JBUON 2020; 25(1): 432-447
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Establishing recurrence indicators and stratifying pancreatic ductal adenocarcinoma based on routine laboratory exams. Is it time to incorporate these parameters in daily clinical practice?

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Summary

Purpose: *Systemic inflammation plays a crucial role in carcinogenesis and progression of pancreatic cancer, due to its influence on tumor angiogenesis, invasion and metastasis. The association of CA 19-9, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can identify patients with different prognoses.*

Methods: *We reviewed 148 pancreatic cancer patients' charts diagnosed from January 2006 to December 2018 in a tertiary hospital. Cox proportional survival models were used to evaluate the impact of each factor on recurrence-free and overall survival (OS).*

Results: *When assessing risk of relapse, the presence of angiolymphatic invasion was associated with an 80% chance of recurrence in 5 years. Among other factors associated with OS, the estimated risk of death in patients with CA 19-9>300 U/mL was 2.37-fold higher compared to lower values. In addition, the risk of death was 60% and 76% higher in patients with NLR>3 and PLR>150, respectively. Patients within these 3 categories had a median OS of only 7.5 months, lower than all-comer patients with stage IV disease, with median OS estimated at 9.84 months.*

Conclusion: *The laboratory variables CA 19-9, NLR and PLR together can contribute to a better stratification of patients with pancreatic adenocarcinoma beyond conventional staging. Prospective initiatives using these factors together can demonstrate different subgroups of patients who benefit from new treatment strategies.*

Key words: *CA 19-9, neutrophil-to-lymphocyte ratio, pancreatic cancer, pancreatic neoplasms, platelets-to-lymphocyte ratio*

Introduction

Pancreatic cancer is the fourth cause of cancer death in the United States, considering men and women [1]. Approximately 430,000 deaths are estimated each year around the world [2]. The prognosis is most often reserved and the OS rate at 5 years is around 9% [1]. Surgical resection is the only potentially curative method for pancreatic cancer. However, only 20% of the patients present at diagnosis with resectable disease [3]. For patients with metastatic or unresectable pancreatic cancer, systemic chemotherapy is the main treatment [4]. Therefore, clinical staging and identification of prognostic factors are important for estimating risks and selecting appropriate treatment modalities for each case [5].

Systemic inflammation plays a crucial role in the carcinogenesis and progression of pancreatic cancer, affecting all aspects of tumor development, and as a result it may influence the response to therapies [6,7]. The molecular pathways of cancer-

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Received: 10/05/2019; Accepted: 19/06/2019

related inflammation are being unraveled, resulting in identification of new target molecules that could lead to better diagnosis and treatment [6].

Many studies have shown that high intratumoral neutrophil counts contribute to the survival of tumor cells due to the supposed suppressive effect on leukocyte activation [8] and inhibition of lymphoid cells [9]. Platelets also contribute to metastatic mechanisms by protecting circulating tumor cells from immunological mechanisms and facilitating endothelial permeability for the development of secondary lesions [10].

In concordance with this evidence, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can estimate the magnitude of systemic inflammation in cancer patients [5,11]. Despite being derived from routine and low-cost laboratory tests, such markers may play an important role in the stratification of pancreatic cancer and in the prediction of patient survival [5]. In addition to inflammatory markers, other factors have already been associated with prognosis in pancreatic cancer, the most studied being CA19-9; their levels correlate with outcomes in both metastatic and resectable disease [12-14].

Some groups developed nomograms based on clinical and anatomopathological criteria for the evaluation of prognosis in pancreatic adenocarcinoma. Although validated, there are some limitations to their broader use, since not all the information necessary for reproduction in daily clinical practice is routinely obtained [9,15-17].

The primary endpoint of this study was to determine factors associated with disease recurrence and OS, evaluating the possibility of stratifying pancreatic adenocarcinoma only with routine laboratory exams such as NLR and PLR ratios and CA 19-9 levels, providing simple and reproducible prognostic information of the disease. For this purpose, analyses of progression-free survival, as well as OS, were performed in resectable or borderline disease at diagnosis and metastatic disease.

Methods

Patients

Patients with pancreatic ductal adenocarcinoma seen at Hospital Israelita Albert Einstein, a tertiary hospital in São Paulo, Brazil, from January 2006 to December 2018 were included. Those with incomplete data for the analysis were excluded from the study. Data were collected on patient's sex and age, clinical and pathologic stage at diagnosis (8th edition of TNM staging system of pancreatic cancer by AJCC/UICC) , angiolymphatic invasion (IAL) and perineural invasion (PNI), smoking status, diabetes, Eastern Cooperative Oncology Group (ECOG) performance status, systemic treatments including perioperative and metastatic treatments, radiotherapy, surgery of the primary tumor, baseline CA 19-9, neutrophils, lymphocytes and platelets at diagnosis calculating the NLR and PLR. The cutoff points considered for analysis were NLR higher than 3 and PLR ratio higher than 150 as cutoff points associated with worse oncologic outcomes in previous studies. We also evaluated the cutoff of 5 for NLR since we didn´t have cutoff validated in this situation [18-21]. Progression-free survival (PFS) was determined as the period between the beginning of treatment to be evaluated and the date of progression. Overall survival (OS) was determined by the period between the diagnosis and the date of death or last seen.

Statistics

The quantitative variables were described by mean, standard deviation, median and interquartile range (IIQ: 1st and 3rd quartiles), in addition to extreme values. Qualitative variables were described by means of absolute and relative frequency [22]. Initially, graphs of the cumulative incidence functions and non-parametric tests of Gray [23] were made to assess the behavior of progression over time in the categories of possible risk factors (or protection). The technique chosen to measure the risk of progression for each explanatory variable, including the quantitative variables, was Fine-Gray competitive risk survival models [24]. In order to verify the proportional risk assumption of the models, Schoenfeld waste graphs were used. We considered the beginning of the study (time equal to zero) to remove the time dependence of the interpretation [24]. Factors possibly associated with time to progression were assessed using simple linear regression models.

In order to improve the analysis, the logarithm of the progression time was used as an outcome and consequently, the interpretation of the models was given from the mean ratio. The second part of the work involved the analysis of time to death from cancer. To evaluate the possible factors associated with the occurrence of this outcome, Cox simple proportional hazards models were used. The risk-proportionality assumption was tested using the Schoenfeld waste [25]. For the analyses the statistical package R [26] was used, besides the survival and cmprsk packages used for the survival analysis. The level of significance was set at 5%.

Results

The total sample comprised 148 patients with pancreatic adenocarcinoma, 83 of them belonging to the resectable/borderline group at diagnosis and 65 to the unresectable/metastatic group at diagnosis. The analysis was done for these two groups separately, and subsequently, the analysis of all patients.

Resectable and borderline resectable patients

Gray tests of cumulative incidence of progression

Appendices A, B and C present the description of the study variables for the 83 patients belonging

to the resectable/borderline group; 39 (47.0%) patients had not experienced progression throughout the study, while 44 (53%) had. The median age of the patients was 67 years, around 50% were men, 60% non-smokers and 60% reported having diabetes at the time of diagnosis. About 70% of the patients were classified as Eastern Cooperative Group (ECOG) Performance Status 1, and 48% (n=40) died of the disease.

Of the patients who were resected (98%), 36% had pT3 as pathological tumor staging and around 50% had positive lymph nodes. Most of them (70%) were classified as tumor grade 2 and 60% had angiolymphatic invasion (IAL). The mean CA 19-9 value was 78 U/mL (1.26-4962.00). About 30% had jaundice at diagnosis. Only 14 patients received neoadjuvant therapy (FOLFIRINOX in 10 patients), 65% received gemcitabine-based adjuvant therapy. In 47.6% of the patients the NLR was higher than 3 at diagnosis, and more than 5 in 28% of the patients. Of the total, 46% had PLR greater than 150.

