**Open Access Library Journal**
2024, Volume 11, e11384
ISSN Online: 2333-9721
ISSN Print: 2333-9705

# Descriptive Study of Localized Pancreas Cancers: Experience of CHU Hassan II of Fes

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**How to cite this paper:** Chouef, J., Amaadour, L., Medyouni, H., Siyouri, O., Elhakym, S., Elhilali, H., Oualla, K., Benbrahim, Z., Arifi, S. and Mellas, N. (2024) Descriptive Study of Localized Pancreas Cancers: Experience of CHU Hassan II of Fes. *Open Access Library Journal*, **11**: e11384.
http://doi.org/10.4236/oalib.1111384

**Received:** March 1, 2024
**Accepted:** April 20, 2024
**Published:** April 23, 2024



## Abstract

Pancreatic cancer is on the rise, ranking 13th among cancer sites in the world and 5th among digestive cancers. Real-life national data on patients with localized pancreatic adenocarcinoma are lacking in the medical literature given their number, which is often not representative because most diagnoses are made at the metastatic stage. The main objective of this study, which is part of the activity report of the Medical Oncology Department of the Hassan II University Hospital of Fez, is to report the survival results of localized pancreatic adenocarcinomas collected at the said department and to determine the prognostic factors associated with this survival depending on the year while comparing them to global results.

## Subject Areas

Medical Oncology

## Keywords

Pancreatic Cancer, Adenocarcinoma, Surgery, Adjuvant Chemotherapy

## 1. Introduction

Pancreatic cancer is on the rise, ranking 13th among cancer sites in the world and 5th among digestive cancers. [1] [2]

Between 20% and 40% of tumors appear localized [3]. The therapeutic approach for localized ADK of the pancreas is based on the identification of its resectability by triphasic injected MRI or CT. The latter is the subject of consensus; it is the relationship of the tumor with the vascular structures, mainly portal and Celio-mesenteric, which determines its feasibility [4] [5]. The classifications agree on the resectable nature in the absence of vascular involvement and unre-

sectable when the arterial contact is more than 180˚ in circumference.

Real-life national data on patients with localized pancreatic adenocarcinoma are lacking in the medical literature given their number, which is often not representative because most diagnoses are made at the metastatic stage.

The main objective of this study, which is part of the activity report of the Medical Oncology Department of the Hassan II University Hospital of Fez, is to report the survival results of localized pancreatic adenocarcinomas collected at the said department and to determine the prognostic factors associated with this survival depending on the year while comparing them to global results.

## 2. Methodology

This is a retrospective descriptive and analytical study of patients admitted for the management of localized ADK of the pancreas proven histologically and treated by surgery followed by adjuvant chemotherapy over a period extending from January 2014 to June 2022 within the Medical Oncology Department of the Hassan II University Hospital of Fez.

We excluded pancreatic neuroendocrine tumors, metastatic pancreatic cancers, unresectable pancreatic tumors, patients not treated with adjuvant chemotherapy, files without histological proof.

The data for this retrospective study were collected from the register of the Medical Oncology Department of the Hassan II University Hospital of Fez, the computerized database and telephone calls to patients or their families. The statistical study, both descriptive and analytical, was carried out using Microsoft Office Excel software. The data were then transferred and analyzed using SPSS software. Qualitative variables were expressed as a percentage and quantitative variables as mean ± standard deviation. Overall survival as well as relapse-free survival were analyzed according to the Kaplan-Meier method and expressed as median. Chi-square test and logistic regression model were used to determine the association between prognostic factors and patient survival.

## 3. Results

During the period of our study, the medical oncology department of the HASSAN II University Hospital of Fez collected 31 cases of localized ADK of the pancreas resectable and treated by adjuvant chemotherapy, which corresponds to 10% of all pancreatic cancers all stages combined. The annual frequency of new cases was generally homogeneous. The average age of our patients at the time of diagnosis of ADK of the pancreas was 54.35 ± 11.33 years with extremes ranging from 29 years to 72 years, a male predominance was objectified with a sex ratio of 1.58.

