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Original Article

Neoadjuvant therapy impact in early pancreatic cancer: "bioborderline" vs. "non-bioborderline"

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Backgrounds/Aims: To analyze the results of the neoadjuvant treatment of patients in our center with early pancreatic cancer.
Methods: Eighty-four patients with early pancreatic cancer (I–II) were included, of which 59 were considered "bioborderline" (carbohydrate antigen [CA] 19-9 > 37 U/L), and 25 were considered "non-bioborderline" (CA19-9 < 37 U/L). The R0 resection rate, presence of negative nodes, survival, and recurrence rates were analyzed in two groups, the NEO group (neoadjuvant + surgery) and the non-NEO group (upfront surgery).
Results: A 28.6% pathologic complete response was observed in the NEO group of the whole sample. The residual R0 was 85.7%, and nodes were negative in 78.6% of the patients in the NEO group of bioborderline patients. All non-bioborderline patients treated with neoadjuvant were R0, and no affected nodes were observed in any of them. The median overall survival (OS) in patients with elevated CA19-9 levels in the NEO group was 31.4 months vs. 13.1 months in the non-NEO (log-rank test $p = 0.006$), with a 62% relative reduction in the mortality rate (hazard ratio = 0.38, 95% confidence interval: 0.20–0.79; $p = 0.008$). The median OS in patients with normal CA19-9 levels in the NEO group was 65.9 months vs. 16.2 months in the non-NEO group, without statistically significant differences between the two but with a trend toward significance (log-rank test $p = 0.08$).
Conclusions: A neoadjuvant strategy seemed to improve local control and the survival of patients with early pancreatic cancer, both those with elevated CA19-9 and normal marker levels.

Key Words: Pancreatic neoplasms; Neoadjuvant therapy; Biomarkers; Early pancreatic cancer

INTRODUCTION

Pancreatic ductal adenocarcinoma is an aggressive neoplasm with a survival rate below 5% at 5 years. It is considered the fourth most common cause of cancer death in men and women (behind lung, colon, and prostate cancers in men and breast cancers in women) in both the United States and Europe, with more than 48,000 and more than 35,000 deaths per year, respectively. It is expected that pancreatic ductal adenocarcinoma will become the second leading cause of death by 2030, surpassed only by lung cancer [1].

Approximately 15% to 20% of patients are candidates for curative resection at the time of diagnosis since most patients are diagnosed at an advanced stage of the disease. Unfortunately, resection alone has low cure rates, with median overall survival (OS) rates of approximately 20 months (10%) [2-4]. Additionally, adjuvant treatments like chemotherapy, radiotherapy, or both have been tried in a multimodality approach [5].

Studies such as ESPAC-1, CONKO-001, and ESPAC-4 clinical trials have shown evidence of the benefit of adjuvant chemotherapy in terms of OS and disease-free survival (DFS). Despite this, about 50% of patients treated with curative resection at

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entry do not receive planned adjuvant treatment due to complications, low-performance status, rejection, or early disease recurrence [6-8].

These observations led us to evaluate neoadjuvant therapy in patients with potentially resectable tumors. Although at diagnosis, this is a resectable disease with no clinical or radiological evidence of distant disease, approximately 17% of patients exhibited occult metastatic disease, and more than 70% of patients showed lymph node metastases after surgery, suggesting that it was a micrometastatic disease from the beginning [9,10].

Neoadjuvant therapy is currently recommended in patients with locally advanced or borderline-resectable tumors. In the initial series, patients with borderline disease who underwent neoadjuvant treatment and surgery had better survival than those initially resectable [6,11,12]. This fact has led to evaluating this strategy in resectable tumors, also showing a survival benefit in favor of neoadjuvant treatment. In the strategic shift, resectability is not established solely by anatomical factors but takes on elements of tumor biology. Recently, the term bioborderline has been coined. This concept encompasses anatomically resectable tumors with elevated carbohydrate antigen (CA) 19-9 values (> 37 U/mL) in early clinical stages I–II, according to the updated TNM classification of the American Joint Committee on Cancer (AJCC) 7th–8th Edition [13-16].

Several studies have demonstrated an adverse prognosis in patients with elevated CA19-9 concerning hidden hematogenous metastases, increased recurrence rates, early progression, and ultimately poorer survival. This concept implies that in some centers, elevated CA19-9 is an indication to treat resectable patients with neoadjuvant treatment [15,17-19].

Radiotherapy is a valuable component of multimodality treatment for localized pancreatic cancer. Intraoperative radiotherapy (IORT) is a precise component of radiotherapy that can intensify the irradiation effect for cancer control involving an anatomically well-defined volume [20].

The study aimed to analyze the results of neoadjuvant treatment carried out in a tertiary hospital in patients with early pancreatic cancer, classified as bioborderline and non-bioborderline.