Table 1 compares the results of the incidence curves for the variables by event of interest (disease progression). The only statistically significant difference was found for the progression incidence curves defined by angiolymphatic invasion (p=0.019). Figure 1 shows the incidence of disease progression in around 80% of patients with angiolymphatic invasion over 5 years after resection of the primary. No associations were found with risk of disease progression and NLR or PLR.

Models for competitive risk

Variables that presented association with progression were positive lymph node ratio (LNR), defined as ratio of positive lymph nodes to all lymph nodes removed (p=0.033), IAL (p= 0.001) and baseline CA 19-9 (p=0.010). According to the models, the increase in one unit of the ratio of positive lymph node numbers to total lymph nodes (LNR) multiplied the risk of progression by 5.71, while the presence of IAL multiplied the risk of progression by 47.11 and an increase of each 100 units of baseline CA 19-9 increased the risk of progression by 3%.

Unresectable and metastatic patients

Appendices D, E and F show the description of the variables for the 65 individuals belonging to the unresectable/metastatic group at diagnosis. Twelve (18.5%) of them did not experience progression during the study and 53 (81.5%) experienced progression.

The median age of the patients was 71 years, with around 60% men, 60% non-smokers and 40%

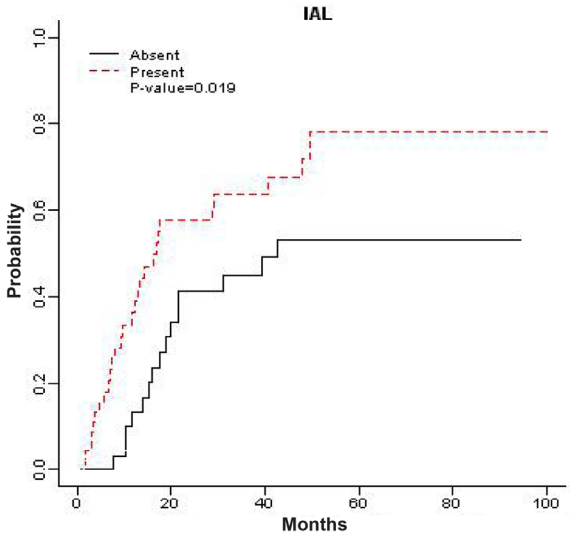

Figure 1. Accumulated incidence curves for the IAL variable only for the occurrence of progression. The p value refers to the Gray curve comparison test.

Table 1. Gray test for cumulative incidence curves of progression according to groups of respective variables for each event in the resectable/borderline group

Variables	*Event*	*Groups*	*p value*
Grade	Progression	1 x 2 x 3	0.318
Jaundice	Progression	Absent x Present	0.102
Angiolymphatic invasion (IAL)	Progression	Absent x Present	**0.019**
Perineural invasion (PNI)	Progression	Absent x Present	0.305
Neoadjuvant chemotherapy	Progression	No x Gemcitabine x FOLFIRINOX	0.697
Ratio Neutrophils/Lymphocytes	Progression	≤3 x >3	0.346
Ratio Neutrophils/Lymphocytes	Progression	≤5 x >5	0.998
Ratio Platelet/Lymphocytes	Progression	≤150 x >150	0.259
Baseline CA 19.9 (U/mL)	Progression	≤300 x >300	0.364
Stage (N)	Progression	N0 x N1 x N2	0.196
Stage (T)	Progression	T1 and T2 x T3 and T4	0.552

Bold number denotes statistical significance

reporting diabetes at the time of diagnosis. About 70% of the patients were classified as ECOG Performance Status 1, and 95% (62) died. The mean CA 19-9 was 578.80 (79.12-3034.50) and about 26% had jaundice.

Of the total, 22% received FOLFIRINOX as first-line treatment and around 60% received regimens based on gemcitabine. Only 50% of the patients in this sample received a second-line treatment and 20% received a third-line treatment. In 70% of the patients, NLR was higher than 3 at diagnosis, and higher than 5 in 17% of the patients. Of the total, 54.7% presented with PLR greater than 150.

Gray tests of cumulative incidence of progression

The only statistically significant difference was found for the progression incidence curves defined by groups below and above 5 in the NLR (p<0.001).

Models for competitive risk

Variables that showed association with progression were NLR (quantitative) (p=0.012), NLR (cutoff=5) (p=0.002), PLR (cutoff=150) (p=0.048) and baseline CA 19-9 (quantitative) (p<0.001).

According to the models, increasing one unit of the NLR increased the risk of progression by 19%, the risk of progression of patients who had NLR greater than 5 was 2.72 times the risk ratio for patients with a ratio of less than or equal to 5. The risk of progression for patients with PLR greater than 150 at diagnosis was equal to 5.33 times the risk of those with the lowest or equal to 150. The increase of each 500 units of baseline CA 19.9 was associated with an increased risk of progression by 1%.

Overall survival analysis

As expected, stages IIB, III and IV had a significant difference in relation to stage I, with p values of 0.046, less than 0.001 and less than 0.001, respectively; in relation to stage I, the risk of death from cancer was multiplied by 2.19 in patients in stage IIB, 3.85 in patients in stage III and 9.31 in patients in stage IV (Figure 2).

Evaluating the factors by log rank tests, the curves that showed a significant difference were the groups with baseline CA 19-9 above and below 300 U/mL (p<0.001), the groups with NLR above and below 3 (p=0.021), and PLR groups above and below 150 (p=0.004). According to Cox models, it was estimated that the risk of death from cancer in patients with baseline CA 19-9 above 300 U/mL was equal to 2.37 times the risk of patients below 300 U/mL. The increase of one unit in the ratio of PLR increased the risk of death by 2%. Finally, the risk of death in patients with NLR above 3 was 60% higher than the risk for those with a ratio below 3, and the risk for patients with PLR above 150 was 76% higher than the risk of those with a ratio below 150, and also an increase of 500 units in baseline CA 19-9 increased the risk of death by 1%. Table 2 presents the median OS in months of the patients according to the presence of these factors.

In order to verify the cumulative effect of the baseline variables CA 19-9, NLR and PLR on survival, they were grouped in the following categories:

A. CA 19-9 > 300 U/mL
B. NLR > 3
C. PLR > 150
D. (CA 19-9 > 300 U/mL + NLR > 3)
   or (CA 19-9 > 300U/mL + PLR > 150)
   or (PLR > 150 + NLR > 3)
E. CA 19-9 > 300 U/mL + NLR > 3 + PLR > 150

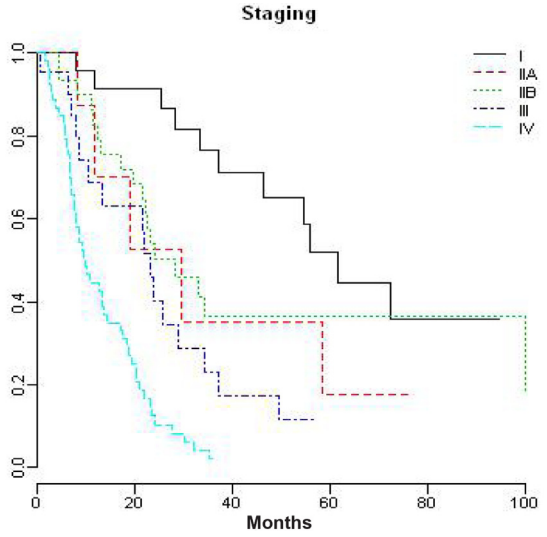

Figure 2. Kaplan-Meier curves for staging and overall survival. Stages IIB, III and IV had a significant difference in overall survival in comparison with stage I, with p values 0.046, less than 0.01 and less than 0.001, respectively.