Diabetes and tobacco were the most frequently encountered factors. (Table 1)

The time between the first clinical manifestations and the discovery of cancer was 3.24 ± 3.1 months (with a maximum of 12 months and a minimum of 15 days). The most frequent functional symptoms were: static choleric jaundice,

**Table 1.** Distribution of patients according to history.

| Pathological history | | Workforce | Percentage |
|---|---|---|---|
| **Personal medical history:** | | | |
| ✓ | Chronic pancreatitis | 2 | 6.5% |
| ✓ | Chronic cholecystitis | 1 | 3.2% |
| ✓ | Cancer | 2 | 6.5% |
| **Comorbidities:** | | | |
| ✓ | Diabetes | 8 | 25.8% |
| ✓ | HT | 3 | 9.7% |
| ✓ | Heart disease | 0 | 0% |
| ✓ | Obesity | 0 | 0% |
| **Toxic habits:** | | | |
| ✓ | Smoking | 9 | 29% |
| ✓ | Alcoholism | 2 | 6.5% |
| ✓ | Cannabism | 0 | 0% |
| **Personal surgical history:** | | | |
| ✓ | Cholecystectomy | 1 | 3.2% |
| ✓ | Thyroidectomy | 1 | 3.2% |
| ✓ | Hernia and Appendectomy | 1 | 3.2% |
| ✓ | Nephrectomy | 1 | 3.2% |
| **Family history:** | | | |
| ✓ | Diabetes | 0 | 0% |
| ✓ | Chronic pancreatitis | 0 | 0% |
| ✓ | HT | 1 | 3.2% |
| ✓ | Cancer | 4 | 12.9% |
| **Without any particular history** | | 10 | 32.26% |

cachexia and abdominal pain (epigastralgia and CDH pain). Furthermore, 10% of patients consulted for non-specific symptoms such as fever, vomiting, and transit disorders.

The diagnosis was made by a biopsy. All the biopsies performed were obtained endoscopically during an endoscopic retrograde cholangio-pancreatography ERCP. The samples were of pancreatic origin: pancreatic parenchyma 60% of cases and the papilla 40% of cases. The most common histological type is ductal carcinoma (77.4%) with a predominance of the moderately differentiated subtype in 61.3% of cases.

The surgery consisted of DPC, the resection was R 0 in 90.3% of cases. 38.7% of tumors showed infiltration of the duodenal wall through its D2 segment. Ex-

tension to the retro-portal blade in 1 case (3.2%) and to peripancreatic adipose tissue in 3.2% of cases. Vascular emboli were discovered in 9 patients or 29%. Peripancreatic lymph node involvement (especially retropancreatic) is present in 21 patients or 67.7% and a capsular rupture was noted in just 3 cases. The presence of perineural encroachments was noted in 19 patients or 61.3%.

The average time to start of adjuvant treatment was 2.48 ± 1.3. The different protocols are as follows: Gemcitabine monotherapy: done in 20 patients or 54.8%, Folfirinox + GCSF: in 10 patients or 32.3%, Gemcitabine + Capecitabine: in 1 patient. All patients completed 6 months of treatment

The side effects varied depending on the protocol, and reported by the patients were mainly grade 1 - 2. Furthermore, 22.6% of cases presented side effects of guards 3 - 4. The main adverse effects reported by the patients during their treatment with adjuvant chemotherapy are mentioned in Table 2.

The median survival was 71 ± 7.5 months with a 95% confidence interval (56.3; 85.8) months. (See Figure 1)

The recurrence-free survival of our population was 70% at 3 years, 40% at 5 years and 17% at 10 years (end of the study). The median survival was 55.2 ± 2.5 months with an interval of 95% confidence (50.33; 60.1) months. (See Figure 2)

Survival rates are summarized in Table 3.

