

# Real-World Evidence in Localized Pancreatic: Coping with Uncertainty in Unselected Populations

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## Abstract

**Background:** Localized pancreatic cancer, including resectable (R), borderline resectable (BR) and locally advanced unresectable disease (LAU), is considered in clinical guidelines for diverse treatment options based on clinical trials in selected populations. Hence, exploring with real world evidence (RWE) clinicians' preferences for treatment options and their results seems pertinent. **Methods:** In a set of consecutive patients with localized pancreatic cancer assisted in a third level hospital from January 2013 to December 2022, medical records, symptoms, diagnostic process, distribution between subtypes, and treatment plans, with safety and efficacy results, were assessed. **Results:** A total of 152 patients with localized disease were included (43.4% R, 21.0% BR, 33.6% LAU). The population characteristics exemplified differences between daily practice and clinical trials. Tumor location and symptoms were as expected. Treatment plan was conditioned by PS or comorbidities in 23.0% of patients. In patients with R disease, surgery followed by different adjuvant chemotherapy (CT) regimes was the antineoplastic treatment of choice (64.8%) with efficacy results (OS 37.5 months; 95% CI 18.4 - 56.7), in the range of contemporary standards. The common use of neoadjuvant CT for BR disease (94.4%), with surgery in 50% of them, and its results (OS 30.8 months; 95% CI 10.5 - 51.2) reflected current controversies of treatment recommendations and evolution in this scenario. Palliative CT with or without radiotherapy was the standard specific treatment in LAU disease (95.1%) with survival results (PFS: 10.8 months; 95% CI 8.8 - 12.7. OS: 20.3 months; 95% CI 13.5 - 27.2) that justify the distinct character and the specific study of

this entity. **Conclusion:** RWE for localized pancreatic cancer aroused from the analysis of this population confirms the distinct nature of patients assisted in daily practice, as well as mirrors the complexity of decision making in clinical assumptions in which achieving stronger evidence should be paramount.

## Keywords

Real-World Evidence, Localized, Pancreatic, Cancer

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## 1. Introduction

Pancreatic cancer is the fourth leading cause of cancer death in Europe, accounting for more than 3% of new cancer diagnoses but approximately 7% of cancer deaths, and being the only considered major site of cancer showing unfavorable trends for both sexes. Similar trends have been observed in the United States [1]. In Spain, pancreatic cancer is expected to be the fourth cancer in incidence in 2024, with 4777 cases, and was the third cause of cancer related deaths in 2022, with 7973 deaths [2]. Apart from smoking, which is the main risk factor for pancreatic cancer, overweight, obesity, diabetes, and heavy alcohol consumption are also among known risk factors.

At diagnosis, more than half of patients present with locally advanced pancreatic cancer (borderline resectable or unresectable), one third present synchronous metastatic disease, and approximately 10% present clinically defined resectable disease [3]. Prognosis depends mainly on staging at diagnosis, based on UICC TNM staging as well as on anatomical, biological, and conditional factors [4] [5], obtained through image and blood tests, with clinical evaluation, which in conclusion will determine treatment plan.

Local and locoregional pancreatic cancer is divided in resectable (R), borderline resectable (BR), and locally advanced unresectable (LAU), with different treatment recommendations. While initial surgery followed by adjuvant chemotherapy (CT) is the unquestionable treatment of choice for R disease, the variety of treatment choices (different types of CT combined or not with radiotherapy (RT), and with option of final radical surgery) with limited scientific grounding in BR and LAU disease justify the upfront consideration of patients to be enrolled in clinical trials when available [6].

The complexity of diagnosis, staging, and categorization, along with the evolving variety of multidisciplinary treatment options based upon suboptimal evidence in very selected populations (6, 7) led us to explore clinical presentation, diagnostic procedures, and treatment strategies results in a Spanish tertiary medical oncology department as a pilot experience in the TRAPECIO study for a subsequent national scope project.

## 2. Methods

Patients with localized pancreatic ductal adenocarcinoma consecutively assisted

in the Medical Oncology Department of Elche - Vega Baja between January 2013 and December 2022 were included for this study. Data related to clinical presentation, diagnosis, categorization, initial and final therapeutic strategy, safety, compliance, and efficacy of treatment were obtained from handwritten and electronic medical records, as well as laboratory and image archives.

The Department of Medical Oncology of Elche - Vega Baja depends on a unique headship, with oncology medical staff in both centers (Elche University Hospital and Vega Baja Hospital), but with clinical heads, clinical trials and research unit located in Elche University Hospital.

Patients with localized pancreatic ductal adenocarcinoma were referred to Medical Oncology Department in Elche University Hospital or Vega Baja Hospital for oncological medical treatment (including CT and/or RT) from Gastroenterology and Internal Medicine Departments of Elche University Hospital and Vega Baja Hospital. Weekly multidisciplinary tumor boards were held in both Elche University and Vega Baja Hospital, where medical oncologists of Elche University Hospital were represented for agreed treatment decisions. Surgery, when performed, was carried out in the hospital (Elche or Vega Baja) where patient was initially diagnosed.