Table 2. Median survival time and variables

Variables	*Group*	*Median survival (months)*
Baseline CA 19-9 (U/mL)	≤300	28.20
	>300	13.20
Ratio Neutrophils/Lymphocytes	≤3	28.00
	>3	17.10
Ratio Platelet/Lymphocytes	≤150	27.50
	>150	17.10
Staging	I	61.51
	IIA	29.47
	IIB	28.06
	III	23.03
	IV	9.84

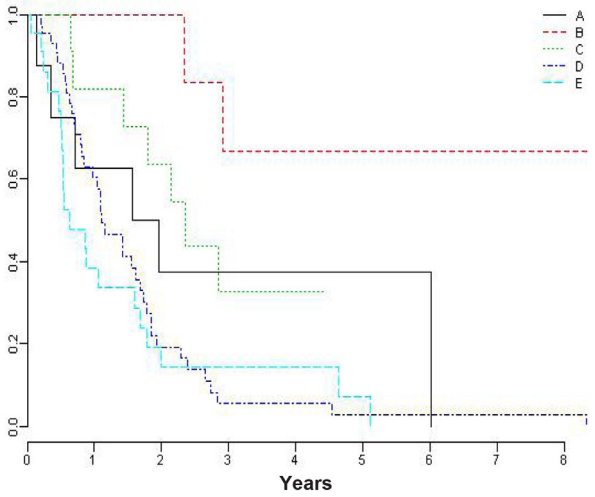

Figure 3. Kaplan-Meier curves for the groups formed from the combinations of the variables CA 19-9, NLR and PLR: **(A)** CA 19-9 > 300 U/mL, **(B)** NLR > 3, **(C)** PLR > 150, **(D)** CA 19-9 > 300 U/mL + NLR > 3 or CA 19-9 > 300 U/mL + PLR > 150 or PLR > 150 + NLR > 3, **(E)** CA 19-9 > 300 U/mL + NLR> 3 + PLR > 150. A x B x C x D x E: p=0.001; A x B: p=0.044; B x D: p<0.001; C x D: p<0.011; C x E: p=0.02.

The curve that indicated the three variables with high values (category E) showed the worst survival. Considering only one of the variables with a high value (categories A, B and C), having only baseline CA 19-9 value above 300 was found to be the worst case for survival (category A). With this stratification it was possible to notice distinct groups of patients, with median survival without any of these risk factors being 33.2 months, while it was 28.2 months for patients with just PLR > 150 and 21.1 months for patients with just CA 19-9 > 300 U/mL. For patients in the category D (two risk factors), median OS was 13.2 months, and for patients with all 3 risks factors, median OS was 7.5 months. Kaplan-Meier curves for survival in each category are shown in Figure 3.

Discussion

In this group of patients treated for pancreatic adenocarcinoma in a tertiary center, their evaluation with resectable disease showed that the presence of positive lymph nodes, a high lymph node rate, high levels of CA 19-9 at diagnosis, and presence of angiolymphatic invasion are factors related to recurrence after resection of the primary tumor in localized disease.

It is worth mentioning that the risk of relapse related to the presence of angiolymphatic invasion (IAL) was much higher than the presence of positive lymph nodes and CA 19-9 values. The association of IAL with worse outcomes was evaluated by another group in a study with a small number of patients (n=38) which showed an association mainly in patients with negative lymph nodes [27]. Other previous studies also associated IAL with worse survival [28,29].

It is interesting to note that the randomized CONKO-001 and ESPAC-4 trials (treatments evaluated: gemcitabine, gemcitabine and capecitabine respectively) did not prospectively evaluate the presence of IAL. In the PRODIGE-24 study, which demonstrated the superiority of the FOLFIRINOX regimen in the adjuvant scenario compared to gemcitabine, around 70% of the patients presented with IAL in both arms, and its presence tended to be associated with greater recurrence rate (HR 1.29; 95% CI: 0.99-1.68; p = 0.054) [30-32].

Regarding CA 19-9, the last consensus by specialists included the marker at a 500 U/mL cutoff in the borderline biological pancreatic adenocarcinoma definition [33]. In our study, each 100 U/mL increase in the marker raised the risk of recurrence by 3%. The presence of positive lymph nodes and lymph node ratio has an extensive literature demonstrating worse outcomes including recurrence-free survival and OS [13,32,34]. In our study, in the analysis of competitive models, increasing one unit in the lymph node rate increased the risk of recurrence 5 times.

In the evaluation of factors associated with progression in the first-line of systemic treatment in patients diagnosed with advanced disease (92% received first-line chemotherapy), the factors associated with progression were CA 19-9 levels, and both NLR and PLR. Notably, the analysis of factors associated with worse overall survival were the same.

The impact of cellular components and cancer has been widely studied in the last decade. Tumor-associated neutrophils (TAN) and neutrophils in the bloodstream of patients with advanced cancer are associated with poor prognosis in several tumors, including bronchoalveolar carcinoma [35], melanoma [36], renal cell carcinoma [37], and head and neck squamous cell carcinoma (HNSCC) [38]. Studies have shown that these neutrophils have an immunosuppressive effect, due to a likely inhibitory effect on leukocytes [8] and the ability to inhibit lymphoid cell activation [9]. In pancreatic adenocarcinoma, specifically high neutrophilic-infiltrates have been associated with tumor subtypes of worse prognosis [39]. Neutrophil analyses in the bloodstream, on the other hand, demonstrated antitumor and cytotoxic effects, both *in vitro* and *in vivo*, suggesting a protective effect [40-42]. Thus, the actual impact of neutrophil levels in the bloodstream in cancer patients is not yet fully elucidated [43,44].

It is also known that circulating tumor cells (CTC) activate and aggregate platelets. These recognition signals are amplified by cell surface receptors, cellular products, extracellular factors and immune cells. This platelet interaction with blood environment ends up suppressing immunological mechanisms and facilitating endothelial permeability and CTC survival for the development of secondary lesions [10,45].

The NLR and PLR relationships start from these observations and clinical evaluation. A meta-analysis with 17 cohorts defined that the PLR ratio is a potential marker in pancreatic adenocarcinoma [22], whereas NLR ratio is associated with worse survival in several tumors [46-49]. Three meta-analyses with a sample of more than 8000 patients defined that NLR is a good prognostic marker for pancreatic adenocarcinoma, but due to the heterogeneity of the studies included no adequate cutoff has yet been defined [18,21,50].

When we evaluated these factors included in the different survival categories, we observed that the risk of death of CA19-9> 300 U/mL at diagnosis was around 2.3 times higher than in those with no elevated levels. This cutoff was based on one of the largest series of resected pancreatic adenocarcinoma published [13]. The risk of death in patients with NLR above 3 was found to be 60% higher, whereas for patients with PLR above 150, the risk was 76% higher.

It was noted that with the categorization in 5 groups, we had patients in different spectra, ranging from a median survival of the group with only PLR> 150 of 28.2 months, to only 7.5 months in patients with the 3 risk factors present. This value was lower than the estimated median survival of patients with stage IV disease (9.84 months). The survival rate achieved in this study, considering different tumors stages, were comparable to contemporary data, demonstrating the applicability of the proposed categorization in patients treated with combinations of current regimens and treatment strategies [51].

There were some limitations in our study. First, our data is limited by the retrospective nature of data analysis and a relatively small sample of patients. Second, this study was conducted in a single institution. Despite these limitations, our analysis is consistent with other groups' findings that have already proposed stratification models based on laboratory exams [52-54].

