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Delays to surgery following chemoradiotherapy lead to poorer oncologic outcomes in patients with localized pancreatic adenocarcinoma

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Abbreviations. PDAC Pancreatic ductal adenocarcinoma, NCRT Neoadjuvant chemoradiotherapy, PD Pancreatoduodenectomy CT Computed Tomography Pancreatoduodenectomy

Authors contributions

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ABSTRACT

Background. Although neoadjuvant chemoradiotherapy (NCRT) and surgery are accepted as treatments for pancreatic ductal adenocarcinoma (PDAC), some authors have highlighted the risks of delaying surgery.

Our objective was to analyze the impact of prolonging the time interval between NCRT and surgery (NCRT-TTS) in PDAC.

Methods. Patients treated with NCRT and pancreatoduodenectomy (PD) were identified. Clinical, histopathological variables were analyzed on whether NCRT-TTS was greater or less 50 days

Five- and 10-year overall survival (OS) and disease-free survival (DFS) were analyzed depending on whether the delay was greater than 50 days or not.

Results. 100 (8.3%) of 120 eligible patients underwent PD: 61 male, median age of 63.7 years. In 71 (71%) patients the median NCRT-TTS was 39 (24-50) days and in 29 (29%) 61 days.

There were no differences between the two groups except for CA 19-9 levels, the incidence of cholangitis, ASA score, intraoperative blood transfusions and degree of histopathologic response (all $p< 0.001$).

Median DFS when the NCRT-TTS was less than 50 days was higher than when the interval exceeded 50 days - 51.0 months (95% CI 20.3-81.6) vs 17.0 months (95% CI 10.9-23.0); HR (95% CI 1.08-3.46), p=0.026.

Five-year DFS was higher in the subgroup with the NCRT-TTS of less than 50 days compared to the group with an interval of more than 50 days - 43.5% vs 23.65% (HR 1.812 95% CI 1.001-3.280), p= 0.050

Conclusions. An increase in the NCRT-TTS > 50 days is associated with poorer OS and DFS in patients with localized PDAC treated with NCRT and PD.

Keywords: Neoadjuvant therapy. Pancreatectomy. Surgical timing. Outcomes.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) remains a devastating disease and currently represents the fourth cause of all deaths from cancer(1).

Although the standard treatment of resectable PDAC (stages I-II) is first surgery then adjuvant chemotherapy, over the last decade substantial advances have been made in neoadjuvant treatment, where PDAC is considered a systemic disease. (1, 2, 3, 4)

In the debate generated by the neoadjuvant approach, some authors have highlighted the negative effect of delaying surgery in potentially resectable tumors (5, 6).

In the present study we analyze the impact of increasing the time interval between the completion of treatment (NCRT) and surgery on the long-term oncologic outcomes of a series of patients with localized PDAC treated with neoadjuvant chemoradiotherapy and pancreaticoduodenectomy (PD).

METHODS

Study design and selection criteria.

A retrospective study was performed using a prospective database of all patients diagnosed with localized PDAC and treated with neoadjuvant chemoradiotherapy and surgery between 2000 and 2018.

The study was approved by the Research Ethics Committee of the center (reference 2021.098).

We included all patients over the age of 18 with histologic confirmation of PDAC, localized in the head of the pancreas and treated with NCRT and PD. Patients' tumors were staged prior to treatment using computed tomography (CT) and endoscopic Ultrasound (EUS), following the criteria of the National Comprehensive Cancer Network(7). Patients in whom disease progressed during treatment, those who did not complete the treatment, those for whom resection was contraindicated due to the presence of hidden metastases or local spread of the tumor as observed during laparotomy, were excluded. In patients with bilirubin levels over 5 mg/dL an endoscopic biliary prosthesis was put in place before treatment was begun.

Two chemotherapy regimens were administered. The first from 2000 to 2011, which consisted of Gemcitabine (1000mg/m^2)-Capecitabine (850-1000 mg/m^2) and Oxaliplatin (85 mg/m^2) and the second from 2012 onwards. This was a modified

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FOLFIRINOX regimen, based on Oxaliplatin (85 mg/m^2), Irinotecan (150 mg/m^2), 5-Fluorouracil (5-FU) (2.400mg/m^2) and calcium folinate (Leucovorin calcium; 400mg/m^2) for 4 weeks.