Table 2. The main adverse effects were reported according to the protocols and according to the number of patients.

| Toxicity \ Protocol | | GEM | FOLFIRINOX | GEM-CAP | CAP |
|---|---|---|---|---|---|
| Digestive | Nausea vomiting | 2 | 3 | - | - |
| | Diarrhea | 1 | - | | |
| | Mucositis | - | 1 | | |
| Haematological | Neutropenia | 7 | 6 | - | - |
| | Thrombocytopenia | 4 | - | | |
| | Anemia | 6 | 1 | | |
| Neurological | Peripheral neuropathy | 1 | - | - | - |
| Asthenia | | 2 | 3 | - | 1 |
| Liver cytolysis | | 3 | 3 | - | - |
| Ascites | | 2 | - | - | - |

Table 3. Overall survival rate and recurrence-free survival.

| Years | OS (%) | SSR (%) |
|---|---|---|
| **1 year** | 100% | 95% |
| **3 years** | 92% | 70% |
| **5 years** | 68% | 40% |
| **10 years** | 10% | 17% |

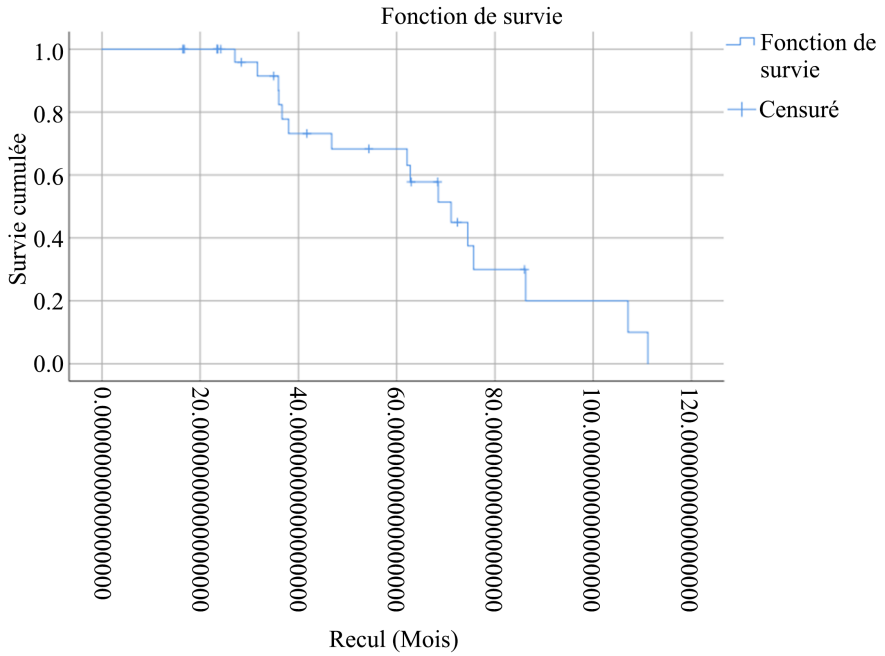


**Figure 1.** Overall survival of our patients (Kaplan-Meier).

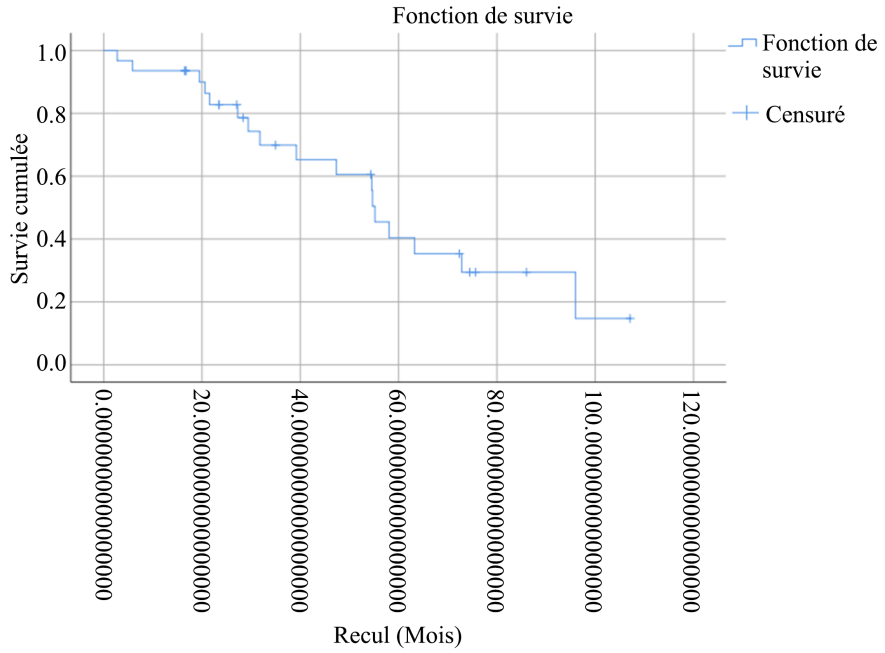


**Figure 2.** Recurrence-free survival of our patients modifies diagram.

## 4. Discussion

According to statistics from GLOBOCAN 2020 (Global cancer observatory), 495,773 new cases of pancreatic cancer were diagnosed worldwide, or 2.6% of cancers; the number of deaths is estimated at 466,003 cases or 4.7%. Pancreatic cancer thus occupies 12th place among all cancers and constitutes the 5th digestive cancer.

In Morocco, according to GLOBOCAN 2020, 1278 new cases were recorded, or 2.2%. Pancreatic adenocarcinoma thus ranks 14th among all cancers and remains the 5th digestive cancer with a number of deaths estimated at 1220 cases or 3.5% and a standardized incidence of approximately 2.96 cases per 100,000 inhabitants. The incidence of pancreatic cancer in Morocco remains lower than that of developed countries and is close to that of Maghreb countries. Pancreatic cancer is typically a disease of older people. It is extremely rare before the age of 30% and 90% of newly diagnosed patients are over 55 years old, the majority of them being over 70 and 80 years old. In our study, age is probably presented as a risk factor for pancreatic cancer given that the average age was 54.35 years and the age group of 50 - 60 years was the most affected.