In agreement with our results of the prognostic significance of these markers, more recent phase 3 studies in pancreatic adenocarcinoma increasingly consider the possibility of including inflammatory markers such as NLR to predict subgroups of patients with better prognosis [55]. This is endorsed by the COMM-PACT expert initiative, a consensus statement on baseline variables required and recommended in randomized clinical trials investigating first-line systemic therapy for advanced pancreatic cancer published in 2018, which includes NLR as a mandatory variable [56].

The laboratory variables CA 19-9, NLR and PLR together can contribute to a better stratification of patients with pancreatic adenocarcinoma beyond conventional staging. Prospective initiatives using these factors together could demonstrate different subgroups of patients who benefit from new treatment strategies.

Informed consent

The research ethics committee of the institution was consulted on the conduct of the study and approved it in accordance with existing national standards (CAAE: 81744017.6.0000.0071), due to be a retrospective study, an exemption of the consent term was requested. All datasets on which the conclusions of the report rely are available on request.

Conflict of interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
2. GLOBOCAN 2018: Estimated cancer incidence, mortality and prevalence worldwide in 2018. Available at: http://globocan.iarc.fr/. Acessed in 04/24/2019
3. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. Lancet 2004;363:1049-57.
4. Hwang I, Kang J, Ip HNN et al. Prognostic factors in patients with metastatic or recurrent pancreatic cancer treated with first-line nab-paclitaxel plus gemcitabine:

implication of inflammation-based scores. Invest New Drug 2019;37:584-90.
5. Oh D, Pyo J, Son BK. Prognostic roles of inflammatory markers in pancreatic cancer: comparison between the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio. Gastroent Res Pract 2018;2018:9745601.
6. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436-44.
7. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883-99.
8. Zhang J, Qiao X, Shi H et al. Circulating tumor-associated neutrophils (cTAN) contribute to circulating tumor cell survival by suppressing peripheral leukocyte activation. Tumor Biol 2016;37:5397-404.
9. Schmielau J, Finn OJ. Activated granulocytes and granulocyte derived hydrogen peroxide are the underlying mechanism of suppression of T-cell function in advanced cancer patients. Cancer Res 2001;61:4756-60.
10. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer 2011;11:123-34.
11. Proctor MJ, Morrison DS, Talwar D et al. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. Eur J Cancer 2011;47:2633-41.
12. Deng QL, Dong S, Wang L et al. Development and validation of a nomogram for predicting survival in patients with advanced pancreatic ductal adenocarcinoma. Sci Rep 2017;7:11524.
13. Matsumoto I, Murakami Y, Shinzeki M et al. Proposed preoperative risk factors for early recurrence in patients with resectable pancreatic ductal adenocarcinoma after surgical resection: a multi-center retrospective study. Pancreatology 2015;15:674-80.
14. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence-based appraisal. J Gastrointest Oncol 2012;3:105-19.
15. Imrie CW. Host systemic inflammatory response influences outcome in pancreatic cancer. Pancreatology 2015;15:327-30.
16. Vernerey D, Huguet F, Vienot A et al. Prognostic nomogram and score to predict overall survival in locally advanced untreated pancreatic cancer (PROLAP). Br J Cancer 2016;115:281-9.
17. Song W, Miao D, Chen L. Nomogram for predicting survival in patients with pancreatic cancer. OncoTargets Ther 2018;11:539-45.
18. Yang JJ, Hu ZG, Shi WX, Deng T, He SQ, Yuan SG. Prognostic significance of neutrophil to lymphocyte ratio in pancreatic cancer: a meta-analysis. World J Gastroenterol 2015;21:2807-15.
19. Asaoka T, Miyamoto A, Maeda S et al. Prognostic impact of preoperative NLR and CA19-9 in pancreatic cancer. Pancreatology 2016;16:434-40.
20. Zhou Y, Wei Q, Fan J, Cheng S, Ding W, Hua Z. Prognostic role of the neutrophil-to-lymphocyte ratio in pancreatic cancer: A meta-analysis containing 8252 patients. Clin Chim Acta 2018;479:181-9.
21. Zhou Y, Cheng S, Fathy AH, Qian H, Zhao Y. Prognostic value of platelet-to-lymphocyte ratio in pancreatic cancer: a comprehensive meta-analysis of 17 cohort studies. OncoTargets Ther 2018;11:1899-1908.
22. Morettin PA, Hazzan S, Bussab WO. Calculation: function of one and several variables. Publisher Saraiva 2010.
23. Scrucca L, Santucci A, Aversa F. Regression modeling of competing risk using R: an in depth guide for clinicians. Macmillan Publishers Limited 2010.
24. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Ass 1999;94:496-509.
25. Colosimo EA, Giolo SR. Applied survival analysis. São Paulo:Blucher 2006.
26. R Core Team. R: A Language and Environment for Statistical Computing. (R Foundation for Statistical Computing) Assessed on 2018, https://www.R-project.org/
27. Almeida RVS, Pacheco-Jr AM, Silva RA, Moricz A, Campos T. Angiolymphatic invasion as a prognostic factor in resected N0 pancreatic adenocarcinoma. Arq Bras Cirur Digest 2017;30:42-6.
28. Chen JWC, Bhandari M, Astill DS et al. Predicting patient survival after pancreaticoduodenectomy for malignancy: histopathological criteria based on perineural infiltration and lymphovascular invasion. HPB 2010;12:101-8.
29. Hong SM, Goggins M, Wolfgang CL et al. Vascular invasion in infiltrating ductal adenocarcinoma of the pancreas can mimic pancreatic intraepithelial neoplasia: a histopathologic study of 209 cases. Am J Surg Pathol 2012;36:235-41.
30. Oettle H, Neuhaus P, Hochhaus A et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA 2013;310:1473-81.
31. Neoptolemos JP, Palmer DH, Ghaneh P et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet 2017;389:1011-24.
32. Conroy T, Hammel P, Hebbar M et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med 2018;379:2395-2406.
33. Isaji S, Mizuno S, Windsor JA et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology 2018;18:2-11.
34. Ferrone CR, Kattan MW, Tomlinson JS, Thayer SP, Brennan MF, Warshaw AL. Validation of a postresection pancreatic adenocarcinoma nomogram for disease-specific survival. J Clin Oncol 2005;23:7529-35.
35. Wislez M, Rabbe N, Marchal J et al. Hepatocyte growth factor production by neutrophils infiltrating bronchioloalveolar subtype pulmonary adenocarcinoma: role in tumor progression and death. Cancer Res 2003;63:1405-12.
36. Schmidt H, Bastholt L, Geertsen P et al. Elevated neutrophil and monocyte counts in peripheral blood are associated with poor survival in patients with metastatic melanoma: a prognostic mode. Br J Cancer 2005;93:273-8.
37. Jensen HK, Donskov F, Marcussen N, Nordsmark M,

Lundbeck F, von der Maase H. Presence of intratumoral neutrophils is an independent prognostic factor in localized renal cell carcinoma. J Clin Oncol 2009;27:4709-17.