Primary endpoint of TRAPECIO, a descriptive and analytical retrospective cohort study, is to analyze treatment strategy and results in patients with localized pancreatic ductal adenocarcinoma, including R, BR, and LAU, assisted in Elche University Hospital between January 2013 and December 2022. Secondary endpoints include: to analyze diagnostic process of localized pancreatic cancer, to analyze treatment strategy of localized pancreatic cancer according to different types of presentation, and to evaluate in terms of safety and efficacy the treatment of localized pancreatic cancer according to different types of presentation.

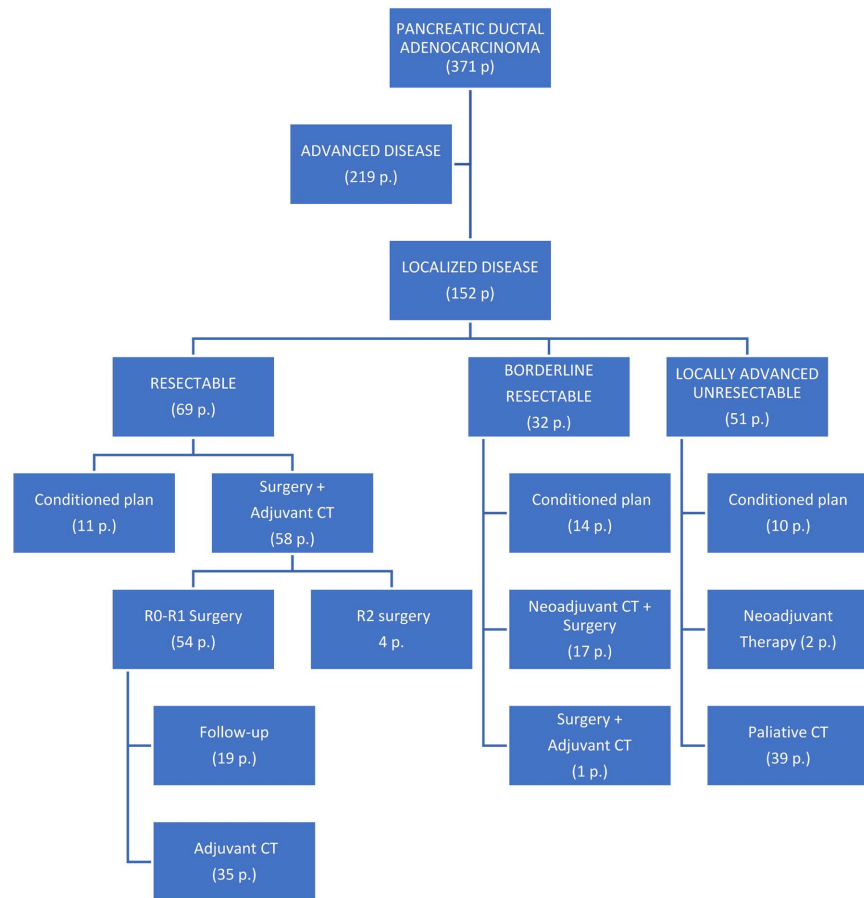
This study complies with ethical requirements of Declaration of Helsinki and with Good Clinical Practice Guidelines. Patients signed informed consent at diagnosis for inclusion in Elche University Digestive Tumors Registry for investigational purposes with optional revocation. The document was written up for collection and exploitation of clinical data with investigational purposes and was approved by Elche University Hospital Ethical Committee.

Statistical analysis was carried out using IBM SPSS Statistics 29. Continuous random variables were summarized as central tendency and dispersion measures (median, range, mean, confidence interval). The quantitative variables were expressed as percentages. The confidence interval was calculated at 95% of confidence. Kaplan-Meier and life tables were used to analyze the Overall Survival. Comparison between curves was performed using the log rank test.

### **3. Results**

#### **3.1. Global Population**

Between January 2013 and December 2022 a total of 371 patients diagnosed of



**Figure 1.** Patient distribution (consort) diagram of patients with localized pancreatic cancer in TRAPECIO. Abrev.: CT, chemotherapy; RT, radiotherapy.

pancreatic ductal adenocarcinoma were referred to Elche - Vega Baja Medical Oncology Department. 152 patients (41.0%) had localized disease at diagnosis: 43.4% (69 p.) of them with R disease, 21.0% (32 p.) with BR disease, and 33.6% (52 p.) with LAU disease (**Figure 1**). An increase in the proportion of patients with localized disease was demonstrated between the first and the second five-year period of the study (2013-2017: 35.7%; 2018-2023: 44.3%). Although 34.2% of patients (52) with localized disease were diagnosed in Vega Baja Hospital, 76.3% of patients (116) were assisted in Elche General Hospital.