The ADK therapeutic approach of the localized pancreas is based on the determination of its localized character and its resectability by triphasic injected MRI or CT. Respectability is a matter of consensus; these are the relationships of the tumor with the mainly portal vascular structures and Celio-mesenteric which determine its limits [4] [5]. The classifications agree on the resectable nature in the absence of vascular involvement and unresectable when contact arterial is more than 180˚ in circumference. On the other hand, the definition of respectability uncertain, called borderline, remains subject to interpretation. Damage to the venous axisporto-mesenteric may not contraindicate surgery if it is possible to resect the segment affected with reconstruction. [6] [7] [8]. The 5-year survival rate is close to 20% and at 10 years, it does not exceed 10%. To improve the results of surgery, the adjuvant treatment has shown that the 5-year survival rate can be increased by 10% in using 5-FU or gemcitabine-based chemotherapy and reported prolonged recurrence-free survival of 13.4 months vs 6.9 months compared to surgery alone. According to literature data, several prognostic factors influence the survival of patients with localized ADK of the pancreas, in particular the functional index of Karnofsky, tumor stage, lymph node invasion, type of resection and differentiation and adjuvant treatment. [10] [ADK of the pancreas is more common in men than in women [10]. In our study, we had a M/F sex ratio of 1.58. This figure is close to those found in several studies. The etiology of pancreatic cancer has been the subject of extensive study and numerous pooled analyses. Several risk factors have been identified and can be divided into two categories: modifiable (smoking, alcohol, obesity, dietary factors and exposure to toxic substances) and non-modifiable (sex, age, ethnicity, diabetes mellitus, family history of pancreatic cancer, genetic factors, chronic infections, non-O blood group and chronic pancreatitis). [11] [12]