At the end of the chemotherapy and reevaluation with CA-19.9 levels and thoracic and abdominal CT, external radiotherapy was administered for 4-5 weeks (50.4 Gy/28 fractions at 1.8-2 Gy/fraction, combined with Capecitabine (825 mg/m^2) or a continuous infusion of Fluorouracil (225 mg/m^2/d).

The interval between the neoadjuvant treatment and surgery was defined as the number of days elapsing from the end of the CRT to surgery.

Surgery was performed between 4 and 7 weeks after completion of chemoradiotherapy and after radiologic restaging using CT (8).

In some patients, additional adjuvant chemotherapy was administered (Gemcitabine 1000 mg/m^2), depending on oncologic criteria and degree of histologic response, perineural invasion or lymph node involvement (ypN+).

The following data were obtained from all patients: age, sex, body mass index (Kg/m^2), American Society of Anesthesiologists (ASA)-physical Status score(9), and baseline levels of carbohydrate antigen 19.9 (CA-19.9).

Two authors recorded all operative complications using the Dindo-Clavien classification(10).

All specimens were analyzed following the guidelines of the American College of Pathologists for carcinoma of the exocrine pancreas(11). Histologic response was assessed using the scheme of Ryan(12) comprising 4 grades: from grade 0, or complete response (CR), no viable cancer cells to grade 3, extensive residual cancer with no evident tumor regression. Perineural invasion (PNI) and lymphovascular invasion (LVI) were defined using the criteria of Batsakis et al(13) and Chatterjee et al(14) respectively.

TNM staging was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC)(15).

Patients were assessed every 3-4 months in the first two years, every 6 months in the third and fourth years and every 12 months from the fifth year onwards.

At each check-up, a physical examination was performed, CA-19.9 levels were determined and an abdominal CT scan was performed (16)

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Statistical Analysis.

Continuous variables are presented as medians and ranges and were compared using the Mann-Whitney U test or Kruskal-Wallis tests as appropriate. Categorical variables are described as absolute values and percentages and were analyzed using the Chi-squared test or Fisher´s exact test as appropriate. The univariate relation between each independent variable and recurrence was evaluated using a single factor logistic model for continuous variables and Pearson´s chi-squared test for categorical variables. Independent variables with a p value < 0.05 were considered for the logistic regression model. Results of the multivariate adjusted Cox analysis are reported together with hazard ratios (HR) and the corresponding 95% confidence intervals (95% CI). Statistical tests were two-sided and P values < 0.05 were considered to be statistically significant.

Overall survival (OS) was calculated from diagnosis to death from any cause, or the last check-up. Disease-free survival (DFS) was defined as the time from diagnosis to the detection of tumor recurrence or death.

Median patient survival was estimated using Kaplan-Meier curves with the corresponding 95% confidence intervals.

Statistical analysis was performed using SPSS Statistics 25.0 for Windows software package (SPSS, Inc, Armonk, NY).

RESULTS

Between January 2000 and January 2020, 120 patients with PDAC localized to the head of the pancreas were treated with NCRT. Of these 120 patients, 20 patients were excluded for the following reasons: in 13 the disease progressed during treatment and 7 patients did not complete the full treatment: 4 died during treatment, 1 discontinued treatment and 2 due to their general bad state of health. PD was performed in 100 patients (83.3%).

Figure 1 shows the corresponding flow diagram.

Table 1 shows the histopathologic, clinical and demographic characteristics of the cohort.

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The median overall time interval between completion of CRT and surgery (CRT-TTS) was 46.7 days (24-125). In 71 patients (71%), the CRT-TTS was less than 50 days (median 39; range 24-50) and in 29 (29%) greater than 50 days (median 61; range 51-125). Causes of the delay to surgery were chemotherapy-related toxicity in 2 patients, patient choice due to logistic or economic reasons in 11 patients, extended neoadjuvant chemotherapy in 8 patients, 6 due to cholangitis and 2 due to infection.

Operative time and length of hospital stay were 316 min (216-703) and 8 days (0-29).

90-day operative mortality was 2% and 56 (56%) of patients experienced post-operative complications of which 34 (60.7%) were minor (Dindo-Clavien I-II).. Twelve patients needed to be readmitted to hospital in the first 90 days.