No difference was observed in median age at diagnosis in the global population (68.2 years; 40 - 93), patients with advanced disease (67.6 years; 40 - 93), and with localized disease (69.0 years; 41 - 92). Pancreatic cancer was more frequently diagnosed in men (59.6%), but this predominance was less displayed in localized disease (55.3% localized, 53.6% R, 53.1% BR, 58.8% LAU) and more pronounced in advanced disease (63.0%). ECOG performance status (PS) in localized disease (75.6% ECOG 0 - 1) was worse in non-initially R disease (ECOG 0 - 1: 85.5% R, 62.5% BR, 68.7% LAU). Median number of comorbidities, excluding diabetes, in localized disease was 1.03 (0 - 4, SD 0.963) with ischemic cardiomyopathy as the most prevalent (11.8% of patients). Diabetes Mellitus was present in 45.4% of pa-

tients with localized disease, with median time from diagnosis of 6 years, and no differences in frequency or time from diagnosis in categories of localized disease.

For localized disease, abdominal pain (R 46.4%; BR 68.8%; LAU 76.5), weight loss (R 33.3%; BR 53.1%; LAU 72.5%), digestive rhythm disturbances (R 8.7%; BR 12.5%; LAU 19.6%), and median evolution time of symptoms (days; R 10%; 25.5%; LAU 60%) increased from resectable to unresectable disease. Primary tumor location in the head of the pancreas was associated to less abdominal pain (head 57.4%; body 80%; tail 70%) and median evolution time of symptoms (days; head 14.5%; body 47.5%; tail 90%), but more incidence of jaundice (head 52.5%, body 5%; tail 0%) (**Table 1**).

Diagnostic process for localized disease was outpatient in 25% of patients. Image test performed to patients included abdominal ultrasound (46.1%), CT scan (99.7%; biphasic CT scan 35.5%), MRI (45.4%; pancreatic 43.4%; liver 2%), PET-CT (9.2%), and endoscopic ultrasound (EUS) (88.2%). Diagnostic laparoscopy was performed in 2% of patients. Serum Ca 19.9 value was meaningful (rejected in case of increased bilirubin) in 64.5% of patients (98), with a median value of 227.5 U/ml (2 - 42,200), and an increased median value according to type of localized disease (R 92 (4 - 7310); BR 398.1 (5 - 2200), LAU 987 (2 - 42,100)). EUS was the most sensitive diagnostic test for pathology confirmation of ductal adenocarcinoma of the pancreas (91.6%), and was the most frequent method for obtaining pathology sample for diagnosis (86.2%).

**Table 1.** Characteristics of patients with localized disease at diagnosis. Abrev.: ECOG PS, Eastern Cooperative Oncology Group Performance Status; DM, Diabetes Mellitus.

	GLOBAL	RESECTABLE	BORDERLINE RESECTABLE	LOCALLY ADVANCED UNRESECTABLE
Number of patients (%)	152	69 (45.4)	32 (21.1)	51 (33.5)
Age, years (range)	69.0 (41 - 92)	68.4 (41 - 92)	69.6 (46 - 89)	69.5 (52 - 88)
Female (%)	44.7	46.4	46.9	41.2
ECOG PS 2 - 4 (%)	24.3	14.3	37.5	31.4
Charlson Comorbidities ≥ 2 (%)	23.7	NA	NA	NA
DM (%)	45.4	43.5	56.3	41.2
Evolution time of DM (days, range)	72.0 (0 - 360)	78.0 (0 - 240)	45.0 (2 - 180)	60.0 (2 - 360)
Median number of medications (range)	4.6 (0 - 16)	NA	NA	NA
Abdominal pain	61.2	46.4	68.8	76.5
Jaundice	42.8	49.3	43.8	33.3
Weight loss ≥ 10%	31.6	16.0	28.1	37.3
Evolution time of symptoms (days, range)	21.0 (0 - 180)	10.0 (0 - 180)	25.5 (0 - 150)	60.0 (0 - 180)

Tumor was located in the head of the pancreas in 122 p. (80.3%), in the body in 20 p. (13.2%), and in the tail in 10 p. (6.6%). Tumors located in the body of the pancreas tended to be more frequently LAU (65% vs 28.7% and 30% in head and tail, respectively).

Excluding 6 patients with less than 12 months of follow-up, median follow-up time for the remaining 146 patients was 5.1 years, with median over survival of 19.6 months (CI 95%, 16.7 - 22.4).