Adjuvant chemotherapy has been shown to improve survival, and upfront surgery followed by adjuvant therapy remains the standard of care for all patients with resectable pancreatic ADK. Chemotherapy provides a survival benefit regardless of T, N and R status [13]. It must be started 4 to 8 weeks following the surgical procedure for a duration of 6 months. These treatments are administered intravenously or orally. This approach has been validated since the 2000s with the results of two randomized phase III studies (ESPAC-1 and CONKO-001)

which allowed a doubling of 5-year survival rates through the use of 5 FU modulated by acid. Folic acid (LV) or gemcitabine, compared to a strategy of surgery alone (21 vs. 10% and 21 vs. 8%, respectively). [14] [15]

The ESPAC-1 study (European Study Group for Pancreatic Cancer) highlighted the benefit of chemotherapy based on 5 FU + LV (425 mg/m$^2$ of 5 FU and 20 mg/m$^2$ of LV IV 5 consecutive days every month for 6 months). In fact, there is no significant difference depending on whether there is chemoradiotherapy or not (median survival: 15.5 months). On the other hand, there is a 6-month survival benefit for adjuvant chemotherapy (19.7 months versus 14 months for the arm without chemotherapy). [14]

The CONKO-001 trial randomized 368 patients after R0 or R1 surgery to receive gemcitabine (n = 179) or to be subject to simple monitoring (n = 177). The primary endpoint was recurrence-free survival (RFS). The RFS in the gemcitabine arm (13.4 months) was higher than that in the monitoring arm alone (6.9 months); $p < 0.001$. The median OS was 22.1 months in the gemcitabine arm and 20.2 months in the control arm ($p < 0.06$) with an estimated 3-year OS of 34% vs 20.5% respectively [16]. The results of this study with longer follow-up were reported at the American Society of Clinical Oncology (ASCO) congress in 2008 [17]. Gemcitabine significantly improved the median OS vs observation (22.8 versus 20.2 months, $p = 0.005$) and the number of patients surviving at 3 and 5 years which was 36.5% and 21.0% with gemcitabine vs. 19.5% and 9.0% for the observation arm respectively. The conclusion of this study is that gemcitabine for 6 months improves the RFS and OS of patients who have had complete resection of pancreatic adenocarcinoma [15] [18].

Since then, 5 main randomized trials have improved the oncological outcomes of patients operated on for localized pancreatic ADK.

The ESPAC 3 trial randomized patients between 5 FU and folinic acid (Mayo Clinic regimen (6 cycles) and gemcitabine (1000 mg/m$^2$ D1, D8, D14/4 week X 6). The primary endpoint was OS Median OS was 23 months in the 5 FU/AF arm and 23.6 months (95% CI, 21.4 - 26.4) in the gemcitabine arm ($p = 0.39$). was noted in 14% of patients in the 5 FU/folinic acid arm versus 7.5% in the gemcitabine arm ($p < 0.001$) [19]. Due to the more acceptable safety profile of gemcitabine on therapeutic results, this is preferred to 5 FU in the adjuvant situation. In 2017, the phase III ESPAC-4 study showed an increase in median survival at 28 months versus 25.5 months (hazard ratio [HR]: 0.82, $p = 0.032$) with the gemcitabine plus capecitabine combination versus gemcitabine alone [20]. The 5-year survival was 16.3% (10.2 - 23.7) in the GEM arm and 28.8% (22.9 - 35.2) in the GEM-CAP arm. Grade 3 - 4 side effects (n = 481) occurred in 196/366 patients with GEM, and 226/359 patients (n = 608) with GEM-CAP ($p = 0.242$). The GEM-CAP combination was associated with an OS superior to that obtained with GEM monotherapy in patients operated for pancreatic ADK, with acceptable toxicity.

