Original Research

GASTROENTEROLOGY

Pancreatic cancer: a persistently challenging prognosis - a single center three-year retrospective study

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Abstract

Background. Pancreatic adenocarcinoma (PDAC) is a leading cause of cancer-related mortality due to its aggressive progression and late diagnosis. Despite advances in diagnosis and treatment, survival outcomes remain poor, with a median survival of 5.8 months.

Objective. The aim of the study is to evaluate the impact of diagnostic and therapeutic approaches on survival outcomes in patients with pancreatic adenocarcinoma, while also assessing the risk factors for PDAC.

Methods. This study is a retrospective analysis of 68 patients with suspected pancreatic tumors who underwent endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNAB) between 2019 and 2022 at the Cluj-Napoca County Emergency Clinical Hospital. Patient demographics, risk factors, histopathological results, and treatment outcomes were analyzed using statistical methods.

Results. Of 68 patients, 35 were diagnosed with PDAC. Modifiable risk factors, such as alcohol and smoking, alongside non-modifiable factors like age and hereditary predisposition, were prominent. Among PDAC patients, 42.8% received palliative chemotherapy, while only 8.6% underwent curative surgical intervention due to advanced disease stages. Median survival varied significantly based on treatment: 2.4 months for untreated patients versus 8.1 months for those receiving oncological or surgical management (p=0.0082).

Conclusion. Modifiable and non-modifiable risk factors significantly raise the incidence of pancreatic cancer. Therefore, employing a multidisciplinary approach to detect the disease in its early stages and optimize personalized treatment plans can enhance patient outcomes. At the same time, traditional oncological treatments improve survival and quality of life, but newer approaches, such as immunotherapy combined with conventional radiotherapy, chemotherapy, molecular targeted therapy, and other diverse treatment modalities, have the potential to further extend survival.

Keywords: pancreatic adenocarcinoma, echo-endoscopy, oncological treatment

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Introduction

Pancreatic adenocarcinoma is the most common pancreatic cancer, representing 90% of cases, and originates in the enzyme-producing tissues of the pancreas. Symptoms such as jaundice, abdominal pain, significant weight loss, fatigue, and appetite loss typically manifest in advanced stages, delaying diagnosis and leading to widespread metastasis [1,2].

Pancreatic ductal adenocarcinoma (PDAC), a highly lethal malignancy that mimics the glandular structure of pancreatic ducts, remains a leading cause of cancer mortality. Despite recent advances in treatment, which have increased the 5-year survival rate to 10%, pancreatic cancer is currently the third leading cause of cancer deaths and is projected to become the second by 2030 [3,4].

Etiology

Pancreatic cancer is linked to both non-modifiable and modifiable risk factors. Non-modifiable factors include age, gender, blood type, diabetes, family history, and genetic predisposition. Most cases occur in individuals over 55, peaking between 70 and 80 years. Men exhibit a higher risk, potentially due to protective effects of female steroid hormones. Additionally, individuals with blood types A, AB, or B have a higher risk compared to those with type O [5].

Genetic mutations play a significant role in pancreatic cancer. The K-RAS oncogene and tumor suppressor genes, including p53, SMAD4/DPC4, and CDKN2A, are frequently mutated. Familial predisposition is associated with BRCA1/2 mutations, present in 4-7% of cases, and other genetic syndromes like familial adenomatous polyposis, Gardner syndrome, hereditary non-polyposis colorectal cancer, von Hippel-Lindau syndrome, multiple endocrine neoplasia and familial atypical multiple mole melanoma syndrome. Modifiable risk factors include smoking, obesity, chronic pancreatitis, and alcohol abuse [6].

Treatment

Surgery is the only potentially curative option, but only 15-20% of patients are eligible for resection due to late diagnosis. Even after complete resection, the 5-year survival rate remains low, at 15-30%. Neoadjuvant chemotherapy (NAT) or chemoradiotherapy is recommended for borderline resectable tumors to improve surgical outcomes. In borderline unresectable cases, NAT can increase the likelihood of future resection [7].

FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin), is the most used chemotherapy regimen. Radiotherapy may be added for locally advanced tumors. The main goals of NAT are tumor size reduction, control of micrometastases, and better patient selection for surgery. Postoperative treatment involves adjuvant chemotherapy or chemoradiotherapy to improve long-term prognosis [8-10].

Diagnostic process

Endoscopic ultrasound (EUS) is a key diagnostic tool for pancreatic tumors, offering superior sensitivity (92%-100%), specificity (89%-100%), and accuracy (86%-99%) compared to computed tomography, especially for small tumors (0.5-2 cm). EUS also allows for biopsy, aiding in histopathological diagnosis, which guides treatment decisions [11,12].

Histopathological examination is the gold standard for pancreatic cancer diagnosis. PDAC, the most common and aggressive form, consists of atypical tubular glands within a dense stroma. Mucin production characterizes ductal differentiation in pancreatic tumors, with varying levels across tumor types. Common immunohistochemical markers include cytokeratins (CK7, CK8, CK12, CK18, CK19), CA19-9, B72.3, CA-125, and DUPAN 2, while newer markers such as claudin 18, S-100 protein, mesothelin, and prostate stem cell antigen have also been noted [13-15].

A key feature of PDAC is the desmoplastic reaction, where pancreatic stellate cells produce collagen and extracellular matrix components, creating a fibrotic, hypoxic microenvironment conducive to tumor growth and metastasis. This stroma actively promotes cancer progression and resistance to treatment, partly through proteins like SPARC and the hedgehog signaling pathway [16].

Epithelial-to-mesenchymal transition (EMT) is a critical process in pancreatic cancer progression. During EMT, tumor cells lose epithelial traits and gain mesenchymal properties, facilitating invasion and metastasis. This transition is marked by decreased E-cadherin expression, increased N-cadherin and vimentin levels, and elevated expression of transcription factors such as Snail, Slug, Twist, ZEB1, and ZEB2 [16,17].

Aim of the study

The study aims to evaluate the impact of diagnostic and therapeutic approaches on the survival outcomes of patients with pancreatic adenocarcinoma. Specifically, it seeks to assess the role of ultrasound endoscopy with fine needle aspiration biopsy (EUS-FNAB) in early detection, the efficacy of emerging adjuvant, neoadjuvant, and palliative radio-chemotherapy treatments in prolonging survival, and the importance of histopathological examination in guiding treatment decisions. The study also aims to identify modifiable and non-modifiable risk factors contributing to the incidence of pancreatic cancer, emphasizing the necessity of a multidisciplinary approach to optimize individualized treatment plans for improved patient outcomes.

Methods

Our study is a retrospective study that used the case records of the Gastroenterology department of the Cluj-Napoca County Emergency Clinical Hospital. For this study, it was necessary to analyze the observation sheets

and laboratory tests through the "Atlas Med" application from the archive of the Gastroenterology section from 2019-2022.

During these 3 years, there were 98 echo-endoscopies for patients with suspected pancreatic tumors, of which 68 underwent fine needle aspiration biopsy for histopathological examination. Among the 68 patients who underwent EUS-FNAB, 7 patients required repeat echo-endoscopy due to insufficient material sampled for histopathological analysis. Ten patients had minor complications: abdominal pain of moderate intensity that recovered with the administration of analgesics, minimal bleeding visualized ultrasonographically but with stationary hemoglobin, and mild pancreatic cytolysis syndrome with lipase values up to 2 times the reference value. For this study, the cases were studied according to the following criteria: sex and age (information that was taken from the observation sheets), the final diagnosis of pancreatic tumors based on the results of histopathological examinations (information retrieved from the hospital's digital database through the "AtlasMed" platform), modifiable and non-modifiable risk factors for pancreatic cancer, and the treatment followed after the communication of the histopathological result (oncological, surgical, or both).For modifiable risk factors, we analyzed the main contributors to pancreatic cancer, including obesity, smoking, chronic pancreatitis, and alcohol consumption. These factors, particularly smoking and alcohol consumption, have a high prevalence in the Romanian population. On the other hand, for non-modifiable risk factors, we included age over 50, given the increased risk of cancer with aging. Additionally, we considered the presence of diabetes, gender, and a family history of pancreatic cancer.

