenocarcinoma were excluded from the analysis. Two distinct 12-year periods were analyzed: Period 1, before FOLFIRINOX (patients diagnosed between 2000 and 2011) and Period 2 (patients diagnosed between 2012 and 2023), after FOLFIRINOX introduction. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study protocol was approved by the institutional ethics committee of A.C. Camargo Cancer Center (No. 2462/17) on 12 May 2017. The requirement for informed consent was waived due to the use of de-identified data.

Clinicopathological characteristics (gender, age at diagnosis, and staging), treatment modalities (surgery, chemotherapy, and radiotherapy) and time between diagnosis to treatment initiation (in days) were extracted from medical records and administrative documents. Patients treated partially or totally at other institutions and those without at least one follow-up visit at our center were excluded from the study.

The primary objective was to compare OS rates between the two time periods, with patients subcategorized by stage (I–II, III, or IV). The secondary objective was to evaluate changes in clinicopathological characteristics and treatment modalities between the two periods.

Statistical analysis

OS was defined as the time from cancer diagnosis to death or last follow-up. Survival analysis was performed using the Kaplan-Meier method and log-rank test. Univariate analysis was conducted using Cox proportional hazards regression,

Table 1 Clinicopathological characteristics and treatment modalities

Variables	Period 1 (N=274)	Period 2 (N=804)	P
Gender			
Male	154 (56.2)	395 (49.1)	0.051
Female	120 (43.8)	409 (50.9)	
Age (years)	62.5 [55–71.75]	66 [58–73]	<0.001
Staging			<0.001
I	19 (6.9)	81 (10.1)	
II	25 (9.1)	158 (19.7)	
III	42 (15.3)	104 (12.9)	
IV	188 (68.6)	461 (57.3)	
Surgery	82 (29.9)	229 (28.5)	0.71
Chemotherapy	192 (70.1)	669 (83.2)	<0.001
Radiotherapy	54 (19.7)	121 (15.0)	0.09
Surgery + chemotherapy	31 (11.3)	134 (16.7)	<0.001
Time from diagnosis to treatment (days)	28 [11–51.25]	22 [9–41]	0.03

Data were presented as median [interquartile range] or n (%).

and comparisons of clinicopathological characteristics and treatment modalities were made using Chi-squared tests. Continuous variables were summarized using means, medians and interquartile ranges (IQRs), depending on their distribution. Continuous variables were compared using the non-parametric Mann-Whitney *U* test.

A *P* value of less than 0.05 was considered statistically significant. Records with missing values were excluded from the specific analyses. For patients lost to follow-up, the date of their last documented medical record entry was used as the censoring point in survival analyses. Statistical analyses were conducted using R and RStudio software.

Results

A total of 1,078 patients were included in this analysis, with 274 patients in Period 1 and 804 patients in Period 2 (Table 1). The mean number of patients diagnosed per year was 22.8 in Period 1 and 67.0 in Period 2. The gender distribution in Period 1 included 154 males (56.2%) and 120 females (43.8%), while in Period 2, 395 males (49.1%) and 409 females (50.9%) were identified (*P*=0.051). The median age at diagnosis was 62.5 years (range, 29–92 years) in Period 1, and 66 years (range, 24–95 years) in Period 2 (*P*<0.001). In Period 1, stage distribution was as follows:

19 patients (6.9%) with stage I, 25 (9.1%) with stage II, 42 (15.3%) with stage III, and 188 (68.6%) with stage IV. In Period 2, 81 patients (10.1%) were diagnosed with stage I, 158 (19.7%) with stage II, 104 (12.9%) with stage III, and 461 (57.3%) with stage IV (*P*<0.001).

The median time from diagnosis to initiation of treatment was 28 days (IQR, 11–51.25 days) in Period 1 and 22 days (IQR, 9–41 days) in Period 2 (*P*=0.03). Surgery was performed in 82 patients (29.9%) in Period 1 and 229 patients (28.5%) in Period 2 (*P*=0.71). Chemotherapy was administered to 192 patients (70.1%) in Period 1 and 669 patients (83.2%) in Period 2 (*P*<0.001). Radiotherapy was utilized in 54 patients (19.7%) in Period 1 and 121 patients (15.0%) in Period 2 (*P*=0.09). Multimodal treatment, involving both surgery and chemotherapy, was given to 31 patients (11.3%) in Period 1 and 134 patients (16.7%) in Period 2 (*P*<0.001).