The modified FOLIRINOX was also tested in an adjuvant situation. The results of the French phase III PRODIGE 24 study were presented at the 2018

ASCO congress comparing gemcitabine to Folfirinox-m for 6 months (12 cycles) showed an improvement in DFS (median: 21.6 vs. 12.8 months, HR: 0.58, $p < 0.0001$) and OS under FOLFIRINOX (median: 54.4 vs. 35 months, HR = 0.64, $p = 0.003$) in WHO 0 - 1 patients without major diarrhea or cardiac contraindication to 5-FU [21]. Modified FOLFIRINOX can be considered a reference in this indication; it provides the best results in terms of OS. Gemcitabine, 5 FU or the GEM-CAP combination are options for patients who cannot receive modified FOLFIRINOX.

Concerning targeted therapies, two randomized studies, phase III CONKO-005 (after R0 resection) and phase IIb CONKO-006 (after R1 resection) respectively evaluating the addition of erlotinib or sorafenib to adjuvant gemcitabine did not show improvement in DFS or OS [22].

Whatever chemotherapy is chosen, it is important to carry it out in full (6 months) even if its initiation is delayed (but with a delay not to exceed 3 months) [23].

For the number of chemotherapy cycles, it is important that patients benefit from a sufficient number of courses. However, there is still no consensus regarding the optimal number of chemotherapy cycles.

Despite the significant progress observed in terms of perioperative management and surgical technique, pancreatic resection surgery remains associated with morbidity rates of up to 50%. These complications may be the cause of a delay or failure to administer adjuvant treatment. It is therefore commonly accepted that only 50% to 60% of patients receive adjuvant treatment after pancreatic resection for ADK. [24]

In a recent real-world study, Chikhaldze *et al.* observed that only 62% of patients ultimately received adjuvant CT, and that only 60% of them completed the complete therapeutic sequence, which corresponds to 42% of the population [25]. Thus when the analysis is proposed on an intention-to-treat basis, from diagnosis, the median overall survival after primary surgery then adjuvant CT is only 14.8 months, compared to 18.8 months after neoadjuvant CT [26].

There is no data in the literature comparing the optimal surveillance modalities and rhythms. After surgical resection with curative intent, clinical and paraclinical monitoring could be useful for early diagnosis of recurrences (Tjaden *et al.*, 2016; Tzeng *et al.*, 2012). We can propose depending on the general condition (capable of receiving systemic treatment if recurrence): a clinical examination, a measurement of the serum CA19-9 level if it was high at the time of diagnosis and a TAP CT, every 3 months during the period with the greatest risk of recurrence (2 - 3 years) then at a more spaced rate every 6 - 12 months up to 5 years. [27].

## 5. Limitations of Our Study

The main limitation of the study comes from its retrospective nature and the biases associated with this type of methodology. Indeed, we encountered some dif-

ficulties in relation to the use of files linked to insufficient data or patients lost to follow-up. In addition, the sample size (n = 31) is relatively small, not allowing a good evaluation of prognostic factors for survival, one of the main objectives of our study. This low number is largely due to the focus on advanced and metastatic stages and the very selective criteria for inclusion of cases, particularly for survival data.

## 6. Conclusions

ADK of the pancreas at the localized stage represents a major public health issue despite its relatively low incidence compared to other stages; this is due to the high mortality rate linked to discovery often at fatal stages, explained by the high clinical latency of this type of cancer.

Despite significant progress in the development of medical imaging techniques and the understanding of the pathogenesis of the development of cancerous lesions, the prognosis of affected patients remains poor.

As the improvement in overall survival of localized pancreatic ADK made possible by curative surgery combined with adjuvant chemotherapy is limited (benefit of 10%), numerous studies are currently underway to look for other, more effective therapeutic alternatives such as targeted and the neoadjuvant approaches in order to obtain a positive impact on the major prognostic factors which are largely represented by the characteristics of the tumor.

New perspectives are also open in terms of pancreatic cancer screening with the aim of bringing the diagnosis to a "useful" stage allowing a window of therapeutic effectiveness to be defined.

## Conflicts of Interest

The authors declare no conflicts of interest.

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