38. Trellakis S, Bruderek K, Dumitru CA et al. Polymorphonuclear granulocytes in human head and neck cancer: enhanced inflammatory activity, modulation by cancer cells and expansion in advanced disease. Int J Cancer 2001;129:2183-93.
39. Reid MD, Basturk O, Thirabanjasak D et al. Tumor-infiltrating neutrophils in pancreatic neoplasia. Mod Pathol 2001;24;1612-9.
40. Gerrard TL, Cohen DJ, Kaplan AM. Human neutrophil-mediated cytotoxicity to tumor cells. J Natl Cancer Inst 1981;66:483-8.
41. Pickaver AH, Ratcliffe NA, Williams AE, Smith H. Cytotoxic effects of peritoneal neutrophils on a syngeneic rat tumour. Nature 1972;235:186-7.
42. Katano M, Torisu M. Neutrophil-mediated tumor cell destruction in cancer ascites. Cancer 1982;50:62-8.
43. Fridlender ZG, Albelda SM. Tumor-associated neutrophils: friend or foe? Carcinogenesis 2012;33:949-55.
44. Uribe-Querol E, Rosales C. Neutrophils in cancer: two sides of the same coin. J Immunol Res 2015;2015:983698.
45. Menter DG, Tucker SC, Kopetz S, Sood AK, Crissman JD, Honn KV. Platelets and cancer: a casual or causal relationship: revisited. Cancer Metastasis 2014;33:231- 69.
46. Peng B, Wang YH, Liu YM, Ma LX. Prognostic significance of the neutrophil to lymphocyte ratio in patients with non-small cell lung cancer: a systemic review and meta-analysis. Int J Clin Exp Med 2015;8:3098-3106.
47. He JR, Shen GP, Ren ZF et al. Pretreatment levels of peripheral neutrophils and lymphocytes as independent prognostic factors in patients with nasopharyngeal carcinoma. Head Neck 2012;34:1769-76.
48. Malietzis G, Giacometti M, Kennedy RH, Athanasiou T, Aziz O, Jenkins JT. The emerging role of neutrophil to lymphocyte ratio in determining colorectal cancer treatment outcomes: a systematic review and meta-analysis. Ann Surg Oncol 2014;21:3938-46.
49. Krenn-Pilko S, Langsenlehner U, Stojakovic T et al. The elevated preoperative derived neutrophil-to-lymphocyte ratio predicts poor clinical outcome in breast cancer patients. Br J Cancer 2014;110:2524-30.
50. Cheng H, Long F, Jaiswar M, Yang L, Wang C, Zhou Z. Prognostic role of the neutrophil-to-lymphocyte ratio in pancreatic cancer: a meta-analysis. Sci Rep 2015;5:11026.
51. Kamarajah SK, Burns WR, Frankel TL, Cho CS, Nathan H. Validation of the American Joint Commission on Cancer (AJCC) staging system for patients with pancreatic adenocarcinoma: a Surveillance, Epidemiology and End Results (SEER) analysis. Ann Surg Oncol 2017;24:2023-30.
52. Eyff TF, Bosi HR, Toni MS et al. The role of immunoinflammatory markers in the prognosis and resectability of pancreatic adenocarcinoma. Arq Bras Cir Dig 2018;31:e1366.
53. Song JY, Chen MQ, Guo JH, Lian SF, Xu BH. Combined pretreatment serum CA19-9 and neutrophil-to-lymphocyte ratio as a potential prognostic factor in metastatic pancreatic cancer patients. Medicine 2018;97:e9707.
54. Ye S, Bai L. Comparison and validation of the value of preoperative inflammation marker-based prognostic scores in resectable pancreatic ductal adenocarcinoma. Cancer Manage Res 2018;10:3405-17.
55. Chiorean EG, Von Hoff DD, Tabernero J et al. Second-line therapy after nab-paclitaxel plus gemcitabine or after gemcitabine for patients with metastatic pancreatic cancer. Br J Cancer 2016;115:188-94.
56. Ter Veer E, van Rijssen LB, Besselink MG et al. Consensus statement on mandatory measurements in pancreatic cancer trials (COMM-PACT) for systemic treatment of unresectable disease. Lancet Oncol 2018;19:e151-60.

Appendix A. Description of the demographic variables for the resectable / borderline group separated by progression.

Variables	*Total*	*No progression*	*Progression*
Age, years			
Mean (SD)	67.31 (11.55)	66.85 (11.95)	67.72 (11.31)
Median [IQR]	67.22 [59.97, 74.72]	66.83 [56.87, 72.99]	67.36 [60.38, 75.05]
Sex (N=83), n (%)			
Female	43 (51.8)	19 (48.7)	24 (54.5)
Male	40 (48.2)	20 (51.3)	20 (45.5)
Smoking (N=82), n (%)			
Nonsmoker	51 (62.2)	23 (59.0)	28 (65.1)
Exsmoker	3 (3.7)	3 (7.7)	0 (0.0)
Smoker	28 (34.1)	13 (33.3)	15 (34.9)
No data	1	0	1

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Variables	*Total*	*No progression*	*Progression*
Diabetes (N=82), n (%)			
No	54 (65.9)	27 (69.2)	27 (62.8)
Yes	28 (34.1)	12 (30.8)	16 (37.2)
No data	1	0	1
ECOG at diagnosis (N=83), n (%)			
0	24 (28.9)	14 (35.9)	10 (22.7)
1	58 (69.9)	24 (61.5)	34 (77.3)
2	1 (1.2)	1 (2.6)	0 (0.0)
Current status (N=83), n (%)			
Alive	37 (44.6)	30 (76.9)	7 (15.9)
Deceased	46 (55.4)	9 (23.1)	37 (84.1)
If deceased, death by cancer? (N=83), n (%)			
Alive patient	37 (44.6)	30 (76.9)	7 (15.9)
Yes	40 (48.2)	5 (12.8)	35 (79.5)
No	6 (7.2)	4 (10.3)	2 (4.5)

Appendix B. Description of the tumor variables for the resectable / borderline group separated by progression.

Variables	*Total*	*No progression*	*Progression*
Stage (T) (N=83), n (%)			
cT2	1 (1.2)	1 (2.6)	0 (0.0)
cT4	1 (1.2)	1 (2.6)	0 (0.0)
pT1	11 (13.3)	4 (10.3)	7 (15.9)
pT2	27 (32.5)	12 (30.8)	15 (34.1)
pT3	30 (36.1)	17 (43.6)	13 (29.5)
pT4	1 (1.2)	0 (0.0)	1 (2.3)
ypT0	1 (1.2)	1 (2.6)	0 (0.0)
ypT1	1 (1.2)	0 (0.0)	1 (2.3)
ypT2	6 (7.2)	3 (7.7)	3 (6.8)
ypT3	4 (4.8)	0 (0.0)	4 (9.1)
Grade (N=79), n (%)			
1	7 (8.9)	4 (11.4)	3 (6.8)
2	60 (75.9)	24 (68.6)	36 (81.8)
3	12 (15.2)	7 (20.0)	5 (11.4)
No data	4	4	0
Stage (N) (N=83), n (%)			
cN0	2 (2.4)	2 (5.1)	0 (0.0)
pN0	28 (33.7)	15 (38.5)	13 (29.5)
pN1	31 (37.3)	15 (38.5)	16 (36.4)
pN2	10 (12.0)	3 (7.7)	7 (15.9)
ypN0	9 (10.8)	3 (7.7)	6 (13.6)
ypN1	3 (3.6)	1 (2.6)	2 (4.5)
Total L			
Mean (SD)	18.19 (12.60)	19.35 (14.35)	17.20 (11.00)
Median [IQR]	15.00 [9.00, 25.00]	15.00 [10.00, 25.00]	15.00 [9.00, 24.50]
Positive L			
Mean (SD)	1.84 (3.77)	1.30 (2.11)	2.30 (4.71)
Median [IQR]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]

Appendix C. Description of the clinical variables for the resectable / borderline group separated by progression.