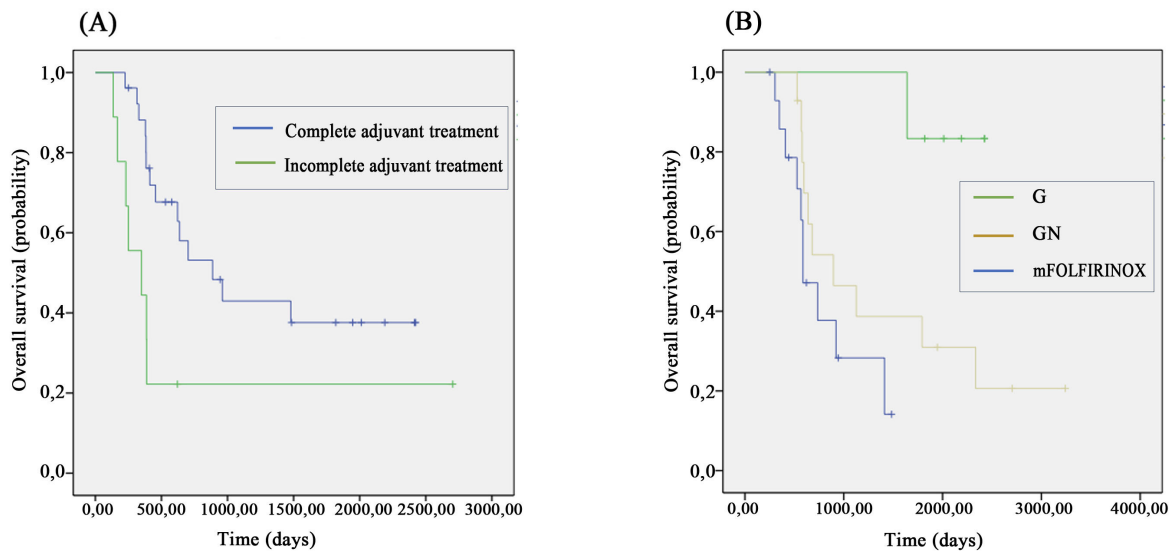
### 3.2. Resectable Disease

In 11 (15.9%) of the 69 patients with R disease treatment plan was conditioned by PS, comorbidities, operability, or patient decision. Consistently, these patients received best supportive care (BSC) alone or suboptimal antineoplastic treatment. In the remaining 58 patients, in whom we will center this R disease analysis, treatment scheduled included initial surgery followed by the consideration of adjuvant CT (**Figure 1**).

Median time between pathology diagnosis and surgery was 39.8 days. Surgery procedures included Whipple in 69% (40 p.), corporocaudalpancreatectomy in 14.3% (8 p.), and total pancreatectomy in 10.3% (6 p.), while tumor was considered unresectable at laparotomy in 6.9% (4 p.). Surgery was R1 in 25.9% (14 p.) of the resected tumors, and more frequently R1 in total and corporocaudalpancreatectomies than in Whipple procedures (50% vs 17.5%). Surgical complications were present in 58.6% of patients (34), with pancreatic fistula as the most frequent complication (47% of all complications). 4 patients (6.9%) died in the postoperative period due to hemodynamic disorders, infections and bleeding.

Pathologic stage after surgery in resected patients was pI in 27.8% (15 p.; 9.3% pIA and 18.5% pIB), pII in 48.1% (26 p.; 13% pIIA and 35.1% pIIB), and pIII in 24.1% (13 p.). After surgery, alive and resected patients (50 p.) had abnormal tests in 32% of cases (16 p.): 13 patients with abnormal Ca 19.9 value, and 3 patients with both abnormal Ca 19.9 value and image test. Abnormal tests after surgery were more frequent after R1 (50% vs 25% after R0), and in stage pIII (58.3% vs 21.4% and 25% in stage pI and pII, respectively).

Only 35 of the 50 patients with resected tumor and alive after postoperative period received adjuvant CT (**Figure 1**). Main reasons for omitting adjuvant CT (15 p.) were: medical judgement (3 p.), fragility after surgery (6 p.), and early progression (3 p.). Adjuvant CT regimes included: mFOLFIRINOX (modified 5-fluorouracil, irinotecan and oxaliplatin) (15 p.; 42.9%), gemcitabine and capecitabine (GC) (6 p.; 17.1%), and G alone (14 p.; 40%). mFOLFIRINOX was more frequently indicated in stage pII (42.8%) and pIII (62.5%) disease, and was de predominant regime from 2018. Median time interval between surgery and adjuvant CT was 55 days (31 - 119). Adjuvant CT was not complete in 9 patients (25.7%) due to toxicity (14.3%; 5 p.) and progression (11.4%; 4 p.). Better compliance of adjuvant CT was seen in GC (100%) than in G (71.4%) and mFOLFIRINOX (66.7%). Adjuvant RT was administered to 6 patients (17.1%), 4 of them after R1 surgery.



**Figure 2.** (A) Overall survival Kaplan-Meier curve of patients with resectable disease with adjuvant chemotherapy depending on treatment compliance. (B) Overall survival Kaplan-Meier curve of patients with resectable disease with adjuvant chemotherapy depending on type of chemotherapy. Abrev.: G, Gemcitabine; GC, Gemcitabine and Capecitabine; mFOLFIRINOX, modified 5-fluorouracil, irinotecan and oxaliplatin combination.