To process and create the tables, we used the spreadsheet program Microsoft Excel 2019 to calculate the minimum, maximum, average, median, and standard deviation, and the statistical analysis was performed using the GraphPad Prism 9 program, where T-Student and Chi-Square tests were used. The level of statistical significance was set at $p<0.05$. The study was approved by the local ethics committee of the Cluj-Napoca County Emergency Clinical Hospital.

Results

Our study included 68 patients who required echo-endoscopy with fine needle biopsy for patients with suspected pancreatic tumor of unspecified etiology, in whom the clinical, paraclinical and imaging diagnosis was inconclusive, or for patients in whom the histopathological result was unavoidable for the initiation of oncological treatment. The gender distribution of patients in our study was 54% male and 46% female (Figure 1). Thus, there is a significant difference in this sense, in favor of the male sex. It should be noted that figure 1 shows the gender distribution in the case of all patients, so we have added figure 2 to identify the gender distribution in the case of PDAC patients. According to the graph, the predominance of the male gender can be observed with a percentage of 57%, compared to the female gender, with a percentage of 43% (Figure 2).

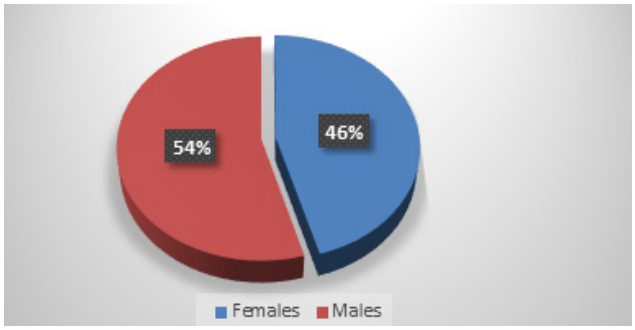

Figure 1. Gender distribution among patients with suspected pancreatic cancer.

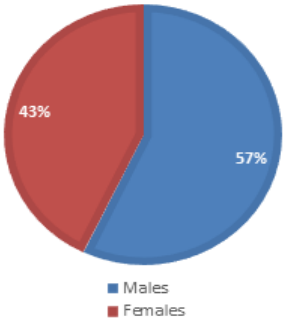

Figure 2. Gender distribution among patients with PDAC.

Of the total number of patients who underwent echo-endoscopy with aspiration biopsy (n=68), 35 had the histopathological diagnosis of pancreatic adenocarcinoma. Figure 3 shows modifiable and non-modifiable risk factors in patients with pancreatic adenocarcinoma. The most important non-modifiable factor was age over 50 years, but hereditary antecedents also had an important weight (17.14%). On the other hand, alcohol was the most common modifiable risk factor in our study (20%), and smoking was in 2nd place (14.28%).

Of the total number of patients who underwent EUS-FNAB in our service with the histopathological result of pancreatic adenocarcinoma (n=35) (Figure 4), 42.8% required palliative chemotherapy, 31.4% of patients did not receive any treatment due to the late diagnosis of PDAC, which was associated with a high-performance status (ECOG 3-4) or multiple comorbidities, making chemotherapy unfeasible. This group also included patients who declined chemotherapy by their own decision. The remaining patients required adjuvant chemotherapy (n=3), neoadjuvant (n=6) and radiotherapy (n=2).

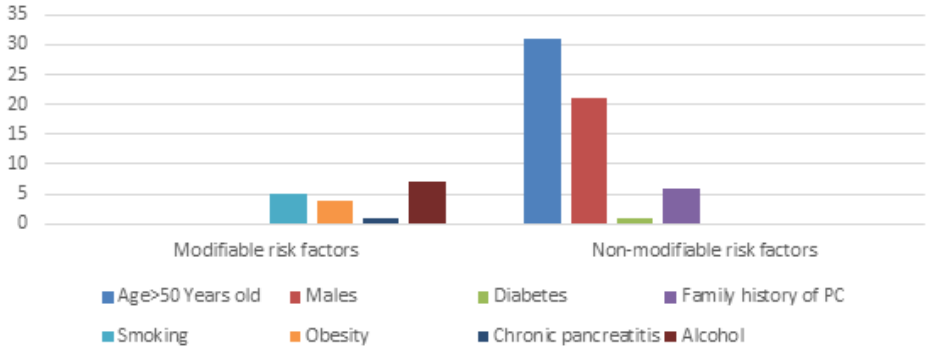

Figure 3. Distribution of risk factors in patients with PDAC.