Variables	*Total*	*No progression*	*Progression*
Ratio Positive L/Total L			
Mean (SD)	0.10 (0.16)	0.08 (0.14)	0.12 (0.17)
Median [IQR]	0.03 [0.00, 0.12]	0.02 [0.00, 0.09]	0.06 [0.00, 0.16]
Stage (M) (N=83), n (%)			
M0	83 (100.0)	39 (100.0)	44 (100.0)
Baseline CA 19.9 (U/mL)			
Mean (SD)	330.57 (796.98)	155.67 (206.78)	465.11 (1030.18)
Median [IQR]	78.45 [21.62, 226.70]	77.72 [13.03, 208.28]	87.20 [35.65, 315.85]
Baseline CA 19.9 (U/mL) (N=69), n (%)			
≤300	53 (76.8)	24 (80.0)	29 (74.4)
>300	16 (23.2)	6 (20.0)	10 (25.6)
No data	14	9	5
Jaundice (N=83), n (%)			
Absent	59 (71.1)	32 (82.1)	27 (61.4)
Present	24 (28.9)	7 (17.9)	17 (38.6)
ALI (N=79), n (%)			
Absent	32 (40.5)	17 (47.2)	15 (34.9)
Present	47 (59.5)	19 (52.8)	28 (65.1)
No data	4	3	1
PNI (N=79), n (%)			
Absent	7 (8.9)	4 (11.1)	3 (7.0)
Present	72 (91.1)	32 (88.9)	40 (93.0)
No data	4	3	1
Surgery (N=83), n (%)			
No	2 (2.4)	2 (5.1)	0 (0.0)
Yes	81 (97.6)	37 (94.9)	44 (100.0)
Margin (N=81), n (%)			
Negative	81 (100.0)	37 (100.0)	44 (100.0)
Previous radiotherapy (N=83), n (%)			
No	77 (92.8)	38 (97.4)	39 (88.6)
Yes	6 (7.2)	1 (2.6)	5 (11.4)
Neoadjuvant chemotherapy (N=83), n (%)			
No	69 (83.1)	33 (84.6)	36 (81.8)
Gemcitabine	4 (4.8)	1 (2.6)	3 (6.8)
FOLFIRINOX	10 (12.0)	5 (12.8)	5 (11.4)
Adjuvant chemotherapy (N=80), n (%)			
No	28 (35.0)	14 (38.9)	14 (31.8)
Gemcitabine	47 (58.8)	18 (50.0)	29 (65.9)
Gemcitabine + 5FU/ Capecitabine	2 (2.5)	2 (5.6)	0 (0.0)
FOLFIRINOX	2 (2.5)	2 (5.6)	0 (0.0)
CDDP + Gemcitabine	1 (1.2)	0 (0.0)	1 (2.3)
No data	3	3	0
Adjuvant radiotherapy (N=83), n (%)			
No	79 (95.2)	39 (100.0)	40 (90.9)
Yes	4 (4.8)	0 (0.0)	4 (9.1)
BRCA status (N=7), n (%)			
Mutant	-	-	1 (14.3)
Wild	-	-	6 (85.7)
Unknown	-	-	37

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Variables	*Total*	*No progression*	*Progression*
Chemo Metastatic 1st line (N=68), n (%)			
No	34 (50.0)	31 (93.9)	3 (8.6)
Gemcitabine	9 (13.2)	0 (0.0)	9 (25.7)
5FU/Capecitabine	2 (2.9)	0 (0.0)	2 (5.7)
FOLFOX	6 (8.8)	0 (0.0)	6 (17.1)
FOLFIRINOX	13 (19.1)	2 (6.1)	11 (31.4)
Gemcitabine + Nab-Paclitaxel	3 (4.4)	0 (0.0)	3 (8.6)
Capecitabine + oxaliplatin	1 (1.5)	0 (0.0)	1 (2.9)
Chemo Metastatic 2nd line (N=68), n (%)			
No	50 (73.5)	33 (100.0)	17 (48.6)
Gemcitabine	5 (7.4)	0 (0.0)	5 (14.3)
FOLFOX	7 (10.3)	0 (0.0)	7 (20.0)
FOLFIRINOX	1 (1.5)	0 (0.0)	1 (2.9)
CDDP + irinotecan	1 (1.5)	0 (0.0)	1 (2.9)
Gemcitabine + Nab-Paclitaxel	1 (1.5)	0 (0.0)	1 (2.9)
S1	1 (1.5)	0 (0.0)	1 (2.9)
Olaparibe	1 (1.5)	0 (0.0)	1 (2.9)
Irinotecan	1 (1.5)	0 (0.0)	1 (2.9)
Chemo Metastatic 3rd line (N=68), n (%)			
No	57 (83.8)	33 (100.0)	24 (68.6)
Gemcitabine	1 (1.5)	0 (0.0)	1 (2.9)
5FU/Capecitabine	1 (1.5)	0 (0.0)	1 (2.9)
FOLFOX	1 (1.5)	0 (0.0)	1 (2.9)
Gem + Nab-Paclitaxel	1 (1.5)	0 (0.0)	1 (2.9)
Paclitaxel	3 (4.4)	0 (0.0)	3 (8.6)
Trametinib	1 (1.5)	0 (0.0)	1 (2.9)
Docetaxel	3 (4.4)	0 (0.0)	3 (8.6)
Baseline (kg)			
Mean (SD)	72.37 (13.52)	74.60 (15.73)	70.40 (11.03)
Median [IQR]	70.00 [63.00, 80.00]	68.45 [65.00, 86.75]	72.00 [60.50, 78.00]
Baseline (cm)			
Mean (SD)	167.26 (10.19)	168.76 (10.71)	165.93 (9.64)
Median [IQR]	168.00 [159.00, 175.00]	168.00 [160.00, 176.00]	168.00 [158.00, 172.00]
Weight at progression (kg)			
Mean (SD)	-	-	64.67 (10.84)
Median [IQR]	-	-	66.00 [57.00, 72.00]
Neutrophils at diagnosis			
Mean (SD)	5147.00 (2300.63)	5363.55 (2466.43)	4959.98 (2158.40)
Median [IQR]	4574.50 [3569.75, 6341.00]	5113.50 [3562.25, 6284.00]	4258.50 [3637.25, 6382.00]
Lymphocytes at diagnosis			
Mean (SD)	1572.10 (811.24)	1582.95 (731.61)	1562.73 (882.57)
Median [IQR]	1439.50 [1107.75, 2078.00]	1435.00 [1161.75, 2053.25]	1439.50 [918.00, 2091.50]
Platelets at diagnosis			
Mean (SD)	214780.49 (65139.36)	213631.58 (65705.49)	215772.73 (65390.37)
Median [IQR]	215500.00 [166250.00, 253750.00]	213500.00 [166250.00, 251250.00]	217000.00 [166750.00, 260750.00]
Ratio Neutrophils/Lymphocytes			
Mean (SD)	4.91 (5.43)	4.69 (5.15)	5.10 (5.72)
Median [IQR]	2.92 [2.08, 5.61]	3.10 [2.10, 5.10]	2.57 [2.04, 5.97]