MATERIALS AND METHODS

A descriptive, observational, and retrospective study was designed on a prospective registry database in which patients diagnosed with pancreatic ductal adenocarcinoma who underwent complete resection with curative intent from January 1996 to December 2016 in a general surgery service of our Hospital were analyzed. The study was approved by the Research Ethics Committee at Gregorio Marañón University Hospital (18/2020). A total of 92 patients were included, previously evaluated by a multidisciplinary committee, with resectable pancreatic cancer (Appendix 1) in an early stage at diagnosis with and/or without complete histological confirmation but who presented compatible radiological images associated with CA19-9 elevation. Finally, the diagnosis was confirmed in the resection specimen; patients with AJCC 8th edition TNM clinical staging in early stages I–II (IA T1N0M0, IB T2N0M0, IIA T3N0M0, IIB T1-3N1M0). This classification was performed mainly by computed tomography (CT) and, in some cases of doubt, echoendoscopy, positron emission tomography (PET-CT), and magnetic resonance imaging (MRI) were also used. The patients underwent pancreatic resection (cephalic duodenopancreatectomy, total and distal pancreatectomy) and were grouped according to whether or not they were treated with neoadjuvant ± IORT. Exclusion criteria were mainly patients with locally advanced and metastatic pancreatic cancer, palliative pancreatic cancer, patients who have not been resected, and those with missing baseline data, such as those without

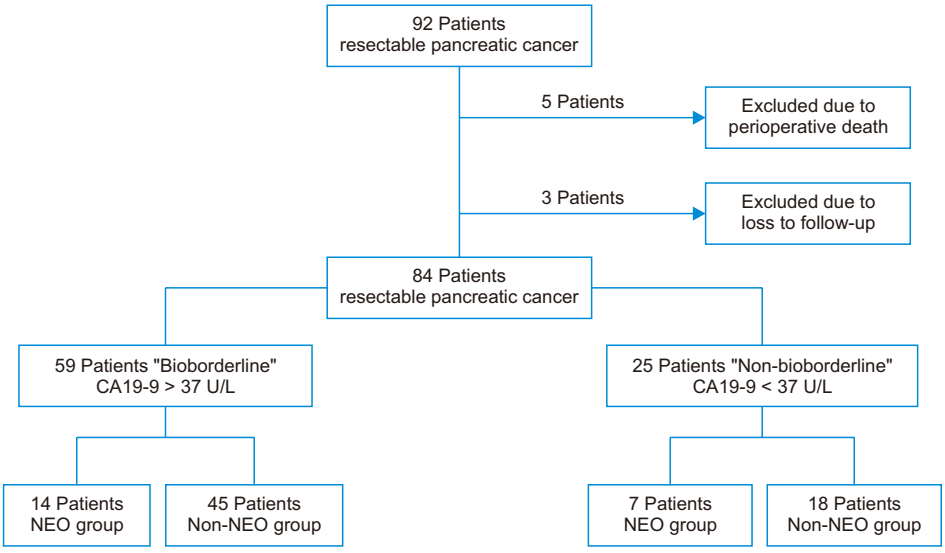

Fig. 1. Flowchart of the groups analyzed. NEO group: neoadjuvant + surgery; non-NEO group: upfront surgery. CA19-9, carbohyd rate antigen 19-9.

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Table 1. Demographic data of the patients

Variable	Total (n = 84)	CA19-9		*p*-value
		> 37 U/mL (n = 59)	< 37 U/mL (n = 25)	
Sex				0.93
Male	51 (60.7)	36 (61.0)	15 (60.0)	
Female	33 (39.3)	23 (39.0)	10 (40.0)	
Median age (IQR)	67 (16)	68 (15)	65 (21)	0.39
ECOG				0.38
0	41 (48.8)	26 (44.1)	15 (60.0)	
1	28 (33.3)	21 (35.6)	7 (28.0)	
2	15 (17.9)	12 (20.3)	3 (12.0)	
Weight loss				0.45
Yes > 15%	25 (29.8)	19 (32.2)	6 (24.0)	
No < 15%	59 (70.2)	40 (67.8)	19 (76.0)	
Jaundice				0.98
Yes	57 (67.9)	40 (67.8)	17(68.0)	
No	27 (32.1)	19 (32.2)	8 (32.0)	
Bilirubin (mg/dL)	5.3 ± 11.3	5.0 ± 8.9	5.5 ± 12.7	0.59
Median CA 19-9 (IQR), (U/mL)	147 (851)	374 (1,351)	8 (28)	< 0.001
Biliary drainage[a]				0.66
Yes	45 (55.5)	32 (57.1)	13 (52.0)	
No	36 (44.4)	24 (42.9)	12 (48.0)	
Clinical stage (cTNM)				0.14
IA (T1N0M0)	12 (14.3)	6 (10.2)	6 (24.0)	
IB (T2N0M0)	37 (44.0)	30 (50.8)	7 (28.0)	
IIA (T3N0M0)	20 (23.8)	12 (20.3)	8 (32.0)	
IIB (T3-T1N1M0)	15 (17.9)	11 (18.6)	4 (16.0)	
Neoadjuvant				0.67
Yes	21 (25.0)	14 (23.7)	7 (28.0)	
No	63 (75.0)	45 (76.3)	18 (72.0)	
Type of resection				0.27
R0	60 (71.4)	43 (72.9)	17 (68.0)	
R1	24 (28.6)	16 (27.1)	8 (32.0)	
Lymph nodes				0.29
(+)	41 (48.8)	31 (52.5)	10 (40.0)	
(–)	43 (51.2)	28 (47.5)	15 (60.0)	
Adjuvant[a]				0.67
Yes	41 (50.6)	28 (49.1)	13 (54.2)	
No	40 (49.4)	29 (50.9)	11 (45.8)	
Type of recurrence				
No recurrence	18 (21.4)	10 (16.9)	8 (32.0)	0.12
Local[b]	36 (42.9)	29 (49.2)	7 (28.0)	0.007
Remote[c]	60 (71.4)	43 (72.9)	17 (68.0)	0.65