Considering patients with resected tumor and alive after postoperative period (50 p.), 60% of them had recurrent disease (30 p.): distant (32%; 16 p.), local (14%, 7 p.), distant and local (10%; 5p.), and only peritoneal (4%; 2 p.). Local relapse was more frequent after R1 surgery (42.8% vs 16.7% in R0). Patients received antineoplastic treatment after surgery in 86.7% of cases (26 p.; 83.3% CT and 9.9 % local therapy).

Median follow-up time of patients with resected tumor (54 p.) was 5.6 years (1.3 - 10.9). Median relapse free survival (RFS) of patients after surgery (50 p.) was 23.2 months (95% CI 6.6 - 39.7). RFS was shorter in patients with abnormal tests after surgery (Log Rank 10.4;  $p = 0.001$ ), while pathologic stage and receiving or not adjuvant CT did not influence in RFS. Considering patients who received adjuvant CT (35 p.), GC (Log Rank 8.1;  $p = 0.017$ ) and compliance (Log Rank 5.6;  $p = 0.018$ ) were associated to longer RFS (**Figure 2(A)**).

Median overall survival (OS) of all R patients was 24.5 months (95% CI 16.4 - 32.7). Median OS of R patients with resected tumor at surgery and alive and without early progression after surgery was 37.5 months (95% CI 18.4 - 56.7). Site of relapsed had impact on OS (Log Rank 15.2;  $p = 0.004$ ), while receiving adjuvant CT did not (Log Rank 0.14;  $p = 0.907$ ). In patients who received adjuvant CT, treatment with CG was associated to better OS (Log Rank 9.7;  $p = 0.008$ ) (**Figure 2(B)**).

### 3.3. Borderline Resectable Disease

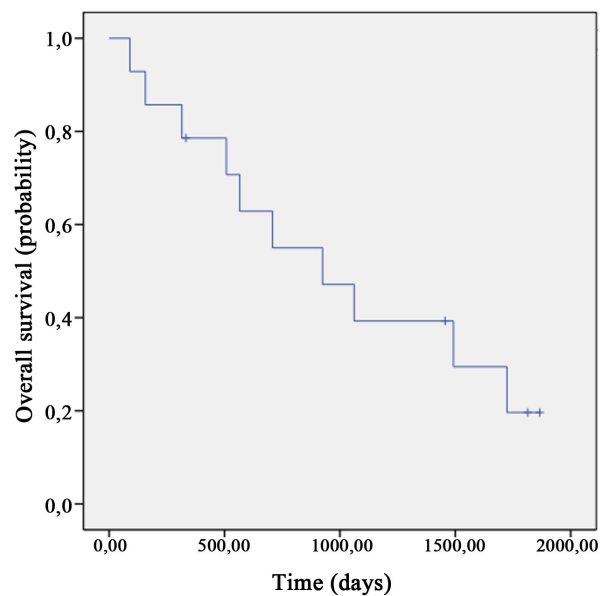
BR disease was anatomically defined (type A) in 90.6% of patients (29 p.) and was considered type B (biological) in only 3 patients. In 14 of the 32 patients (34.4%) with BR disease treatment plan was conditioned by PS, comorbidities or



operability. Consistently, these patients received BSC alone or suboptimal anti-neoplastic treatment. In the remaining 18 patients, the most frequent planned treatment strategy was neoadjuvant chemotherapy followed by surgery (94.4%; 17 p.) (**Figure 1**). Two patients considered for neoadjuvant CT decided to move to other institutions for treatment and were lost to follow-up.

Neoadjuvant treatment in BR disease for the 15 patients treated at our institution consisted of CT (100%) with optional addition of concurrent CT + RT (40%; 6 p.). CT regimes included mFOLFIRINOX (46.7%; 7 p.), gemcitabine + nab-paclitaxel (GN) (46.7%; 7 p.), and gemcitabine + oxaliplatin (GEMOX) (6.6%; 1 p.). Concurrent CT + RT was always performed with long course RT with capecitabine. Treatment duration was longer in case of combined CT and CT + RT (4.7 months; 4.3 - 4.9) than when only CT was used (2.7 months; 0.7 - 4). One patient was lost to follow-up during neoadjuvant treatment. Early treatment interruption due to toxicity occurred in 28.6% of patients (4 p.). Signs of treatment efficacy were demonstrated in 28.6% of patients (4 p.), either in image tests or in serum tumor markers, and only one patient (7.1%) had progressive disease after neoadjuvant treatment.

