Prognostic Factors in Resected Pancreatic Ductal Adenocarcinoma: Is Neutrophil-Lymphocyte Ratio a Useful Marker?

Ignacio Merlo1 · Victoria Ardiles2 · Rodrigo Sanchez-ClarkÁ1 · Eugenia Fratantoni1 · Eduardo de SantibÁınes2 · Juan Pekolj2 · Oscar Mazza1 · Martín de SantibÁınes2

Accepted: 24 May 2022 / Published online: 2 June 2022
© The Author(s), under exclusive license to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract

Background The aim of this study is to analyze the role of neutrophil–lymphocyte ratio (NLR) and its variation pre- and postoperatively (delta NLR) in the overall survival after pancreatectomy for pancreatic ductal adenocarcinoma (PDAC) at a single center and to identify factors associated with overall survival.

Methods A retrospective study of consecutive patients undergoing pancreatectomy due to PDAC or undifferentiated carcinoma from January 2010 to January 2020 was performed. Association between the evaluated factors and overall survival was analyzed using a log-rank test and Cox proportional hazard regression model.

Results Overall, 242 patients underwent pancreatectomy for PDAC or undifferentiated carcinoma. OS was 22.8 months (95% confidence interval (CI): 19.5–29), and survival rates at 1, 3, and 5 years were 72%, 32.5%, and 20.8%, respectively. NLR and delta NLR were not significantly associated with survival (hazard ratio (HR) = 1.14, 95%CI: 0.77–1.68, \( p = 0.5 \)). Lymph node ratio was significantly associated (HR = 1.66, 95%CI: 1.21–2.26, \( p = 0.001 \)) in the bivariate analysis. In multivariable analysis, the only factors that were significantly associated with survival were perineural invasion (HR = 1.94, 95%CI: 1.21–3.14, \( p = 0.006 \)), surgical margin (HR = 1.83, 95%CI: 1.10–3.02, \( p = 0.019 \)), tumor size (HR = 1.01, 95%CI: 1.003–1.027, \( p = 0.16 \)), postoperative CA 19–9 level (HR = 1.001, \( p < 0.001 \)), and completion of adjuvant treatment (HR = 0.53, 95%CI: 0.35–0.8, \( p = 0.002 \)).

Conclusion Neutrophil–lymphocyte ratio and delta NLR were not associated with the overall survival in this cohort. Risk factors such as perineural invasion, surgical margins, CA19-9 level, and tumor size showed worse survival in this study, whereas completing adjuvant treatment was a protective factor.

Keywords Neutrophil-to-lymphocyte ratio · Survival analysis · Pancreatic cancer · Perineural invasion

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease with 458,918 new cases diagnosed each year worldwide [1]. It is the fourth leading cause of cancer-related death in the USA, and it is predicted to become the second leading cause by 2030 [2]. In addition, it is expected to be the second cause of death related to cancer in the next decade in western countries, due to improvements in other tumor treatments that have increased their overall survival at a faster rate than pancreatic cancer treatment. Moreover, the aging of the general population, who are more susceptible to cancer than young people, also contributes to the prediction of a rise in pancreas cancer mortality in the future. Surgery is involved in the only chance of cure of pancreatic cancer, but 5-year survival rates after surgical resection alone are low, approximately 10% according to different series [3, 4]. Nevertheless, the development of adjuvant treatments with chemotherapy has increased survival in patients who underwent surgery [5, 6]. In Latin America, there is a lack of information about long-term results after surgical treatment of pancreatic cancer. Therefore, reporting oncological outcomes after multidisciplinary treatment and identifying factors associated with overall survival are important steps towards understanding this aggressive disease.
Currently, several studies have identified different prognostic oncological factors such as surgical margins, serum carbohydrate antigen 19–9 (CA 19–9) level, vascular resection, and pathological characteristics such as perineural or perivascular invasion [7]. Firstly, perineural invasion (PNI) is defined as the presence of cancer cells along nerves and/or within the epineural, perineural, and endoneural spaces of the neuronal sheath. Despite the fact that it has been described in several solid tumors, PNI has its highest prevalence in pancreatic ductal adenocarcinoma with a range varying between 70 and 98% [8]. Moreover, PNI is detected in nearly three quarters of the early stages of PDAC and in microscopic PDAC, suggesting that it could represent an early event in cancer progression [9, 10]. The role of PNI in cancer research has been traditionally underestimated since it was considered as a non-active process, with less relevance compared with hematogenous and lymphatic spread. But new evidence shows neural regulation in cancer and cancer cell-induced axonogenesis [11].

Interestingly, changes in the systemic inflammatory response to tumor cell manifestation of systemic inflammation can be measured by blood-based parameters. In particular, the neutrophil–lymphocyte ratio (NLR) has been assumed to be an easily available and trustable marker to predict patients’ survival in different types of patients with primary operable cancer, such as colorectal, gastroesophageal, renal, hepatocarcinoma, and lung cancer [12]. In PDAC, controversial data exist regarding NLR [13, 14]. Therefore, it would be interesting to find a predictor that reflects that taking into account changes in inflammatory parameters before and after surgical treatment. Delta NLR or the difference between postoperative and preoperative values can be expressed as an increasing or decreasing trend. This parameter has been proven useful in other tumor types; consequently, we included this variable with special interest in our study.