Values are presented as number (%) or mean ± standard deviation.
ECOG, Eastern Cooperative Oncology Group (assesses the quality of life or performance status; IQR, interquartile range; cTNM, clinical stage, early classification by computed axial tomography before neoadjuvant therapy (AJCC 7th edition TNM in early stages); R0, no residual tumor; R1, microscopic residual tumor.
[a]Some values are missing.
[b]Local includes: isolated local recurrence and local recurrence + distant metastasis.
[c]Remote includes: isolated distant metastasis and local recurrence + distant metastasis.

Table 2. OS and DFS ("Bioborderline" vs. "Non-Bioborderline")

Variable	Kaplan–Meier, %(SE)				Cox	
	12 mon	36 mon	60 mon	*p*-value (log-rank test)	HR (95% CI)	*p*-value
OS (CA 19-9)						
< 37 U/L	76 (0.85)	32 (0.93)	28 (0.90)	0.030	1	0.032
> 37 U/L	59.3 (0.64)	23.1 (0.53)	16 (0.48)		1.79 (1.05–3.07)	
DFS (CA 19-9)						
< 37 U/L	60 (0.58)	39.6 (0.99)	17.6 (0.13)	0.040	1	0.043
>37 U/L	43 (0.66)	22.5 (0.55)	6.6 (0.52)		1.79 (1.02–3.18)	

HR, hazard ratio; CI, confidence interval; SE, standard error; OS, overall survival; DFS, disease-free survival.

CA19-9 levels at diagnosis.

Patients with elevated CA19-9 levels, taken as a reference point based on the literature value of greater than 37 U/mL, associated with early clinical stage by radiological imaging (CT) that confirmed anatomical resectability, were considered as bioborderline; and patients with early clinical stage by radiological imaging (CT) and normal CA19-9 at diagnosis were considered as non-bioborderline.

At the beginning of the study, eight patients were excluded from 92 in the series due to their incapability to follow-up and peri-operative death, performing a first analysis of the series (n = 84) between patients with CA19-9 > 37 U/mL (n = 59) and patients with the same characteristics but with CA19-9 levels below 37 U/mL (n = 25) (Fig. 1).

Demographic characteristics were compared, resection rates, clinical stage, OS, and DFS. After evaluating the results, further analysis was performed, subgrouping the bioborderline and non-bioborderline patients according to whether they received neoadjuvant treatment. The NEO group consisted of patients who received neoadjuvant treatment based mainly on chemotherapy (Tegafur 1,200 mg [ten patients] or Gemcitabine alone [six patients], and five patients received FOLFIRINOX depending on their age and comorbidities) and external radiotherapy (from 30 to 55 Gy in daily fractions of 1.8 Gy), in addition to surgery with IORT (1,250 cGy) ± adjuvant chemotherapy (mainly Gemcitabine alone [four patients], Gemcitabine + Paclitaxel [three patients], and FOLFIRINOX [two cases]). These patients were restaged after preoperative treatment with imaging to assess resectability and CA19-9 levels. The non-NEO groups included patients who underwent surgery ± adjuvant chemotherapy (mainly Tegafur [22 patients] + Gemcitabine alone [eight patients], and FOLFIRINOX [one patient]).

Between-group comparisons were made between demographic data, restaging after histologic analysis of the specimen, CA19-9 preoperative, after neoadjuvant postoperative complications according to Clavien-Dindo classification, R0-R1 resection, nodal negativity, recurrence rates, OS, and DFS.

A descriptive analysis was performed, expressing qualitative variables as absolute values and percentages and quantitative variables as mean ± standard deviation, or median ± interquartile range. Normality analysis of the variables was performed with the Kolmogorov-Smirnov test.

Means of continuous variables with normal distributions were compared using the two-tailed t-test. Non-parametric tests (Mann–Whitney U test and Kruskal-Wallis test) were used to compare continuous variables without normal distributions or few cases. Categorical data were analyzed using Pearson's chi-squared test or Fischer's exact test.

Survival analysis was performed using the Kaplan Meier method, with OS defined as the time from diagnosis to death and DFS after treatment until recurrence at follow-up. Survival curves were compared with the log-rank test.

For the analysis of risk factors, Cox's regression was used with those variables with significant results in the univariate analysis. *p*-values < 0.05 were considered statistically significant for all comparisons. IBM SPSS version 23.0 for Mac (IBM Corp., Armonk, NY, USA) was used in the statistical analysis.