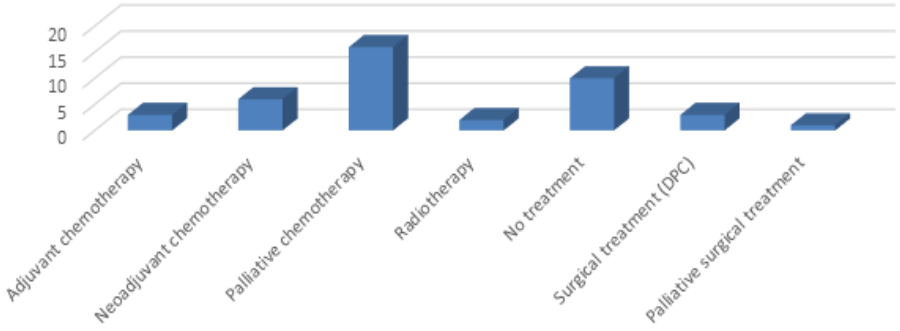

Figure 4. Survival time distribution by treatment approach, including untreated patients.

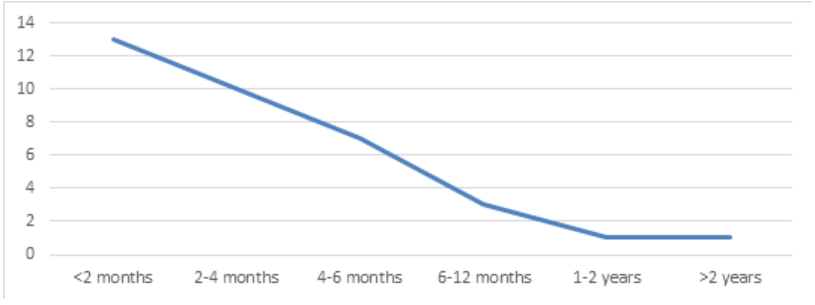

Figure 5. Distribution of survival time after histopathological confirmation of PDAC.

Palliative treatment in the case of the 15 patients had an average duration of 4.1 months until the death of the patients. As previously mentioned, the only curative treatment in PC is surgical treatment, namely CDP (Cephalic Duodenopancreatectomy). In the case of our study, only 3 patients benefited from surgical treatment, due to the advanced TNM stage that did not allow safe surgical intervention.

Figure 5 shows the distribution of the survival period after the histopathological diagnosis in the case of patients with pancreatic adenocarcinoma. The survival period with the higher incidence is under 2 months (n=13). The median survival for patients included in our study was 6.2 months.

To evaluate survival differences among patients with PDAC, we analyzed Kaplan-Meier survival curves (Figure 6) across three groups: those who received treatment (n=25), those who were ineligible due to poor performance status (ECOG 3-4) or multiple comorbidities

(n=7), and those who declined treatment by personal choice (n=3). This analysis aimed to determine whether a statistically significant difference exists between these groups, especially between the two groups that have not received treatment.

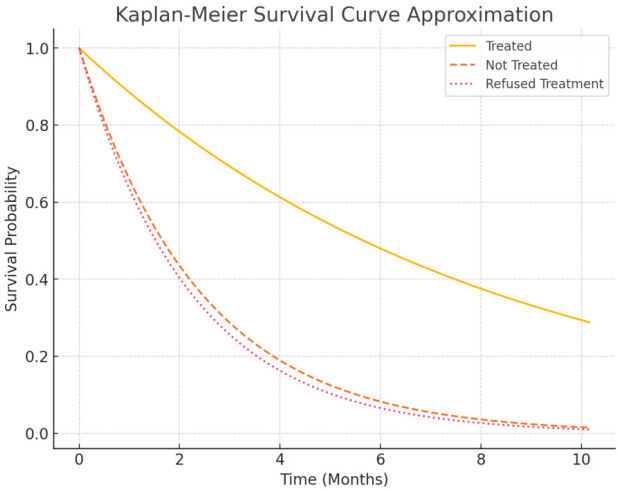

Figure 6. Comparison of survival outcomes among treated, untreated, and those who refused treatment.