Most tumors (n=57; 57%) corresponded to pathologic stage ypI (IA n=30 and IB n=27), 23 to stage ypII and 12 to stage ypIII as defined by the AJCC. Twenty patients (20%) had lymphovascular invasion and 39 (39%) perineural invasion (Table 1).

With a median overall survival of 47.0 months (95% CI 18.7-75.2) and median disease-free survival of 34.0 months (95% CI 11.1-56.8);

The 5- and 10-year overall survival of the series was 48.8% and 39.6%, respectively. Figure 2 shows the disease-free survival curve of the patients at 5 (38.1%) and 10 years (32.3%).

Table 2 shows the multivariate analysis of the factors associated with overall and disease-free survival at 5 years adjusted for age, sex, ASA score, TNM stage, BMI, PNI, LVI, tumor margin involvement and histologic response. In this analysis, lymphovascular invasion was negatively associated with overall survival (HR 2.980, 95% CI 1.515-5.864, p<0.02) and disease-free survival (HR 2.382, 95%CI 1.269-4.470, p<0.007). A CRT-TTS greater than 50 days also significantly affected both overall survival (HR 2.165, 95% CI 1.072-4.374, p=0.031) and disease-free survival (HR 2.061, 95% CI 1.122-3.785, p=0.020).

Given the negative impact of a time interval of more than 50 days between CRT and surgery on survival, we analyzed the factors associated with this delay (Table 3). Of the factors analyzed, CA 19-9 levels, the presence of cholangitis, ASA physical status score, and a greater degree of pathologic response (Ryan score 0-1) were all associated with a more than 50-day delay in surgery (all p <0.05). TNM staging, PNI, LVI, the incidence of complications and adjuvant chemotherapy were similar across both groups.

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When we studied OS and DFS in relation to the NCRT-TTS interval, we found differences in OS and DFS. The median OS of the patients with a CRT-TTS interval of less or more than 50 days was 66 months (95% CI 15.7-116.2) and 39.0 months (95% CI 5,5-72.4); p=0.045.

We did find significant differences in DFS. The median DFS for patients with a CRT-TTS interval of less or more than 50 days was 51.0 months (95% CI 20.3-81.6) and 17.0 months (95% CI 10.9-23.0).

Figure 3 shows the DFS Kaplan-Meier survival curves for both populations and significantly better outcomes can be seen for patients who had a CRT-TTS interval of less than 50 days (43.5% vs 23.65%; HR 1.94 95% CI 1.08-3.46; p=0.026). In the curves, a rapid fall is evident in the first two years.

DISCUSSION

Over the last decade, neoadjuvant CRT followed by surgery has become established as the most appropriate treatment for localized PDAC (2).

The advantages and disadvantages of the neoadjuvant treatment of resectable tumors have been widely reported and debated in the last decade (2, 4, 5).

In our series, we were able to perform resections in 83.3% (n=100) of the patients initially treated with NCRT, a figure similar to that reported by Evans et al (17), (85%) and slightly higher than that reported in two multicenter studies (78%)(18, 19) and in the recent Preopanc Trial (61%) (4).

To our knowledge, this is the first study to show that the prolongation of the time interval between completion of the chemoradiotherapy and surgery (>50 days) in DCP is associated with a 20% reduction in OS and DFS in localized DCP.

Such a negative finding has recently been reported in cancer of the, esophagus, rectum and in the resection of liver metastases from colorectal cancer(20). Curiously, the time interval between CRT and surgery –7 weeks– and the impact on survival –almost 20%– is the same as in our analysis.

There are various reasons which may explain this phenomenon. Firstly, and we believe the most likely reason, is that delaying surgery (> 7 weeks) is associated with not giving or significantly delaying the administration of additional adjuvant chemotherapy in a crucial period as is that immediately following surgery.

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Several studies indirectly confirm this hypothesis reporting better oncologic outcomes when neoadjuvant therapy is prolonged prior to surgery(21)

Secondly, the reason for delaying surgery more than 7 weeks maybe due to the poorer performance status of the patients after the neoadjuvant treatment. In our series, such patients presented a higher ASA physical status score, greater incidence of cholangitis, significantly higher CA-19.9 levels, all of which suggest that they were weaker patients with tumors with a worse prognosis(22). Thirdly, it is well known that the prolongation of the NCRT-TTS interval leads to an increase in tissue fibrosis –especially in patients with a biliary prosthesis–, which increases surgical difficulty and operative morbidity and mortality.