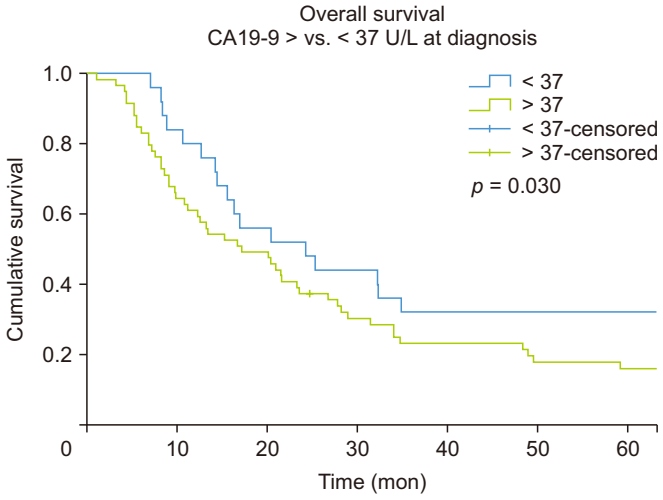

Fig. 2. Comparison of overall survival between groups "Bioborderline vs. Non-bioborderline".

RESULTS

A baseline analysis was performed between the bioborderline group (consisting of 59 [70.2%] patients with CA19-9 > 37 U/mL) vs. the non-bioborderline group (composed of 25 [29.8%] patients with CA19-9 < 37 U/mL). The baseline characteristics of patients in both groups are summarized in Table 1.

The R0 resection rate of the group with elevated CA19-9 was 72.9%, compared to 68.0% of the group with CA19-9 normal values; and the R1 rate was 27.1%, compared to 32.0%, respectively, with no significant differences between the two groups ($p = 0.27$).

While analyzing the histologic poor prognostic factors, it was observed that 51.2% of the patients in this series had negative lymph nodes. Regarding recurrence, the group with CA19-9 > 37 U/L had a stronger tendency to recurrence: 49.2%, compared to 28% of patients with CA19-9 < 37 U/L ($p = 0.07$). However, concerning distant recurrence (71.4%), no significant differences were observed in the distribution between the two groups.

When analyzing survival in these groups (Table 2), it was observed that the median OS in the bioborderline group was 17 months vs. 24 months in the non-bioborderline group, finding

Table 3. Clinicopathological characteristics ("Bioborderline")

Variable	NEO group (n = 14)	Non-NEO group (n = 45)	*p*-value
Sex			0.73
Male	8 (57.1)	28 (62.2)	
Female	6 (42.9)	17 (37.8)	
Median age (IQR)	66 (10)	65 (10.4)	0.78
Weight loss			0.12
Yes > 15%.	7 (50.0)	12 (26.7)	
No < 15%.	7 (50.0)	33 (73.3)	
Jaundice			0.35
Yes	8 (57.1)	32 (71.1)	
No	6 (42.9)	13 (28.9)	
CA 19-9 (U/mL)			
Median (IQR)	145 (589)	464 (1,918)	0.05
Post NEO	14 (33.8)	-	0.005
Post Surg.	12 (33.0)	353 (1,688)	0.007
ECOG			0.99
0	6 (42.9)	20 (44.4)	
1	5 (35.7)	16 (35.6)	
2	3 (21.4)	9 (20.0)	
ECOG Post Surg			0.14
0	5 (35.7)	4 (8.9)	
1	4 (28.6)	22 (48.9)	
2	5 (35.7)	16 (35.6)	
3	0 (0)	2 (4.4)	
4	0 (0)	1 (2.2)	
Preoperative stage (AJCC)[a)]			0.38
IA (T1N0M0)	1 (7.1)	5 (11.1)	
IB (T2N0M0)	5 (35.7)	25 (55.6)	
IIA (T3N0M0)	5 (35.7)	7 (15.6)	
IIB (T1-T3N1M0)	3 (21.4)	8 (17.8)	
Postoperative stage (AJCC)[a)]			0.002
No tumor (pRC)	4 (28.6)	0 (0)	
0 (TisN0M0)	0 (0)	1 (2.2)	
IA (T1N0M0)	1 (7.1)	0 (0)	
IB (T2N0M0)	3 (21.4)	5 (11.1)	
IIA (T3N0M0)	3 (21.4.)	11 (24.4)	
IIB (T1-3N1M0)	1 (7.1)	18 (40.0)	
III (T1-3N2M0) or (T4M0)	2 (14.3)	10 (22.2)	

Table 3. Continued

Variable	NEO group (n = 14)	Non-NEO group (n = 45)	*p*-value
NEO-QX interval, median in days (IQR)	35 (22.0)	-	0.20
Type of surgery			0.68
PD	9 (64.3)	34 (75.6)	
Total pancreatectomy	4 (28.6)	8 (17.8)	
Distal pancreatectomy	1 (7.1)	3 (6.7)	
IORT (Intraoperative radiotherapy)			< 0.001
Yes	13 (92.9)	4 (8.9)	
No	1 (7.1)	41 (91.1)	
Type of resection			0.21
R0	12 (85.7)	31 (68.9)	
R1	2 (14.3)	14 (31.1)	
Lymph nodes			0.008
(+)	3 (21.4)	28 (62.2)	
(–)	11 (78.6)	17 (37.8)	
Adjuvant[b)]			0.80
Yes	6 (42.9)	22 (48.9)	
No	7 (50.0)	22 (48.9)	
Follow-up time, median (IQR)	28 (58)	13 (24)	0.018
Type of recurrence			
No recurrence	3 (21.4)	7 (15.6)	0.68
Local[c)]	3 (21.4)	26 (57.8)	0.018
Remote[d)]	10 (71.4)	33 (73.3)	0.88