To evaluate the influence of individual factors on overall survival, we conducted a multivariate Cox proportional hazards regression analysis (Figure 7 and Table I). This model incorporated multiple covariates, including gender, age, performance status, and comorbidities, alongside time-to-death and event status (death or censored survival). As shown in table V, age was significantly associated with increased mortality risk, with a hazard ratio (HR) of 1.38 (95% CI: 1.26–1.52; $p < 0.0001$). This indicates that each additional year of age is associated with a 38% increase in the hazard of death, independent of other variables. The confidence interval does not cross 1, confirming a statistically robust association. In contrast, comorbidities were not significantly associated with survival outcomes (HR = 1.11; 95% CI: 0.48–2.59; $p = 0.81$), although a slight increase in hazard cannot be entirely ruled out.

Table II shows the statistical analysis of the death rate after 6 months in the case of pancreatic adenocarcinoma compared to other types of pancreatic tumors. The P value was 0.0001 ($p<0.05$), which means that there is a statistically significant difference between the presence of PDAC and the death of the patient earlier than 6 months from diagnosis, so we can rule out the hypothesis H0 (null hypothesis) and instead we will accept the alternative hypothesis H1. We can therefore state that adenocarcinoma has a very high short-term mortality rate.

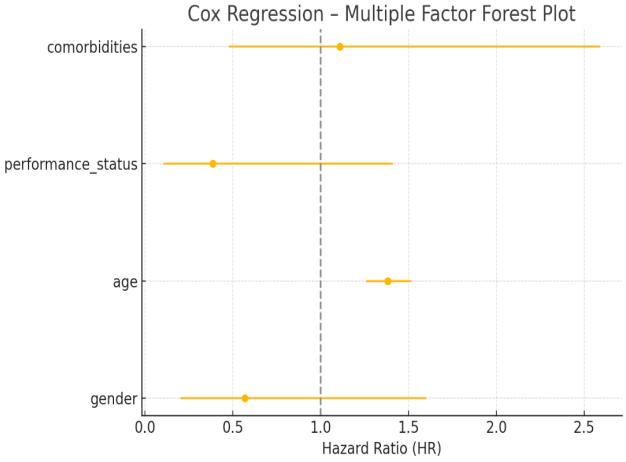

Figure 7. Analysis of multiple individual factors influencing overall survival in patients with PDAC.

Table III presents the statistical analysis of the difference in the mortality rate in patients with pancreatic adenocarcinoma who underwent oncological or surgical treatment compared to patients who did not undergo treatment. The treatment group included also patients with grade IV adenocarcinoma, but with low performance status (ECOG 0-2). In contrast, patients in the non-treatment group had a high-performance status (ECOG grade 3-4), who were unable to undergo treatment due to their critical condition. P value was 0.0082 ($p<0.05$), which means that there is a statistically significant difference between survival beyond 6 months and the initiation of surgical and/or oncological treatment in patients with PDAC, so we can rule out the hypothesis H0 (null hypothesis) and instead we will accept the alternative hypothesis H1. We can therefore state that the initiation of oncological and/or surgical treatment in the case of PC patients increases the survival rate compared to patients who do not follow any treatment.

Table I. Analysis of multiple individual factors influencing overall survival in patients with PDAC.

Variable	HR (Hazard Ratio)	95% CI Lower	95% CI upper	p-value
Gender (male)	0.57	0.20	1.60	0.285
Age	1.38	1.26	1.52	<0.001
Performance status	0.39	0.11	1.41	0.150
Comorbidities	1.11	0.48	2.59	0.808

Table II. Statistical analysis of the 6-month mortality rate in PDAC compared to other types of pancreatic tumors.

Survival >6 months	Pancreatic adenocarcinoma	Other types of pancreatic tumors	TOTAL	P Value (α=0.05)
Yes	5	30	35	P=0.0001
No	30	3	33	
TOTAL	35	33	68	

Table III. Analysis of differences in mortality rates among patients with PDAC who received oncological or surgical treatment compared to those who received no treatment.