Finally, our analysis confirms that microscopic LVI is a major negative risk factor for OS and DFS in PDAC treated with NCRT, a finding consistent with the study by Kubo et al. among others(23, 24).

Limitations

We are aware of the limitations of our study as it is a retrospective analysis of a limited number of cases from a single institution, although all data were collected prospectively. However, as we have been less restrictive in the neoadjuvant treatment, we believe that our experience is closer to the current trend in the treatment of localized cancer of the pancreas.

Another limitation is the bias from only including patients undergoing resection in the survival analysis, without reporting results by intention to treat.

Strengths of the study include the homogeneity in the surgical treatment, the fact that it is a single center study and the rigorous and long follow-up.

CONCLUSIONS

An increase in the time interval (> 7 weeks) between the completion of CRT and pancreatoduodenectomy is associated with a reduction in overall and disease-free survival at 5 and 10 years from diagnosis in the neoadjuvant treatment of localized cancer of the pancreas.

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Key points

- Neoadjuvant chemotherapy and surgery are accepted as treatment for pancreatic ductal carcinoma
- Delaying surgery has been associated with negative impact in gastrointestinal tumor son long-term survival
- An increase in the time interveal (>7 weeks) between completion of chemo-radiotherapy and surgery is associated with a reduction in overall and disease-free survival
- This finding support the additional chemotherapy when a more than 7 weeks delay is expected
- Lymphovascular invasion is a major negative risk factor for Os and DFS in pancreatic cancer

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Figure 1.

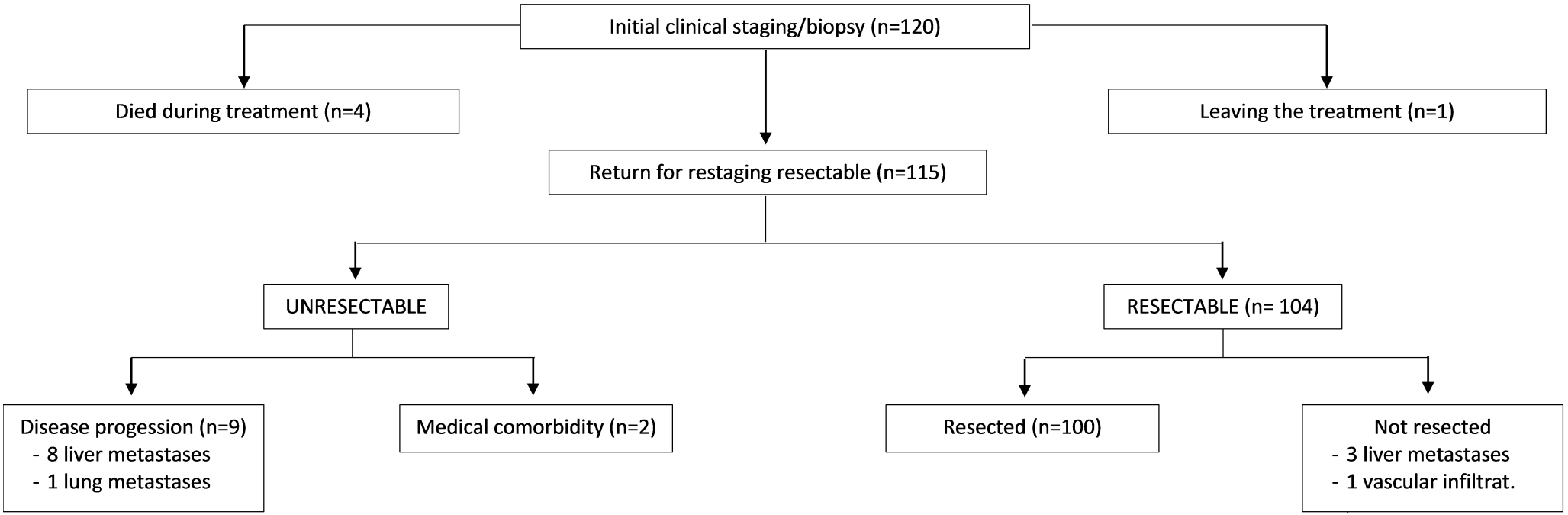
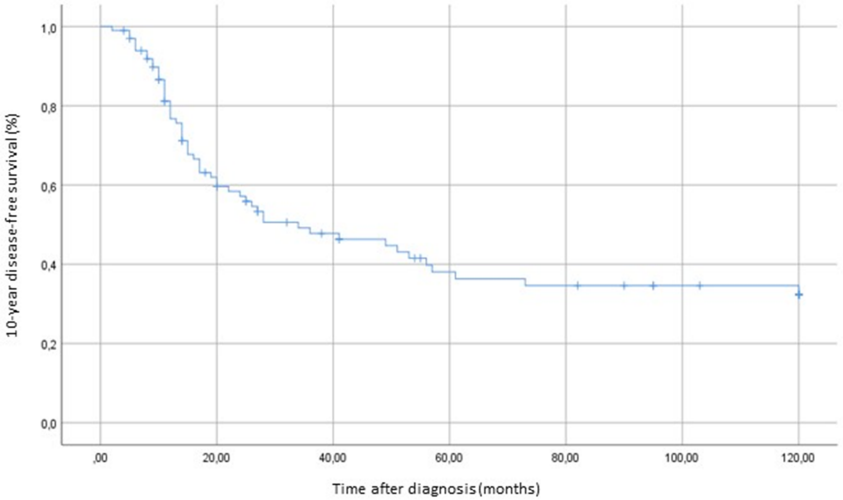