Values are presented as number (%).
IQR, Interquartile range; Post NEO, post neoadjuvant treatment levels; Post Surg, after surgical treatment; PD, Whipple's cephalic duodenopancreatectomy; R0, no residual tumor; R1, microscopic residual tumor; NEO-QX Interval, interval time between neoadjuvant and surgery.
[a)] AJCC Prognostic Groups, 7th edition.
[b)] Some values are missing.
[c)] Local includes: isolated local recurrence and local recurrence + distant metastasis.
[d)] Remote includes: isolated distant metastasis and local recurrence + distant metastasis .

statistically significant differences between the two (p = 0.030) (Fig. 2). After conducting risk analysis by Cox regression, it was observed that patients with CA19-9 > 37 U/L have a mortality rate 1.8-times higher than the CA19-9 < 37 U/L group (p = 0.032).

Bioborderline

To evaluate the impact of neoadjuvant treatment in both groups separately, patients that were considered as bioborderline and non-bioborderline, were further divided into two subgroups, according to whether or not they had undergone neoadjuvant treatment.

Of the 59 patients included in the bioborderline group, 23.7% (n = 14) received neoadjuvant treatment (NEO group), and 76.3% (n = 45) underwent initial surgery (non-NEO group). The baseline and clinicopathological characteristics of the patients in both groups are summarized in Table 3.

The pathologic response to neoadjuvant treatment was evaluated and a 28.6% pathologic complete response (pCR) in the NEO group was recorded. Although there were no significant differences in tumor residue between the neoadjuvant group and the upfront surgery group, there was a greater tendency for complete resection R0 in favor of the NEO group: 85.7% vs. 68.9%, respectively. However, the microscopic residual (R1) has an inverse tendency: 14.3% in this group vs. 31.1% in the non-NEO group (p = 0.21).

While analyzing the histological poor prognostic factors, 78.6% of the NEO group was observed to have negative lymph nodes, compared to 37.8% of the non-NEO group, with significant differences between them (p = 0.008) (Table 3).

Regarding recurrence, a statistical difference was observed at the local level in favor of neoadjuvant treatment, with 21.4% vs. 57.8% (p = 0.018). Nevertheless, concerning distant recurrence, a similar distribution was observed in both groups.

The total peri-operative morbidity rate was 51.9%; a 53.5% in the non-NEO patients, compared to 44.4% in the NEO group (p = 0.97). Peri-operative mortality was 4.7%, observed only in the non-NEO group.

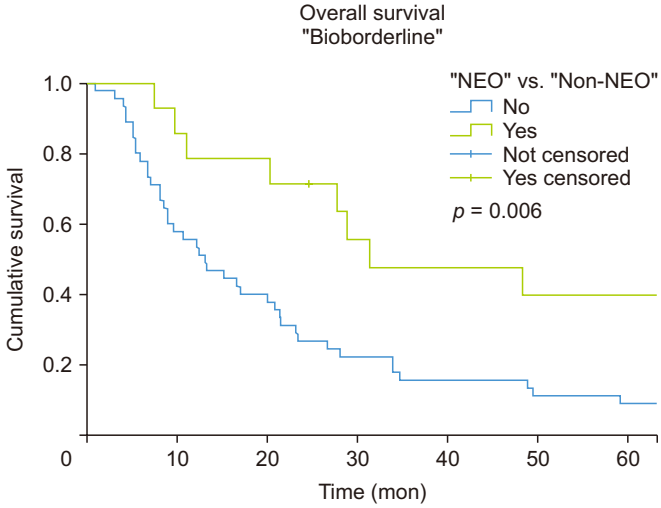

Fig. 3. Overall survival of Bioborderline "NEO vs. Non-NEO". NEO, Neoadjuvant group; Non-NEO, non-neoadjuvant group.

If the survival rates were analyzed in the present study group, an important impact of neoadjuvant treatment is noted. The median OS in the NEO group was 31.4 months vs. 13.1 months in the non-NEO group, finding statistically significant differences between the two (p = 0.006) (Fig. 3). After conducting risk analysis with Cox regression, neoadjuvant patients presented a relative reduction of 62% in the mortality rate (p = 0.008) (Table 4).

Non-bioborderline

On the other hand, concerning the non-bioborderline group, of the 25 patients included in the study, 28.0% (n = 7) received neoadjuvant treatment (NEO group), and 72.0% (n = 18) underwent initial surgery (non-NEO group). The baseline and clinicopathological characteristics of the patients in both groups are summarized in Table 5.

Table 4. OS and DFS (neoadjuvant in "Bioborderline")

Variable	Kaplan-Meier, %(SE)				Cox	
	12 mon	36 mon	60 mon	p-value (log-rank test)	HR (95% CI)	p-value
OS						
Neoadjuvant				0.006		0.008
Yes	78.6 (0.11)	47.6 (0.14)	31.7 (0.13)		0.38 (0.20–0.79)	
No	53.3 (0.074)	15.6 (0.054)	8.9 (0.042)		1	
DFS						
Neoadjuvant				0.013		0.016
Yes	78 (0.11)	31.2 (0.13)	31.2 (0.13)		0.42 (0.21–0.85)	
No	29.1 (0.70)	12.1(0.51)	9.7 (0.46)		1	

HR, hazard ratio; CI, confidence interval; SE, standard error; OS, overall survival; DFS, disease-free survival.

