Editorial

Investigating survival patterns in pancreatic adenocarcinoma over two decades after introducing FOLFIRINOX

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We commend the authors Felismino *et al.* for their thoughtful and timely contribution entitled "Evolving survival patterns in pancreatic adenocarcinoma: a 23-year retrospective observational analysis". In this important study, the authors present a robust retrospective analysis of treatment outcomes in patients with pancreatic adenocarcinoma (PDAC) treated at a major cancer center in Brazil. By analyzing a large cohort over a 23-year period, the authors offer a valuable window into the temporal evolution of clinical outcomes, treatment patterns, and demographic shifts associated with PDAC. By structuring their analysis around the pre- and post-FOLFIRINOX eras, the study captures one of the most significant changes in systemic therapy for pancreatic cancer in recent decades and contextualizes it within real-world clinical practice (1).

A total of 1,078 patients were analyzed, with 274 in Period 1 (pre-FOLFIRINOX) and 804 in Period 2 (post-FOLFIRINOX). Period 2 showed a higher proportion of female patients (50.9% *vs.* 43.8%, P=0.051) and an increase in median age at diagnosis (66 *vs.* 62.5 years, P<0.001). Early-stage (I–II) tumors were more frequently diagnosed in Period 2 (29.8% *vs.* 16%, P<0.001). Use of chemotherapy (70.1% to 83.2%, P<0.001) and multimodal therapy (11.3% to 16.7%, P<0.001) increased over time. Median overall survival improved from 7.3 to 13.2 months (P<0.001), with 5-year survival rising from 5.2% to 14.3%. Among early-stage patients, median OS increased from 19.7 to 34.4 months (P=0.01). No significant survival difference was observed for stage III disease (16.7 *vs.* 14.8 months, P=0.76), but outcomes for stage IV significantly improved (4.8 *vs.* 10 months, P<0.001) (1).

PDAC remains one of the most lethal solid malignancies, with a persistently dismal prognosis. Despite advances in surgical technique, chemotherapeutic regimens, and imaging modalities, PDAC is often diagnosed at an advanced stage, limiting curative treatment options and contributing to its high mortality rate. In most industrialized nations, PDAC is now among the top five leading causes of cancer-related death, and its incidence continues to rise globally (2). The reasons behind this increase are multifactorial and likely include aging populations, improved diagnostic capabilities, environmental exposures, and possibly changes in lifestyle and metabolic diseases. Importantly, the authors' findings are situated in the context of a developing country, where access to multidisciplinary cancer care and high-cost therapies may be limited, rendering their data even more impactful. Although mostly detected at an advanced stage, recently not only the median age at diagnosis but also the median overall survival has increased (3).

The therapeutic landscape of PDAC underwent a major paradigm shift in 2011 with the publication of the ACCORD-11 trial by Conroy *et al.*, which demonstrated the superiority of the multi-agent chemotherapy regimen FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) over gemcitabine in patients with metastatic pancreatic cancer and good performance status (4). This was

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followed by Von Hoff *et al.*'s MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial) study, which showed improved outcomes with nab-paclitaxel plus gemcitabine over gemcitabine monotherapy (5). These and other landmark trials provided oncologists with more effective treatment options and led to widespread adoption of these regimens in both metastatic and neoadjuvant settings (6,7). In parallel, surgical techniques have evolved toward more aggressive and anatomically complex resections, supported by advances in vascular reconstruction, intraoperative imaging, and enhanced recovery protocols. In high-volume centers, even patients with borderline resectable or locally advanced disease may now undergo curative-intent surgery following successful neoadjuvant therapy.

Felismino *et al.* provided a comprehensive and nuanced analysis of these trends over more than two decades of care. Their retrospective study found that the median age at diagnosis increased significantly from 62.5 years in Period 1 to 66 years in Period 2, suggesting a demographic shift in the disease population. Simultaneously, the incidence of early-stage disease (stages I and II) increased over time. While the retrospective design precludes establishing causality, these findings are consistent with broader epidemiological data suggesting improved diagnostic yield and possibly greater disease awareness. Early-stage detection is critically important in PDAC, as it significantly improves the likelihood of surgical resection with curative intent, which remains the cornerstone of long-term survival.

The most clinically striking observation in the study is the marked improvement in survival in early-stage PDAC following the introduction of FOLFIRINOX. The authors reported an increase in 5-year overall survival from 23.3% to 37.8%—a notable gain that supports the integration of modern systemic therapies into multimodal treatment regimens. Interestingly, improvements in 5-year OS were much more modest in stage III patients and remained negligible (<5%) in stage IV disease across both periods. This reflects the limited efficacy of current systemic therapies in controlling advanced disease and reinforces the necessity of focusing on early detection, resectability, and tumor biology.

Another important contribution of the study is the documentation of increased utilization of multimodal therapies over time. In addition to more frequent use of systemic chemotherapy, surgical resection appeared to be more commonly pursued in early-stage patients.

One of the most provocative findings in the study is the disproportionate increase in PDAC incidence among younger women (<55 years) compared to men in the same age group. Although the study does not identify specific causes for this trend, it raises important questions about the underlying biology of pancreatic cancer and its risk factors. Traditional risk factors, including smoking, diabetes mellitus, obesity, chronic pancreatitis, and family history do not fully explain this gender-specific shift (8).

Felismino *et al.*'s data also prompt reflection on disparities in cancer care delivery, particularly in middle-income countries like Brazil. Access to complex surgical procedures, advanced chemotherapy regimens, and supportive care can be inconsistent, especially in public healthcare settings. The apparent improvement in outcomes, even within these constraints, speaks to the dedication of the treating teams and underscores the importance of institutional efforts to standardize cancer care and implement evidence-based protocols.

It is important to note that while retrospective studies have inherent limitations, including potential changes in staging criteria, imaging quality, and supportive care, the long follow-up period of over two decades adds a rich layer of context. The authors' use of well-defined time periods and a single institutional cohort enhances internal validity, although generalizability may be somewhat limited. Nevertheless, their real-world data offer critical insights into the evolving natural history of PDAC under routine clinical care and serve as an important benchmark for future research.

Furthermore, the findings have implications for future directions in pancreatic cancer research. As systemic chemotherapy approaches a plateau in its benefit for advanced disease, attention is increasingly turning to precision medicine, immunotherapy, and molecular profiling. Biomarkers such as circulating tumor DNA (ctDNA), CA19-9 dynamics, radiomics, and transcriptomic subtypes are being explored to refine prognosis, guide treatment selection, and monitor minimal residual disease (9-11). Incorporating such technologies into real-world clinical practice will require multidisciplinary collaboration and significant investment in infrastructure, but the potential benefits for patient selection and individualized care are substantial.

In conclusion, the work by Felismino *et al.* represents a valuable addition to the growing body of literature on pancreatic cancer. By leveraging a large institutional dataset over a prolonged period, the authors demonstrate real-world improvements in survival outcomes, particularly in early-stage disease, and highlight important demographic

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and epidemiologic shifts. Their work reaffirms the positive impact of modern systemic therapies while exposing the continuing challenges in managing advanced-stage disease. As the field moves toward precision oncology and integrated care models, studies such as this provide essential context and guidance. We acknowledge the authors on their important contribution and look forward to future research that builds upon these findings to improve the care of patients with pancreatic adenocarcinoma worldwide.

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Footnote

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