Surgical or oncological treatment	Survival >6 months	Survival <6 months	TOTAL	P Value (α=0.05)
Yes	18	7	25	P=0.0082
No	2	8	10	
TOTAL	20	15	35	

Table IV. Survival rate analysis among PDAC patients who did not receive treatment.

	Median	Average	Standard Deviation	Minimum	Maximum
Survival (months) (n=10)	2	2.4	1,647	1	6

Table V. Survival rate analysis among PDAC patients who received treatment.

	Median	Average	Standard Deviation	Minimum	Maximum
Survival (months) (n=25)	6	8.166	7,346	2	36

In tables IV and V we analyzed the data on the survival rate of patients with pancreatic adenocarcinoma according to the presence or absence of oncological or surgical treatment. The median survival in the group of patients without treatment was only 2.4 months, and on the other hand, patients with PC treated oncological and/or surgically had an overall survival of 8.1 months. Thus, initiation of treatment in PC increases survival, but short-term mortality remains very high.

Discussion

According to GLOBOCAN, the incidence of PC is higher in men (5.7 per 100,000 inhabitants) compared to women (4.1 per 100,000 inhabitants). This disparity suggests that differences in environmental exposures and genetic variations may contribute to the increased incidence of PC among the male population. It is also observed that gender differences in PC incidence tend to decrease with advancing age, this is due to the decrease of steroid hormones in females after menopause, which may have a protective role [18].

Our study's findings align with data reported in specialized journals, supporting the assertion that both modifiable and non-modifiable risk factors influence the risk of developing pancreatic adenocarcinoma. Modifiable risk factors, such as alcohol consumption and smoking, alongside non-modifiable risks like age and hereditary predisposition, significantly increase the likelihood of PC. A 2015 meta-analysis, which examined 37 etiological factors for PC across 117 reports, underscored the critical role of modifiable risk factors. By integrating these estimates with population prevalences, population attributable or preventable fractions were calculated, revealing that about two-thirds of the major risk factors for PC are potentially modifiable. This presents a unique opportunity to prevent one of the most lethal cancers. Tobacco smoking, with "strong" evidence, is identified as the leading risk factor, with population attributable fractions ranging from 11% to 32% in various populations. Conversely, protective factors such as a history of allergy ("strong" evidence) and increased intake of fruits or folate ("moderate" evidence) were associated with preventable fractions of 3% to 7% and 0% to 12%, respectively. [19-21]

For the 4th chart of this study, we compared our data with a large retrospective study involving 625 patients with PC treated at Shengjing Hospital of China Medical University between 2013 and 2017. Among these patients, 569 were followed for a period ranging from 1 to 75 months, with a median overall survival of 9.3 months. The overall survival rates at 1, 3 and 5 years were 37.8%, 15.1%, and

10.5%, respectively. Our study's results, although differing from the Shengjing Hospital study, are not statistically significant due to the inclusion of untreated patients in our cohort, which slightly reduced the mean survival rate [22]. In our study, the higher mortality in the untreated group may also be attributed to the presence of multiple comorbidities, particularly cardiac pathology.

The Kaplan-Meier survival curves illustrate distinct survival trends among the three patient groups. Patients who received treatment for pancreatic cancer (Treated group) demonstrated the highest survival probability over time. In contrast, patients who did not receive treatment (Untreated group) and those who refused treatment by choice (Refused group) exhibited significantly lower survival probabilities, with both groups experiencing rapid declines. At the start of the observation period (time = 0 months), all groups had a survival probability of 1.0 (100%). Over time, the Treated group maintained a higher survival probability, indicating that patients who underwent treatment tended to live longer. Conversely, the Untreated and Refused groups showed a steep decline in survival early on, suggesting that most patients in these groups did not survive beyond a few months. Comparison Between Groups showed that the treated group exhibited a slower decline in survival probability, reinforcing the significant survival benefit associated with treatment. In contrast, the Untreated and Refused groups had nearly identical survival curves, indicating that the absence of treatment—whether due to unavailability or personal choice—resulted in similarly poor outcomes. The median survival time (when 50% of patients had died) appeared to be considerably longer in the Treated group compared to the other two groups. These findings underscore the critical role of treatment in prolonging survival in pancreatic cancer patients. Without treatment, survival is markedly poor, with death occurring within a few months. Furthermore, refusing treatment leads to outcomes similar to those of untreated patients, highlighting an important consideration for patient counseling and shared decision-making.