Table 5. Clinicopathological characteristics ("Non-bioborderline")

Variable	NEO group (n = 7)	Non-NEO group (n = 18)	*p*-value
Sex			0.045
Male	2 (28.6)	13 (72.2)	
Female	5 (71.4)	5 (27.8)	
Median age (IQR)	62 (12.4)	64 (11.9)	0.72
Weight loss			0.17
Yes > 15%	3 (42.9)	3 (16.7)	
No < 15%	4 (57.1)	15 (83.3)	
Jaundice			0.47
Yes	4 (57.1)	13 (72.2)	
No	3 (42.9)	5 (27.8)	
CA19-9 (U/mL)			
Median (IQR)	7 (23)	10.5 (20.1)	0.44
Post NEO	3 (10)	-	0.89
ECOG			0.039
0	7 (100)	8 (44.4)	
1	0 (0)	7 (38.9)	
2	0 (0)	3 (16.7)	
ECOG Post Surg[a]			0.15
0	6 (85.7)	4 (36.4)	
1	0 (0)	1 (9.1)	
2	1 (14.3)	5 (45.5)	
3	0 (0)	1 (9.1)	
Preoperative stage (AJCC)[b]			0.13
IA (T1N0M0)	0 (0)	6 (33.3)	
IB (T2N0M0)	3 (42.9)	4 (22.2)	
IIA (T3N0M0)	2 (28.6)	6 (33.3)	
IIB (T1-T3N1M0)	2 (28.6)	2 (11.1)	
Postoperative stage (AJCC)[b]			0.01
No tumor (pRC)	2 (28.6)	0 (0)	
IA (T1N0M0)	1 (14.3)	3 (16.7)	
IB (T2N0M0)	1 (14.3)	0 (0)	
IIA (T3N0M0)	3 (42.9)	5 (27.8)	
IIB (T1-3N1M0)	0 (0)	5 (27.8)	
III (T1-3N2M0) or (T4M0)	0 (0)	5 (27.8)	
NEO-QX interval, median in days (IQR)	35 (22)	-	0.20
Type of surgery			0.48
PD	6 (85.7)	13 (72.2)	
Total pancreatectomy	1 (14.3)	3 (16.7)	
Distal pancreatectomy	0 (0)	2 (11.1)	
IORT			0.94
Yes	7 (100)	8 (44.4)	
No	0 (0)	10 (55.6)	
Type of resection			0.01
R0	7 (100)	10 (55.6)	
R1	0 (0))	8 (44.4)	
Lymph nodes			0.01
(+)	0 (0)	10 (55.6)	
(–)	7 (100)	8 (44.4)	
Adjuvant[a]			0.47
Yes	3 (42.9)	10 (50.8)	
No	4 (57.1)	7 (41.2)	
Type of recurrence			
No recurrence	5 (71.4)	3 (16.7)	0.008
Local[c]	0 (0)	7 (38.9)	0.05
Remote[d]	2 (28.6)	15 (83.3)	0.008

Values are presented as number (%).
IQR, interquartile range; IORT, intraoperative radiotherapy; Post NEO, post neoadjuvant treatment levels; Post Surg, after surgical treatment; PD, Whipple's cephalic duodenopancreatectomy; R0, no residual tumor; R1, microscopic residual tumor; NEO-QX Interval, interval time between neoadjuvant and surgery.
[a]Some values are missing.
[b]AJCC Prognostic Groups, 7th edition.
[c]Local includes: isolated local recurrence and local recurrence + distant metastasis
[d]Remote includes: isolated distant metastasis and local recurrence + distant metastasis

In the series distribution according to post-resection histological status, stage migration was also observed in the NEO group, with 28.6% of pCR.

When the tumor residue was analyzed after resection, there was still 44.4% of R1 in the group of upfront surgery. In contrast, in the neoadjuvant group before surgery, all patients were R0, compared to 55.6% of patients without neoadjuvant (p = 0.01).

Analysis of the histological poor prognostic factors showed that 100% of the NEO group presented negative lymph nodes after analysis of the specimen, compared to 44.4% of the non-NEO group, with statistical differences between the two groups (p = 0.01).

Fifty-two percent of the patients in the sample presented postoperative complications. As for recurrence after surgical treatment, less overall recurrence was observed in the NEO group (28.6%) than in the non-NEO group (83.3%) (p = 0.008). No local recurrence was observed in the neoadjuvant group (Table 5).

The median OS in the NEO group was 65.9 months vs. 16.2 months in the non-NEO group, without observing statistically significant differences between the two but with a trend towards significance in favor of the group treated with neoadjuvant therapy (p = 0.08) (Fig. 4). By conducting risk analysis with Cox regression, those patients with neoadjuvant had a 61.0% relative reduction in mortality rate (p = 0.08) (Table 6).