Initial surgery was performed in one patient, and surgery after neoadjuvant treatment was performed in 7 (50%) of the 14 patients with follow-up after neoadjuvant treatment. 50% of patients who received neoadjuvant treatment did not have surgery due to unresectable disease (28.6%; 4 p.), disease progression after neoadjuvant treatment (7.1%; 1 p.), patient refusal (7.1%; 1 p.), and toxic death due to neoadjuvant treatment (7.1%; 1 p.). Surgery was R0 in 71.4% of patients with resected tumor (5 p.). Surgical complications in resected patients occurred in 42.9% of patients (3 p.), with one death (14.3%) due to surgical bleeding. Pathologic stage in resected patients was IA in 2 p. (28.6%), IB in 1 p.



**Figure 3.** Overall survival Kaplan-Meier curve of patients with borderline resectable disease treated with neoadjuvant treatment.



(14.3%) and IIB in 4 p. (57.1%). Regarding adjuvant treatment in patients alive after tumor resection, 5 p. (66.6%) received CT (mFOLFIRINOX 2p.; GC 1p; G 1 p.), and 2 patients did not due to medical judgement (1 p.) and surgical complications (1 p.). Disease recurrence was observed in 4 of these patients (66.6%), all with distant disease, and half of them concurrent with local relapse.

Median follow-up for all BR patients was 10.8 months (0.2 - 62.2), with OS of 15.9 months (95% CI 5.4 - 26.3). For patients receiving neoadjuvant therapy, median follow-up was 27.2 months (3 - 62.2), with median OS of 30.8 months (95% CI 10.5 - 51.2) (**Figure 3**), being 18.9 months (95% CI 15.7 - 22) in patients deemed unresectable at surgery, and 57.5 months (95% CI 41.3 - 73.6) in resected patients with non-surgery related death.

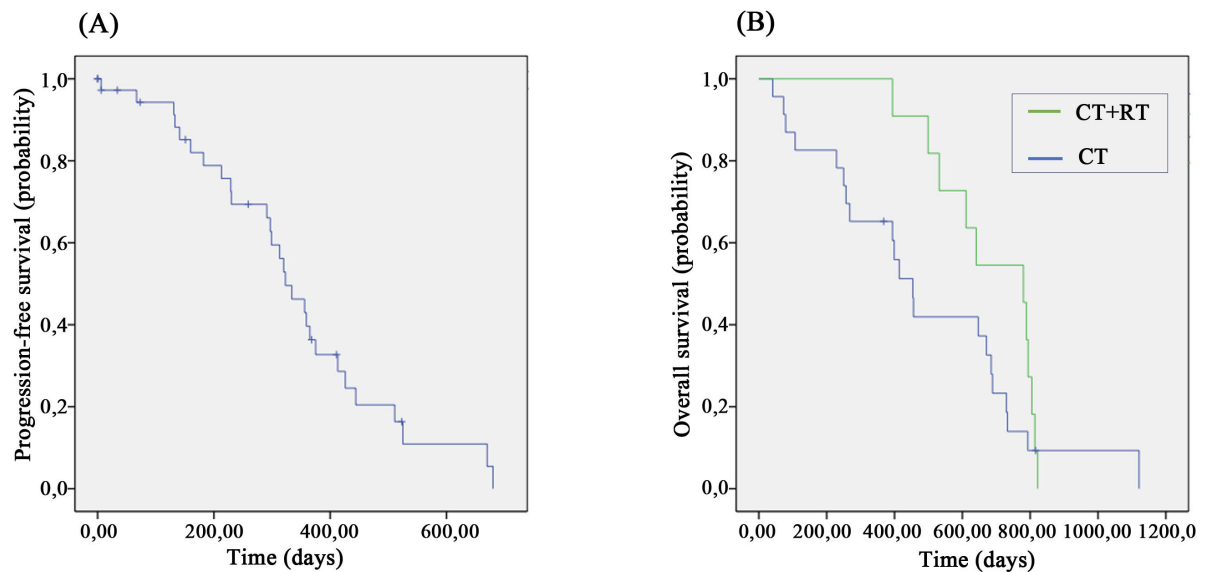
### 3.4. Locally Advanced Unresectable

In 10 of the 51 patients (19.6%) with LAU disease treatment plan was limited by PS or comorbidities. Consistently, these patients received only BSC. Two patients (3.9%), although LAU defined, were considered for neoadjuvant treatment: one patient received CT with GN and was finally not suitable for surgery; and one patient received CT with mFOLFIRINOX followed by CT-RT showing partial response and Whipple R0 surgery was performed followed by adjuvant 5-fluorouracil (5-FU). 39 patients were considered for palliative CT (76.5%), 14 of them (27.4%) with CT-RT at some point of the course of the disease (**Figure 1**).

Palliative first-line CT regimes included GN (61.6%; 24 p.), G (17.9%; 7 p.), FOLFIRINOX (7.7%; 3 p.), GEMOX (5.1%; 2 p.); GC (2.6%; 1 p.), and FOLFOX (2.6%; 1 p.). Median treatment duration was 7.2 months (1.9 - 22.7). Reasons for CT ending were progression (53.8%; 21 p.), pre-planned (23.1%; 9 p.), and toxicity (17.9%; 7 p.), with treatment still ongoing in 2 patients (5.1%). Image or Ca 19.9 response was seen in 63.1% (12 p.) of evaluated patients after CT (19 p.), and in 78.6% (11 p.) of patients after combined CT and CT-RT.