At the time of data cut-off, 261 patients from Period 1 had died, with a median follow-up time of 133.3 months [95% confidence interval (CI): 111.5–not reached]. In Period 2, 541 patients had died, with a median follow-up time of 39.9 months (95% CI: 34.5–45.1). The median OS (mOS) was 7.29 months (95% CI: 6.24–8.74) in Period 1, and 13.24 months (95% CI: 12.45–14.26) in Period 2 (Figure 1A). The 5-year OS rates were 5.2% in Period 1

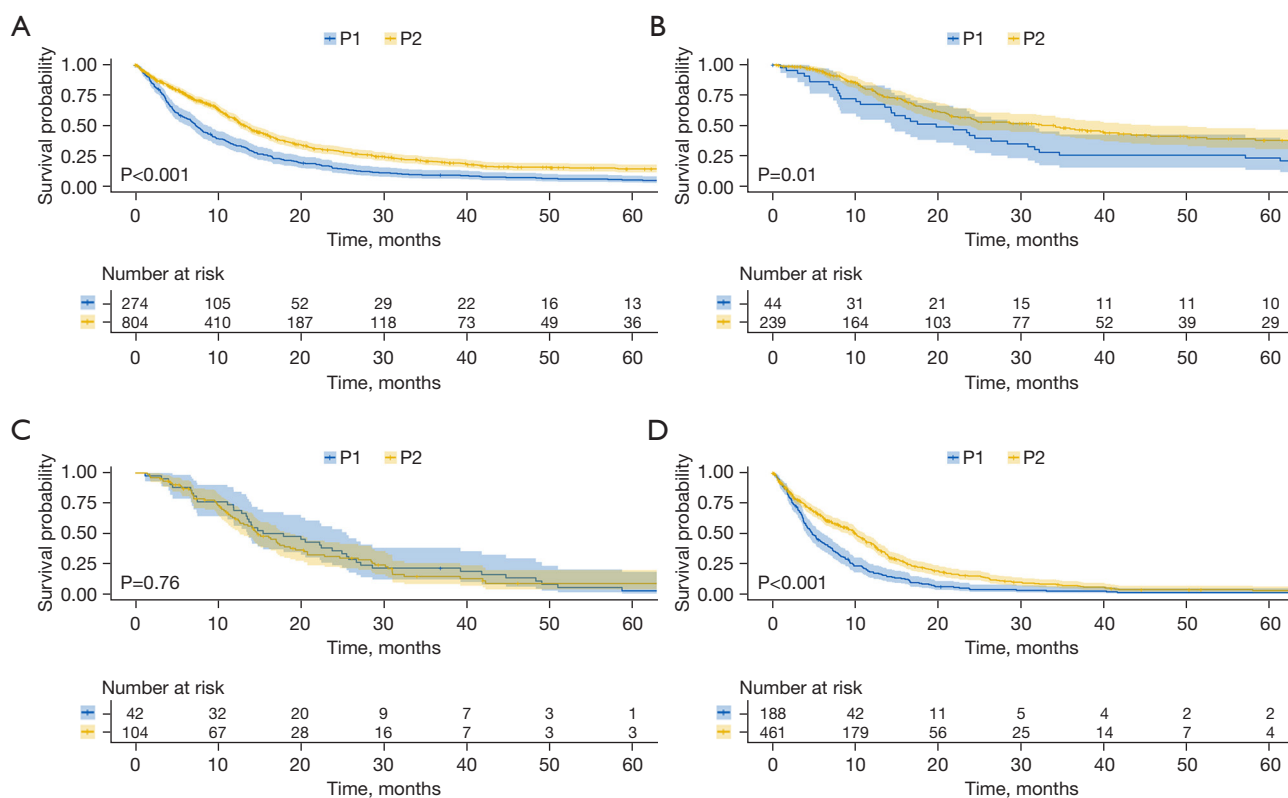


Figure 1 Overall survival. (A) Overall survival for all patients; (B) overall survival for stages I–II; (C) overall survival for stage III; (D) overall survival for stage IV. P1: period 1 (2000–2011); P2: period 2 (2012–2023); HR, hazard ratio; mOS, median overall survival.

and 14.3% in Period 2 [hazard ratio (HR) =0.61, 95% CI: 0.52–0.70, $P<0.001$].

For patients with stages I and II disease, the mOS was 19.7 months (95% CI: 14.3–31.6) in Period 1, and 34.4 months (95% CI: 22.4–45.6) in Period 2 (Figure 1B). The 5-year OS rates were 23.3% in Period 1 and 37.8% in Period 2 (HR =0.63, 95% CI: 0.43–0.91, $P=0.01$). Among patients with stage III disease, the mOS was 16.7 months (95% CI: 13.5–25.5) in Period 1, and 14.8 months (95% CI: 12.6–18.7) in Period 2 (Figure 1C), with 5-year OS rates of 2.7% and 8.7%, respectively (HR =1.06, 95% CI: 0.7–1.57, $P=0.76$). For patients with stage IV disease, the mOS was 4.76 months (95% CI: 4.07–6.18) in Period 1 and 9.99 months (95% CI: 9.07–11.07) in Period 2 (Figure 1D). The 5-year OS rates remained below 5% in both periods (HR =0.60, 95% CI: 0.50–0.72, $P<0.001$).

Discussion

PA remains one of the most lethal malignancies, with a rising incidence in recent years. Screening is currently

limited to high-risk individuals (15), and early-stage symptoms are often vague, leading to late diagnoses in most cases. Consequently, the majority of patients present with advanced disease (16), restricting the potential for curative treatment. Our retrospective analysis supports this trend, showing that most cases are diagnosed at stage IV.