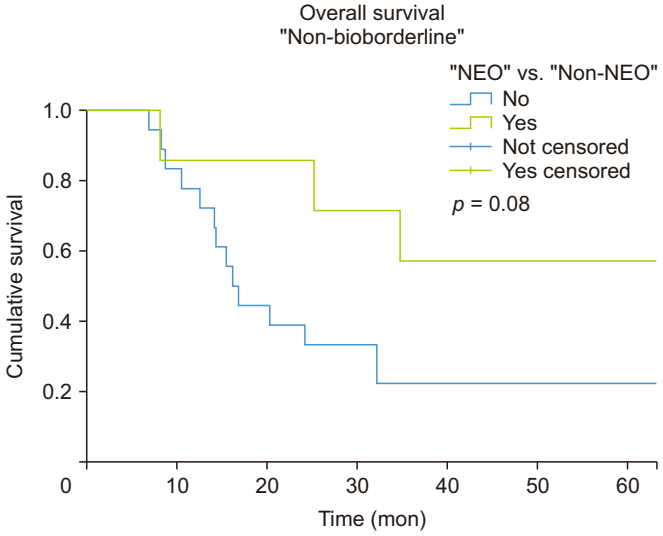

Fig. 4. Overall survival of Non-bioborderline "NEO vs. Non-NEO". NEO, neoadjuvant group; Non-NEO, non-neoadjuvant group.

DISCUSSION

Today the standard of treatment for resectable pancreatic ductal adenocarcinoma remains surgery followed by adjuvant therapy; being a biologically aggressive disease from the onset, even with complete resection, it presents high rates of local and distant recurrence. Several retrospective and prospective phase I/II studies have explored neoadjuvant therapy as an alternative treatment for resectable pancreatic cancer, with promising results. While it appears that even potentially resectable and early-stage diseases would benefit from preoperative multimodality therapy, the optimal neoadjuvant therapeutic strategy is still controversial. The National Comprehensive Cancer Network (NCCN) proposes the possibility of administering neoadjuvant therapy in borderline and high-risk resectable patients. Nevertheless, in the present study, we went further by attempting to assess the impact of neoadjuvant therapy in patients who were initially considered resectable at early stages, comparing survival between groups according to their biological behavior as measured by CA19-9 [11,21,22].

The literature supports neoadjuvant in resectable patients. In 2018, a randomized study, PACT-15, demonstrated improved survival in patients with resectable stage I and II, who were given neoadjuvant, surgery, and adjuvant, versus those treated with surgery and then adjuvant. In addition, more randomized clinical trials are underway, such as PREOPANC-1, NEOPAC, NEPAFOX, NEONAX, and SWOG S1505, which might consolidate neoadjuvant therapy in the treatment of resectable pancreatic cancer [10,23-27]. Findings presented herein align with those described in the literature, and patients with elevated CA19-9 tumor markers have worse OS and DFS [15,17]. In addition, it was confirmed that with an upfront surgery strategy, many patients never receive adjuvant chemotherapy, the only strategy that has been shown to significantly improve survival [6]. Neoadjuvant therapy in this patient population is criticized for increasing the risk of postoperative complications by making surgery more challenging. If severe complications were compared (III–V according to the Clavien-Dindo classification), no statistical differences were observed in the patients, and the tendency was for fewer complications in the neoadjuvant group. In this study sample, an R0 resection was observed and negativity of metastatic nodes in a high rate of patients who received neoadjuvant treatment in both groups, with a survival benefit of neoadjuvant treatment, in contrast to the patients who did not receive neoadjuvant therapy [28].

In this study, a 28.2% of pRC was described in a patient who received neoadjuvant therapy; this high rate is probably due to the effect of chemotherapy treatment in patients with an incipient disease, but we also describe the worse migration in a pathological stage in patients who did not receive neoadjuvant therapy. These changes from the clinical stage to the pathological stage could be in the case of patients without neoadjuvant treatment due to understaging and in the case of patients with

Table 6. OS and DFS (neoadjuvant in "Non-bioborderline")

Variable	Kaplan-Meier, (%) SE				Cox	
	12 mon	36 mon	60 mon	*p*-value (log-rank test)	HR (95% CI)	p-value
OS						
Neoadjuvant				0.08		0.09
Yes	85.7 (0.13)	57.1 (0.19)	42.9 (0.19)		0.39 (0.13–1.18)	
No	72.2 (0.11)	22.2 (0.1)	22.2 (0.1)		1	
DFS						
Neoadjuvant				0.03		0.046
Yes	85.7 (0.13)	71.4 (0.17)	71.4 (0.17)		0.22 (0.05–0.98)	
No	50 (0.12)	22.2 (0.1)	22.2 (0.1)		1	

HR, hazard ratio; CI, confidence interval; SE, standard error; OS, overall survival; DFS, disease-free survival.

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neoadjuvant treatment due to chemotherapy treatment.

The impact of neoadjuvant treatment on local recurrence was particularly noteworthy, with a reduction of more than half in the bioborderline group and no local recurrence observed in the normal biomarker patients. It is believed that the component of intensification with IORT in the NEO group has probably improved the results of our patients in terms of local disease control. Our center's previous publication supports this conclusion on IORT in pancreatic cancer and control of local recurrence [29-32].