The multivariate Cox regression analysis revealed that age was the only variable with a statistically significant association with overall survival. This finding reinforces the well-established observation that the risk of pancreatic ductal adenocarcinoma (PDAC) increases with age, and that elderly patients tend to have poorer survival outcomes. In contrast, gender and performance status did not show statistically significant effects, which may be attributed to the limited sample size or a true absence of association. As previously noted, comorbidities demonstrated a hazard ratio greater than 1, indicating a potential trend toward increased mortality among patients with comorbid conditions. Although the p-value was not statistically significant ($p > 0.05$), this result may be influenced by the relatively small number of patients with comorbidities, limiting the power to detect a meaningful difference.

A comprehensive retrospective study conducted in 2023 analyzed the incidence of PC (n=167) in 21,141 individuals from 4,433 families registered in the National Registry of Familial Pancreatic Cancer. The study used concurrent risk regression to estimate the cumulative probability of PC, finding that the risk is significantly influenced by family history, particularly the degree of relation and the age of onset of PC in relatives. These risk estimates are crucial for designing early detection studies and evaluating the risks and benefits of screening programs [23,24].

Pancreatic cancer remains one of the most aggressive malignancies, with the lowest survival rates among all cancers. As Smeenk et al. noted in a recent critical review of PC therapies, long-term survival is achieved only in a small subset of patients. The poor prognosis of PC is largely attributed to its aggressive biological nature, early metastasis, lack of early specific symptoms, and late clinical diagnosis, which precludes the application of potentially curative treatments. This observation is consistent with data from the Cluj-Napoca County Emergency Clinical Hospital database, where PC is seldom treated curatively through cephalic pancreaticoduodenectomy, with most patients receiving only palliative care [25-27].

The standard of care for PC is initial surgical resection followed by 6 months of adjuvant chemotherapy within 12 weeks of surgery. The foundation of adjuvant chemotherapy was established by the CONKO-1 study. In its 2013 updates, after a median follow-up of 136 months, adjuvant gemcitabine (Gem) improved overall survival (OS) compared with placebo, with a median survival of 22.8 versus 20.2 months. In 2018, the study of the practice-changing phase III PRODIGE-24 showed that, compared with gemcitabine, 6 months of adjuvant mFOLFIRINOX (modified fluorouracil, irinotecan, and oxaliplatin) improved survival from 35 months to 54 [28].

The main limitations of this study stem from its unicentric design and the small sample size, which reduces statistical power and increases the risk of a Type II error (false negative). To draw more robust conclusions, future research should include a larger cohort. Another limitation was the exclusion of patients due to non-compliance with oncological treatment, which may have negatively influenced the results. Additionally, some patients did not attend their scheduled gastroenterology follow-ups, further impacting data completeness. Moreover, the study population is limited to Transylvania, which may not fully represent the entire Romanian population due to demographic heterogeneity. Consequently, a statistical error related to the lack of generalizability may be present.

Conclusion

EUS-FNAB did not improve survival in pancreatic adenocarcinoma due to late diagnosis, aggressive tumor biology, and early dissemination. Radio-chemotherapy

extends survival by about four months, but surgery remains the only curative option.

With a median survival of 5.8 months, pancreatic adenocarcinoma remains highly lethal. Traditional oncologic therapies improve survival and quality of life, but novel approaches, including immunotherapy withtargeted therapies, stroma-modulating agents, and multi-modal treatments, hold promise for further extending survival. Addressing risk factors and ensuring early detection through a multidisciplinary approach are crucial. Advancements in personalized medicine and integrated therapeutic strategies could significantly enhance patient outcomes, making a multidisciplinary approach vital in optimizing treatment strategies for pancreatic cancer.

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