However, a notable finding in our study is the increase in diagnoses at earlier stages (I–II) in recent years. Alongside this shift, OS for these early-stage patients has improved, with a 5-year OS rate of 37.8%. These results underscore the urgent need for improved early detection tools. Additionally, we observed an increasing use of multimodal treatment approaches, primarily involving surgery combined with chemotherapy. Published studies have reinforced the importance of radical resections (17–19) and chemotherapy, whether delivered as neoadjuvant or adjuvant therapy (20,21), in improving curative outcomes for non-metastatic, resectable or potentially resectable tumors.

Chemotherapy regimens have advanced considerably in recent years (22,23). The FOLFIRINOX protocol first demonstrated a significant survival benefit in metastatic

pancreatic cancer (10), quickly becoming a standard since its initial publication in 2011. The decision to divide our analysis into two periods (Period 1: 2000–2011, and Period 2: 2012–2023) was based on the widespread adoption of FOLFIRINOX starting in 2012. Additionally, the combination of nab-paclitaxel plus gemcitabine, which showed superior OS compared to gemcitabine alone in the metastatic setting (11), became available in our country in 2017. Our findings confirm that more active chemotherapy regimens have led to a significant improvement in OS for metastatic patients treated after 2011.

More recently, modified FOLFIRINOX (mFOLFIRINOX) has also demonstrated improved survival in the adjuvant setting when compared to gemcitabine (12,24). Current international guidelines recommend radical resection followed by 6 months of mFOLFIRINOX as the standard of care for fit patients (4,5). Moreover, advancements in less invasive surgical techniques have reduced complication rates (25,26) and promoted quicker recoveries, enabling more patients to complete their treatment regimens. These improvements likely explain the survival gains observed in early-stage (I–II) disease in our cohort.

Notably, a significant proportion of our cohort presented with metastatic disease, which may partially explain the lower rates of multimodal therapy observed (11.3% in Period 1 and 16.7% in Period 2), as most patients with metastatic cancer typically receive chemotherapy as their primary treatment. Additionally, patient conditions, particularly after surgery, may have further limited the administration of adjuvant treatments (27,28).

Nevertheless, no significant survival improvements were seen for stage III patients (T4 or N2 tumors), who often present with borderline resectable disease. This group remains particularly challenging to treat. Current evidence suggests that neoadjuvant chemotherapy or chemoradiotherapy should be employed (29,30), but the optimal regimen remains unclear, and pathological complete response (pCR) rates are low (31).

Finally, our analysis revealed an epidemiological shift in PA. We noted a statistically significant increase in the median age at diagnosis, rising from 62.5 to 66 years in Period 2, alongside a growing proportion of female patients during this period. In a recent nationwide study analyzing data from the National Program of Cancer Registries (2001–2018), researchers observed an overall increase in pancreatic cancer rates among both men and women. Notably, the incidence among women younger than 55 years rose by 2.4% more than in men of the same age,

highlighting a surprising and emerging trend in younger female patients (32). While our findings highlight an older demographic, the rising incidence of early-onset PA underscores the critical need for improved treatment strategies for all age groups.

Our study has several limitations. First, due to the nature of our data source, which comes from medical files but also administrative documents, we were unable to fully describe the treatments received by patients, including specific chemotherapy protocols, settings, dose intensity, and treatment durations. This lack of granularity in treatment data prevents a deeper understanding of treatment patterns and potential variations. Second, we did not evaluate disease-free survival, which is a well-established and important endpoint in PA studies, limiting our ability to assess the effectiveness of interventions in terms of long-term remission. Additionally, the retrospective design of our study may introduce selection bias, as the inclusion of patients was dependent on available administrative records rather than a prospective study design.

Furthermore, we lacked detailed clinical information, such as comorbidities, performance status, and post-treatment complications, which could have influenced treatment decisions and outcomes. Despite these limitations, we present significant data from a large cohort of patients treated in an underrepresented country. Therefore, we believe our findings are valuable as a benchmark for future research in PA care in Brazil.

Conclusions

The findings from this 23-year study highlight improvements in survival outcomes for PA patients, particularly those diagnosed at earlier stages. The increased diagnoses at stage I–II and the significant survival gains observed in these patients reflect advancements in diagnostic tools and therapeutic strategies, including multimodal treatments. However, survival improvements for advanced-stage patients, particularly those with stage III disease, remain limited, emphasizing the need for further research into more effective treatments for these cases.

Additionally, our analysis has revealed important epidemiological trends, such as an increased proportion of female patients. This shift aligns with recent studies reporting a growing incidence of pancreatic cancer, particularly among younger female patients. These findings underscore the need for a comprehensive understanding of the biological features of the disease, including risk factors

in younger individuals. Finally, the increasing complexity of pancreatic cancer cases highlights the necessity for continued innovation in both therapeutic and diagnostic fields.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-2024-942/rc>

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