61.9% (21 p.) of candidate patients (29 p.) finally received second line CT, with liposomal irinotecan (NALIRI) and 5-FU combination as the most used regimen (57.1%; 12 p.), showing disease control in 56.4% of patients (12). Third line CT was administered to 58.3% of candidate patients (7 out of 12 p.).

Median follow-up of LAU patients was 15.1 months (0.5 - 69.3). Median first-line treatment progression free survival (PFS) was 10.8 months (95% CI 8.8 - 12.7) (**Figure 4(A)**) with no statistically significant influence of the use of CT-RT (Log Rank 0.6;  $p = 0.430$ ). Median second line CT PFS was 7.3 months (95% CI 6.3 - 8.3). OS of all LAU patients was 17.7 months (95% CI 12.9 - 24.2). Vascular involvement in LAU disease influenced on median OS: arterial 21.4 months (95% CI 14 - 28.7), vein 13.1 months (95% CI 5.5 - 20.7) (Log Rank 4.4;  $p = 0.036$ ). In patients receiving antineoplastic treatment for LAU disease, with OS of 20.3 months (CI 95%, 13.5 - 27.2), no statistically significant difference was demonstrated in OS between patients receiving CT (15.1 months; 95% CI 12.3 - 17.9) and patients receiving combined CT with CT-RT (26 months; 95% CI 19.6 - 32.4) (Log Rank 1.8;  $p = 0.181$ ) (**Figure 4(B)**), while patients receiving



**Figure 4.** (A) Progression-free survival Kaplan-Meier curve of patients with locally advanced unresectable disease who received antineoplastic treatment. (B) Overall all survival Kaplan-Meier curve of patients with locally advanced unresectable disease who received antineoplastic treatment depending on the type of treatment. Abrev.: CT, Chemotherapy; RT, Radiotherapy.

more than line of CT lived longer (23.0 months; 95% CI 17.7 - 27.2) than patients receiving only one line of CT (8.9 months; 95% CI 2.4 - 15.5) (Log Rank 4.3;  $p = 0.039$ ).

#### 4. Discussion

Recent updates of guidelines covering diagnosis and treatment of localized pancreatic cancer intend to mirror the complexity for clinicians when treating this disease based on PS, multidisciplinary diagnostic and staging process, major and accepted morbid surgery, multiple and dynamic treatment options, and feeble supporting evidence of recommendations in BR and LAU scenarios [6] [7]. Real world evidence (RWE) is a valid and valuable method for both to explore clinical practice and to evaluate treatment results in a real-world setting, specially, when clinical trials and guidelines do not fully consider conditions that may impact on treatment planning, compliance, and results, although this important advantage may involve inherent limitations such as biases of patients, providers and health care itself [8]. The analysis we present covers all forms of localized pancreatic cancer (R, BR, and LAU), describes a non-selected population with comorbidities and impacts of disease (emotional and physical) not represented in clinical trials, with a non-controlled staging process, and a consequent distribution among planned treatment options ranging from BSC alone to sequential combined modality antineoplastic treatment and surgery, which may be modified according to treatment results (efficacy and toxicity) as well as to patient wishes.

Considering main clinical trials which support treatment recommendations in clinical guidelines [7]-[19], the population included in this analysis was slightly

older (68.2 vs 63 - 67 years), with slightly less women (40.4% vs 42% - 46%), worse PS (0% - 12% vs 24.3% ECOG PS 2 - 4), with comorbidities which could entail exclusion of clinical trials, and highly symptomatic (61.2% abdominal pain, 42.8% jaundice, 31.6%  $\geq 10\%$  weight loss).

Diagnostic process and procedures could be considered suboptimal based on certain clinical trials [11] [13] [14] [18], with not routinely performed arterial, venous and portal contrast phase axial scans (35.5%), with few PET-CT (9.2%) and diagnostic laparoscopies (3.3%) performed, and with a proportion of patients with abnormal Ca 19.9 above reported, particularly after surgery in R disease (7.3% vs 27.6%). Nevertheless, all patients who received active treatment and most of the sample (92.1%) had confirmed pathology diagnosis, mainly obtained through EUS (86.2%).

Tumor location and symptoms related to tumor location in our series were as expected [7]. Although there was a foreseeable predominance of metastatic disease at diagnosis of ductal adenocarcinoma of the pancreas, distribution of subtypes of localized disease showed a higher proportion of R (45.4% vs 10% - 20%) at the expense of BR, while LAU incidence was consistent with previously reported (30%) [7] [17].