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Variables	*Total*	*No progression*	*Progression*
Ratio Platelet/Lymphocytes			
Mean (SD)	177.66 (119.25)	162.29 (97.13)	190.94 (135.21)
Median [IQR]	137.70 [106.52, 204.32]	132.64 [112.12, 168.71]	152.06 [106.02, 227.34]
Ratio Neutrophils/Lymphocytes (N=82), n (%)			
≤3	43 (52.4)	18 (47.4)	25 (56.8)
>3	39 (47.6)	20 (52.6)	19 (43.2)
No data	1	1	0
Ratio Neutrophils/Lymphocytes (N=82), n (%)			
≤5	59 (72.0)	28 (73.7)	31 (70.5)
>5	23 (28.0)	10 (26.3)	13 (29.5)
No data	1	1	0
Ratio Platelet/Lymphocytes - n (%) (N=82)			
≤150	44 (53.7)	22 (57.9)	22 (50.0)
>150	38 (46.3)	16 (42.1)	22 (50.0)
No data	1	1	0
Progression - competing with death (N=83), n (%)			
Alive	30 (36.1)	30 (76.9)	0 (0.0)
Progression	44 (53.0)	0 (0.0)	44 (100.0)
Death for any reason	9 (10.8)	9 (23.1)	0 (0.0)
Baseline CA 19.9 (U/mL) (N=69), n (%)			
≤50	27 (39.1)	13 (43.3)	14 (35.9)
>50	42 (60.9)	17 (56.7)	25 (64.1)
No data	14	9	5
Stage (N) (N=83), n (%)			
N0	39 (47.0)	20 (51.3)	19 (43.2)
N1	34 (41.0)	16 (41.0)	18 (40.9)
N2	10 (12.0)	3 (7.7)	7 (15.9)
Stage (T) (N=82), n (%)			
T1 and T2	46 (56.1)	20 (52.6)	26 (59.1)
T3 and T4	36 (43.9)	18 (47.4)	18 (40.9)
Time to progression (months)			
Mean (SD)	-	-	16.58 (12.45)
Median [IQR]	-	-	13.63 [7.64, 20.35]
Time to progression - competing with death (months)			
Mean (SD)	23.37 (23.63)	31.02 (30.26)	16.58 (12.45)
Median [IQR]	14.21 [6.53, 34.90]	25.39 [5.18, 51.25]	13.63 [7.64, 20.35]
Time to death or follow-up (months)			
Mean (SD)	30.66 (25.31)	31.02 (30.26)	30.35 (20.31)
Median [IQR]	25.39 [9.65, 44.23]	25.39 [5.18, 51.25]	25.43 [16.00, 37.30]
Weight in progression minus baseline weight (kg)			
Mean (SD)	-	-	-6.14 (6.72)
Median [IQR]	-	-	-4.50 [-10.75, -2.00]

Appendix D. Description of the demographic variables for the irresectable / metastatic group separated by progression.

Variables	*Total*	*No progression*	*Progression*
Age, years			
Mean (SD)	70.88 (11.57)	70.42 (16.65)	70.98 (10.30)
Median [IQR]	71.13 [65.85, 77.79]	72.21 [62.03, 80.32]	71.13 [66.30, 75.86]

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Variables	*Total*	*No progression*	*Progression*
Sex (N=65), n (%)			
Female	25 (38.5)	5 (41.7)	20 (37.7)
Male	40 (61.5)	7 (58.3)	33 (62.3)
Smoking (N=63), n (%)			
Non-smoker	38 (60.3)	9 (81.8)	29 (55.8)
Ex-smoker	1 (1.6)	0 (0.0)	1 (1.9)
Smoker	24 (38.1)	2 (18.2)	22 (42.3)
No data	2	1	1
Diabetes (N=64), n (%)			
No	38 (59.4)	7 (63.6)	31 (58.5)
Yes	26 (40.6)	4 (36.4)	22 (41.5)
No data	1	1	0
ECOG at diagnosis (N=65), n (%)			
0	8 (12.3)	3 (25.0)	5 (9.4)
1	47 (72.3)	6 (50.0)	41 (77.4)
2	10 (15.4)	3 (25.0)	7 (13.2)
Current status (N=65), n (%)			
Alive	3 (4.6)	0 (0.0)	3 (5.7)
Deceased	62 (95.4)	12 (100.0)	50 (94.3)
If deceased, death by cancer? (N=65), n (%)			
Alive patient	3 (4.6)	0 (0.0)	3 (5.7)
Yes	61 (93.8)	11 (91.7)	50 (94.3)
No	1 (1.5)	1 (8.3)	0 (0.0)

Appendix E. Description of the tumor variables for the irresectable / metastatic group separated by progression.

Variables	*Total*	*No progression*	*Progression*
Stage (T) (N=65), n (%)			
cT2	2 (3.1)	1 (8.3)	1 (1.9)
cT3	1 (1.5)	0 (0.0)	1 (1.9)
cT4	23 (35.4)	7 (58.3)	16 (30.2)
pT1	1 (1.5)	1 (8.3)	0 (0.0)
pT2	2 (3.1)	0 (0.0)	2 (3.8)
Tx	36 (55.4)	3 (25.0)	33 (62.3)
Grade (N=6), n (%)			
1	1 (16.7)	0 (0.0)	1 (25.0)
2	3 (50.0)	2 (100.0)	1 (25.0)
3	2 (33.3)	0 (0.0)	2 (50.0)
No data	59	10	49
Stage (N) - n (%) (N=65)			
cN0	3 (4.6)	2 (16.7)	1 (1.9)
cN1	5 (7.7)	1 (8.3)	4 (7.5)
cN2	6 (9.2)	2 (16.7)	4 (7.5)
pN0	2 (3.1)	1 (8.3)	1 (1.9)
pN2	1 (1.5)	0 (0.0)	1 (1.9)
Nx	48 (73.8)	6 (50.0)	42 (79.2)
Total L			
Mean (SD)	-	-	11.00 (9.90)
Median [IQR]	-	-	11.00 [7.50, 14.50]
Positive L			
Mean (SD)	-	-	6.50 (9.19)
Median [IQR]	-	-	6.50 [3.25, 9.75]

Appendix F. Description of the clinical variables for the irresectable / metastatic group separated by progression.

Variables	*Total*	*No progression*	*Progression*
Positive L/Total L Ratio			
Mean (SD)	-	-	0.36 (0.51)
Median [IQR]	-	-	0.36 [0.18, 0.54]
Stage (M) (N=65), n (%)			
M0	12 (18.5)	4 (33.3)	8 (15.1)
M1	53 (81.5)	8 (66.7)	45 (84.9)
Baseline CA 19.9 (U/mL)			
Mean (SD)	4350.32 (13464.73)	2300.30 (3412.77)	4737.12 (14600.95)
Median [IQR]	578.80 [79.12, 3034.50]	393.30 [64.78, 2948.25]	641.00 [105.00, 2986.00]
Baseline CA 19.9 (U/mL) (N=63), n (%)			
≤300	26 (41.3)	5 (50.0)	21 (39.6)
>300	37 (58.7)	5 (50.0)	32 (60.4)
No data	2	2	0
Jaundice (N=65), n (%)			
Absent	48 (73.8)	10 (83.3)	38 (71.7)
Present	17 (26.2)	2 (16.7)	15 (28.3)
IAL (N=2), n (%)			
Present	2 (100.0)	0 (0.0)	2 (100.0)
No data	63	12	51
IPN (N=2), n (%)			
Present	2 (100.0)	0 (0.0)	2 (100.0)
No data	63	12	51
Surgery (N=65), n (%)			
No	61 (93.8)	12 (100.0)	49 (92.5)
Yes	4 (6.2)	0 (0.0)	4 (7.5)
Margin (N=4), n (%)			
Negative	4 (100.0)	0 (NaN)	4 (100.0)
Previous radiotherapy (N=65), n (%)			
No	60 (92.3)	12 (100.0)	48 (90.6)
Yes	5 (7.7)	0 (0.0)	5 (9.4)
Neoadjuvant chemotherapy (N=65), n (%)			
No	60 (92.3)	11 (91.7)	49 (92.5)
Gemcitabine	3 (4.6)	1 (8.3)	2 (3.8)
5FU or Capecitabine	1 (1.5)	0 (0.0)	1 (1.9)
FOLFIRINOX	1 (1.5)	0 (0.0)	1 (1.9)
Adjuvant chemotherapy (N=65), n (%)			
No	64 (98.5)	12 (100.0)	52 (98.1)
Gemcitabine	1 (1.5)	0 (0.0)	1 (1.9)
Adjuvant RDT (N=65), n (%)			
No	63 (96.9)	11 (91.7)	52 (98.1)
Yes	2 (3.1)	1 (8.3)	1 (1.9)
BRCA status (N=4), n (%)			
Mutant	1 (25.0)	0 (0.0)	1 (25.0)
Wild	3 (75.0)	0 (0.0)	3 (75.0)
Unknown	61	12	49
Chemo Metastatic first line (N=62), n (%)			
No	5 (8.1)	4 (40.0)	1 (1.9)
Gemcitabine	34 (54.8)	3 (30.0)	31 (59.6)
5FU/Cap	2 (3.2)	1 (10.0)	1 (1.9)
FOLFIRI	1 (1.6)	0 (0.0)	1 (1.9)
FOLFIRINOX	14 (22.6)	2 (20.0)	12 (23.1)