Despite sample was small in this study, the effect of neoadjuvant therapy appeared to be influential, placing the patients with the worst prognosis (bioborderline) in a situation equivalent to those who were initially assumed to have a better prognosis because they had normal CA19-9. However, its effect on these non-bioborderline patients was even more beneficial, increasing the median OS by more than double that of the bioborderline (Fig. 3, 4). OS in early-stage patients with high CA19-9, who were given neoadjuvant treatment, was longer compared to early-stage patients with low CA19-9 without neoadjuvant treatment; but if neoadjuvant treatment was administered in these patients, survival more than doubles compared to patients with high CA19-9 treated with neoadjuvant treatment; a promising result not explored in other studies in this type of patients. However, despite the observed benefit, the limitation of the NEO group in non-bioborderline patients in this study is that the sample size is small, which was why these data could be considered statistically significant results. Although this was probably a group that also benefited from neoadjuvant therapy, this could not be demonstrated in the way that has been done in the bioborderline group. This data led us to think that neoadjuvant treatment should probably be administered to all patients with pancreatic cancer, as observed in the PREOPANC study [33], although other randomized studies now underway will give us this answer [34].

This is a retrospective study with a small and non-homogeneous sample concerning the treatments received. However, despite the small and retrospective sample, it involves a reference hospital with hepatobiliopancreatic surgery expertise and an oncology unit. The results in favor of neoadjuvant treatment demonstrated significant statistical differences in survival, as well as an evident clinical impact in a disease with an inferior prognosis (13.1 vs. 31.4 months in the bioborderline group, and 16.2 vs. 65.9 months in the non-Bioborderline group), achieving a 62.0% relative reduction in mortality rate. Therefore, although this study has limitations, it is believed that its findings add value.

Decisions on pancreatic cancer's diagnostic and therapeutic management and resectability should include a multidisciplinary assessment in a high-volume care center. A neoadjuvant strategy is feasible and appears to improve OS and DFS in early pancreatic cancer, even in a setting that is classically associated with adverse prognosis, such as "Bioborderline" patients. Despite the study's limitations, the results of neoadjuvant treatment in patients with normal CA19-9 are encouraging and little explored by other groups, serving as a basis for future studies. Ongoing randomized studies will define the value and indication for neoadjuvant therapy in this setting in which significant survival gains have not been achieved with the classic strategy of upfront surgery.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Appendix 1. Definition of resectable pancreatic cancer [34]

Stage	Anatomy		MCW		NCCN (2019)	MDACC	AHPBA/SSO/ SSAT
Resectable	Artery (CA, SMA, or HA)		No involvement		No involvement	No involvement	No involvement
	Vein (SMV, PV, or SMV-PV confluence)		- No involvement - If involved, ≤ 50% circumference narrowing of vein		- No involvement - ≤ 180° contact without vein contour irregularity.	- No involvement - Abutment (provided vein is patent).	No involvement
Borderline resectable	Artery	CA	Abutment		Head/uncinate: • Contact with CHA without extension to CA or hepatic artery bifurcation • Contact with the SMA of ≤ 180° • Contact with variant arterial anatomy. • Pancreatic body/tail: • Contact with the CA of ≤ 180° • Contact with the CA of > 180° without involvement of the aorta and with intact and GDA.	Abutment	Uninvolved
		SMA	Abutment			Abutment	Abutment
		HA	Short segment abutment/encasement without involving CA or HA bifurcation.			Abutment or short segment encasement	Abutment or short segment encasement
	Vein (SMV, PV, or SMV-PV confluence).		> 50% narrowing[a]		- Contact >180°[a] - Contact ≤180° with contour irregularity or thrombosis of vein[a] - Contact with IVC	- Abutment with impingement and narrowing[a] - Segmental venous occlusion[a]	Abutment, encasement, or short segment occlusion[a]
Locally advanced	Artery		Type A	Type B	Head/uncinate process: • Contact with SMA > 180° • Contact with the CA > 180° Pancreatic body/tail: • Contact of > 180° with the SMA or CA • Contact with the CA and aortic involvement	Encasement of CA, SMA and HA without options for reconstruction	
		CA	Encasement but no extension to aorta[b]	Encasement and extension to aorta			
		SMA	Encasement (>180° but ≤ 270°)	> 270° encasement			
		HA	Encasement and extension to CA[b]	Encasement with extension beyond bifurcation of proper HA			
	Vein (SMV, PV, or SMV-PV confluence)		Occlusion without options for reconstruction.				
Metastatic	Evidence of peritoneal and distant metastases						

Abutment is defined as ≤ 180° contact with vessel and encasement indicates > 180° involvement. MCW, Medical College of Wisconsin; NCCN, National Comprehensive Cancer Network; MDACC, MD Anderson Cancer Center; AHPBA, American Hepato-Pancreato-Biliary Association; SSAT Society for Surgery of the Alimentary Tract; SSO Society for Surgical Oncology; CA, celiac axis; SMA, superior mesenteric artery; HA, hepatic artery; GDA, gastroduodenal artery; SMV, superior mesenteric vein; PV, portal vein.

[a]Amenable for safe and complete resection and venous reconstruction.

[b]Amenable for celiac resection (with or without reconstruction).

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