The fact that planned treatment strategy was conditioned by PS or comorbidities in approximately one out of every four of our patients (15.9% R, 34.4% BR, 19.6% LAU) and that treatment plan consisted of BSC alone in 15.8% of them reflects how dealing with localized pancreatic cancer in daily practice is far from the controlled and selected populations in clinical trials, with a meaningful impact on OS when analyzing the sample as a whole and in different subsets (R 24.5 months; 95% CI 16.3 - 32.7, BR 15.9 months; 95% CI 5.2 - 26.5, LAU 17.7 months; 95% CI 10.3 - 25.2).

In patients with resectable disease surgical procedures were consistent with guidelines [7] although with increased surgical complications [20] in a non-centralized scenario [21]. Notwithstanding positive resection margin was less frequent than in adjuvant treatment clinical trials (25.9% vs 35% - 60%), while comparison of distribution in stages after surgery with these trials is hampered by variability [9] [10] [11]. Adjuvant treatment was not the rule, once again capturing real world, and selection of chemotherapy regimes was influenced by patients' characteristics as well as by the advent of level I evidence, with the confirmation of the relevance of compliance [22]. Regarding adjuvant treatment results in R disease, RFS was 23.4 months (95% CI 4.8 - 42) which is in the range of the best median disease-free survival reported so far with adjuvant CT in pancreatic cancer (21.4 months; 95% CI 17.5 - 26.7) [11], despite less effective regimens were prescribed (42.9% mFOLFIRINOX), in more advanced stages (22.9% stage III), and with more abnormal Ca 19.9 values after surgery (31.4%). No formal comparison can be done among adjuvant CT regimes due to the quantity of patients per regimen, different stages distribution, and compliance, but as predicted [22], influence of compliance and CT scheme on RFS was suggested. OS of patients receiving adjuvant CT was 30.7 months (95% CI 1.9 -

59.5), in the range of the OS reported for GC (28.0; 95% CI 23.5 - 31.5) [10], although this was de less prescribed regime, and between the achieved with the most used CT regimes in our sample (G: 23.0; 95% CI 21.1 - 25.0. mFOLFIRI-NOX: 53.5, 95% CI 43.5 - 58.4) [11].

In patients with BR disease, once excluded already mentioned patients who received no or suboptimal antineoplastic treatment due to constraints, neoadjuvant treatment was the standard treatment, although this strategy was first recommended in guidelines in 2015 and with scarce evidence and no preferred regime [23]. This paucity of evidence and lack of updated recommended treatment combination and sequence, although still current [6], not only was not a restriction to clinicians to plan it, but it was clearly captured in our analysis, where patients received different neoadjuvant CT regimes with or without RT and adjuvant CT. On top of that, tumor was resected in only half of the patients who received neoadjuvant treatment, adding uncertainty to this so-called neoadjuvant instead of conversion therapy, and noticing the complexity of performing clinical trials in this scenario where establishing a control arm for future trials remains controversial [24]. If we restrict to patients receiving neoadjuvant treatment in BR disease, median OS in our set was superior to best published evidence (15.7 months; 95% CI 12.9 - 20.6) [13], maybe influenced BR disease selection criteria and by the use of combination CT regimes.

Focusing on LAU disease patients, although the most frequently planned strategy was palliative CT, even with this premise, the variability in CT treatment composition, duration, and the dynamic incorporation of RT to the treatment strategy, depict what clinical guidelines illustrate in their algorithms [6] [7]. Once the ambioned definitive treatment is given up, sequence of lines of CT in this analysis tended to replicate standards for metastatic disease [25] but with median PFS and OS data which, superior to most recently updated phase III clinical trial results in metastatic disease [26], underlie the prevailing advice for clinical practice and investigations of considering LAU pancreatic cancer a different entity to metastatic disease.

We must acknowledge limitations of our work. This retrospective analysis is based mostly on information registered in clinical records by clinicians, consequently no filtering of inconsistencies usually performed in databases before analysis could be carried out, and data obtained are considered reliable assuming strictness of involved personnel. Sample size, due to clinical practice data obtained from a third level hospital, limits robustness of analysis, even further in subgroups following splitting the sample by type of disease or treatment. Analyses from a single center entail the risk of polluting results by certain aspects unique to the center and not common to the disease. Pancreatic cancer, and particularly pancreatic cancer surgery, is considered a highly specialized discipline, which added to the multidisciplinary nature, question the selection of a third level hospital with limited casuistry as subject of this work. Nevertheless, we would like to underscore that some of the limitations previously described could also be construed as strengths inherent to real-world data and real-world evidence.

## 5. Conclusion

Real world evidence derived from this cohort of localized pancreatic cancer identifies areas for improvement in diagnosis and treatment, reflects that how treatment recommendations may be conditioned by patients in clinical practice, and confirms the wide landscape of strategies that both guidelines and clinicians recommend and plan for patients with R, BR and LAU disease. Larger databases subjected to proposed standards [8] could help to better define current practice and results, as well as to establish baseline for future clinical trials and investigations.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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