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Variables	*Total*	*No progression*	*Progression*
Chemo Metastatic 1st line (N=62), n (%)			
Gem + CDDP	1 (1.6)	0 (0.0)	1 (1.9)
Gem + Nab-Paclitaxel	2 (3.2)	0 (0.0)	2 (3.8)
Docetaxel + Capecitabine	1 (1.6)	0 (0.0)	1 (1.9)
Gem + Erlotinib	1 (1.6)	0 (0.0)	1 (1.9)
Capecitabine + Erlotinib	1 (1.6)	0 (0.0)	1 (1.9)
Chemo Metastatic 2nd line (N=61), n (%)			
No	31 (50.8)	9 (100.0)	22 (42.3)
Gemcitabine	4 (6.6)	0 (0.0)	4 (7.7)
5FU/Cap	5 (8.2)	0 (0.0)	5 (9.6)
FOLFOX	12 (19.7)	0 (0.0)	12 (23.1)
FOLFIRI	1 (1.6)	0 (0.0)	1 (1.9)
FOLFIRINOX	3 (4.9)	0 (0.0)	3 (5.8)
Gem + Nab-Paclitaxel	2 (3.3)	0 (0.0)	2 (3.8)
S1	1 (1.6)	0 (0.0)	1 (1.9)
Cap + oxaliplatin	1 (1.6)	0 (0.0)	1 (1.9)
Cap + Gemcitabine	1 (1.6)	0 (0.0)	1 (1.9)
Chemo Metastatic 3rd line (N=61), n (%)			
No	49 (80.3)	9 (100.0)	40 (76.9)
Gemcitabine	1 (1.6)	0 (0.0)	1 (1.9)
5FU/Cap	3 (4.9)	0 (0.0)	3 (5.8)
CDDP + irinotecan	1 (1.6)	0 (0.0)	1 (1.9)
Gem + Nab-Paclitaxel	1 (1.6)	0 (0.0)	1 (1.9)
Paclitaxel	4 (6.6)	0 (0.0)	4 (7.7)
DCF	1 (1.6)	0 (0.0)	1 (1.9)
Docetaxel	1 (1.6)	0 (0.0)	1 (1.9)
Baseline (kg)			
Mean (SD)	72.96 (11.72)	65.31 (14.27)	74.55 (10.60)
Median [IQR]	71.50 [65.80, 79.25]	64.00 [55.50, 70.50]	73.00 [67.00, 81.00]
Baseline (cm)			
Mean (SD)	169.02 (9.31)	164.70 (9.29)	169.83 (9.17)
Median [IQR]	170.00 [163.50, 176.00]	167.50 [157.75, 170.00]	170.00 [165.00, 176.00]
Weight at progression (kg)			
Mean (SD)	-	-	69.17 (12.18)
Median [IQR]	-	-	68.00 [60.75, 77.25]
Neutrophils at diagnosis			
Mean (SD)	5299.77 (1886.82)	3924.17 (1420.83)	5617.21 (1847.79)
Median [IQR]	4787.00 [4114.75, 6344.50]	3746.50 [3051.50, 4349.25]	5228.00 [4358.00, 6452.50]
Lymphocytes at diagnosis			
Mean (SD)	1497.34 (577.48)	1482.33 (770.87)	1500.81 (532.65)
Median [IQR]	1388.50 [1013.75, 1857.50]	1223.00 [903.00, 2365.75]	1394.00 [1083.75, 1838.25]
Platelets at diagnosis			
Mean (SD)	233123.08 (90903.37)	188833.33 (61104.73)	243150.94 (93943.39)
Median [IQR]	209000.00 [173000.00, 287000.00]	180500.00 [169250.00, 220000.00]	224000.00 [184000.00, 296000.00]
Ratio Neutrophils/Lymphocytes			
Mean (SD)	3.94 (1.88)	3.13 (1.18)	4.13 (1.96)
Median [IQR]	3.47 [2.82, 4.32]	3.25 [2.42, 4.17]	3.55 [2.85, 4.53]
Ratio Platelets/Lymphocytes			
Mean (SD)	172.07 (77.32)	167.89 (105.22)	173.04 (70.65)
Median [IQR]	158.93 [109.63, 209.54]	140.94 [73.07, 262.60]	158.93 [116.73, 203.25]

Continued on the next page

Variables	*Total*	*No progression*	*Progression*
Ratio Neutrophils/Lymphocytes (N=64), n (%)			
≤3	19 (29.7)	4 (33.3)	15 (28.8)
>3	45 (70.3)	8 (66.7)	37 (71.2)
No data	1	0	1
Ratio Neutrophils/Lymphocytes (N=64), n (%)			
≤5	53 (82.8)	12 (100.0)	41 (78.8)
>5	11 (17.2)	0 (0.0)	11 (21.2)
No data	1	0	1
Ratio Platelets/Lymphocytes (N=64), n (%)			
≤150	29 (45.3)	6 (50.0)	23 (44.2)
>150	35 (54.7)	6 (50.0)	29 (55.8)
No data	1	0	1
Progression - competing with death (N=65), n (%)			
Progression	53 (81.5)	0 (0.0)	53 (100.0)
Death for any reason	12 (18.5)	12 (100.0)	0 (0.0)
Baseline CA 19.9 (U/mL) (N=63), n (%)			
≤50	12 (19.0)	2 (20.0)	10 (18.9)
>50	51 (81.0)	8 (80.0)	43 (81.1)
No data	2	2	0
Stage (N) (N=17), n (%)			
N0	5 (29.4)	3 (50.0)	2 (18.2)
N1	5 (29.4)	1 (16.7)	4 (36.4)
N2	7 (41.2)	2 (33.3)	5 (45.5)
Stage (T) (N=29), n (%)			
T1 and T2	5 (17.2)	2 (22.2)	3 (15.0)
T3 and T4	24 (82.8)	7 (77.8)	17 (85.0)
Time progression (months)			
Mean (SD)	-	-	7.81 (6.21)
Median [IQR]	-	-	6.22 [3.62, 9.84]
Time to progression - competing with death (months)			
Mean (SD)	7.95 (6.18)	8.58 (6.29)	7.81 (6.21)
Median [IQR]	6.41 [3.12, 10.26]	8.47 [2.62, 12.86]	6.22 [3.62, 9.84]
Time to death or follow-up (months)			
Mean (SD)	13.60 (10.28)	8.58 (6.29)	14.74 (10.70)
Median [IQR]	9.84 [6.48, 20.20]	8.47 [2.62, 12.86]	10.33 [6.61, 20.76]
Weight in progression minus baseline weight (kg)			
Mean (SD)	-	-	-5.64 (6.24)
Median [IQR]	-	-	-5.00 [-9.25, -1.75]