Figure legends

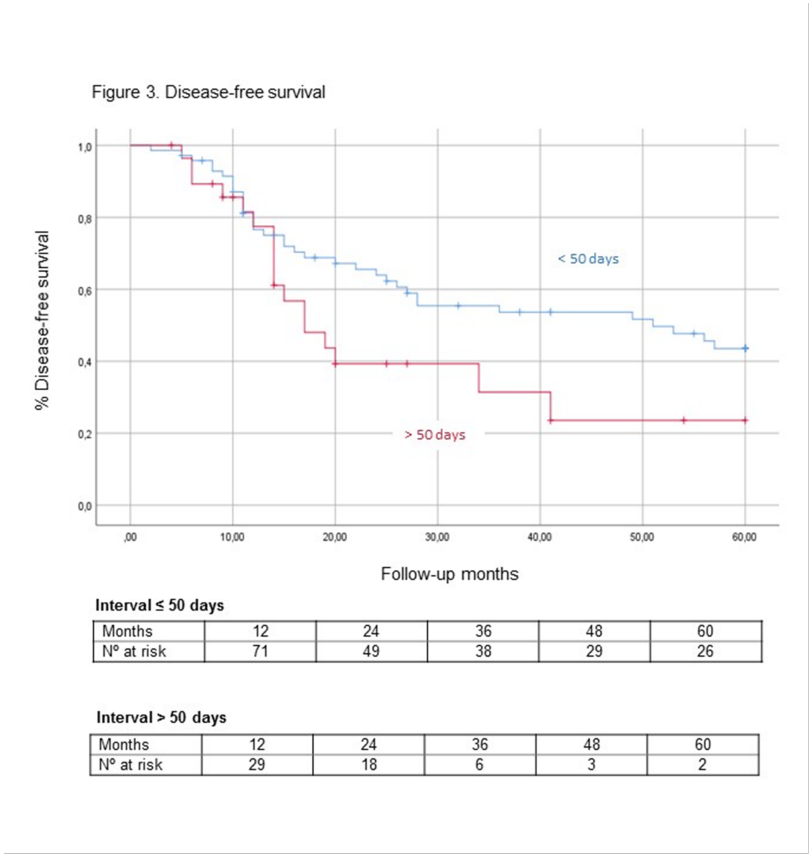
Figure 1 Flowchart showing the selection process for subjects of this study

Figure 2. Disease-free survival



Months	12	24	36	48	60	72	84	96	108	120
N° at risk	100	72	76	34	28	21	20	19	16	14

Figure 2. Kaplan-Meier estimates disease-free survival in patients who underwent NCRT and pancreatoduodenectomy



Interval ≤ 50 days

Months	12	24	36	48	60
N° at risk	71	49	38	29	26

Interval > 50 days

Months	12	24	36	48	60
N° at risk	29	18	6	3	2

Figure 3 Kaplan-Meier estimates disease- survival in patients stratified according to 50 days interval to surgery group or > 50 days interval group