Another element that has been described as a prognostic factor in previous studies is lymph node ratio (LNR), expressed as the rate of positive lymph nodes over total lymph nodes harvested. However, the prognostic power of N-status, number of examined LNs, number of positive lymph nodes, and LNR differed substantially across studies [15, 16].

The identification of prognostic factors might enable a better risk stratification for adjuvant treatment modalities after surgery, evolving into a more personalized treatment. Results regarding overall survival and disease-free survival of our cohort were reported previously in another language [17]. Furthermore, in this study, we aim to analyze the role of neutrophil–lymphocyte ratio and variation of neutrophil–lymphocyte ratio in overall survival after pancreatectomy for pancreatic ductal adenocarcinoma in a cohort from a single, academic, high-volume pancreatic center.

Methods

Population

A retrospective analysis was performed of a cohort with all the patients who received pancreatectomy due to PDAC or undifferentiated carcinoma from January 2010 to January 2020 in a single center. Patients were eligible to be included in the study if they were 18 years of age or older, had undergone a pancreatic resection surgery, and the pathology report informed pancreatic adenocarcinoma or undifferentiated carcinoma. Overall survival (OS) was measured from surgery day to death, and disease-free survival (DFS) was measured from surgery day to recurrence detected by imaging testing and/or increase of tumoral marker according to findings in electronic records of medical history. In cases where data could not be found on medical records, national registries or relatives were reached to obtain missing information. This study was performed according to national and international regulations. The Institutional Ethics Committee for Investigative Protocols approved the study protocol (No. 2836).

Baseline characteristics collected were age, gender, pancreatic surgery extent, venous resection involvement, preoperative and postoperative CA 19–9 levels, preoperative and postoperative lymphocytes and neutrophils count, anatomic pathological diagnosis, tumor differentiation, maximum diameter of the tumor, surgical margins, lymph nodes harvested, lymph nodes compromised by tumoral cells, presence of perineural invasion, presence of perivascular infiltration, staging according 8th edition of TNM staging system, and completion of adjuvant or neoadjuvant treatment [18]. Regarding surgical margins, R0 resection was defined as the absence of any cancer cells within 1 mm of any cut surface of the resected specimen. An R1 resection was defined as at least 1 cancer cell within 1 mm of any surface of the removed specimen. NLR was calculated by dividing the absolute neutrophils count by the absolute lymphocytes count. Preoperative NLR was measured in the routine preoperative work up, within 1 month before surgery. Postoperative NLR was measured 1 month after surgery, taking into account that no acute infection or complications that could have raised neutrophil count were present. Delta NLR was calculated by subtracting NLR postoperative value to preoperative NLR, and two groups were defined according to increasing (>0) or decreasing (<0) trend. Likewise, lymph node ratio was also dichotomized in groups with LNR >0.1 and <0.1 as it was considered to be the optimal cut-off point in previous reports [19]. Postoperative morbidity was classified according to the International Study Group of Pancreatic Surgery (ISGPS) definition and the Clavien–Dindo classification [20, 21].
Statistical Analysis

Continuous variables were reported as median and range or mean and standard deviation when appropriate. Categorical variables were presented as number of frequency and percentages. Survival probability was estimated according to the Kaplan–Meier method, whereas the log-rank test was used for comparison of survival in different groups. Statistical significance was set at 0.05. Associations between studied factors and overall survival were assessed. Bivariate and multivariable survival analysis were performed using the Cox proportional hazards model, with results presented as hazard ratio (HR) with a 95% confidence interval (CI). Variables that were significant in bivariate analysis were included in the final multivariable analysis. Patients with missing data were excluded from the analysis. Statistical analysis was performed in R version 3.6.3 (R Core Team 2020, Vienna, Austria).

Results

Overall, 748 patients underwent consecutive pancreatectomy from January 2010 to January 2020. PDAC diagnosis was found in 230, and undifferentiated carcinoma was found in 12 pathology reports during the study interval counting a total of 242 pancreatic cancer subjects. Patient demographic and tumor characteristics are described in Table 1. As shown in a previous publication of our group, this cohort had a median disease-free survival (DFS) was calculated over a 156-patient dataset. Delta NLR (Fig. 1) was not significantly associated with overall survival in the bivariate analysis (HR = 1.1, 95%CI: 0.6–2.01, p = 0.74). Perineural invasion was significantly associated with worse survival in bivariate analysis (HR = 1.53, 95%CI: 1.063–2.219, p = 0.02) (Fig. 2). Other variables that were identified as risk factors in bivariate analysis were surgical resection (total pancreatectoduodenectomy HR = 2.2, 95%CI: 1.45–3.37, p < 0.001), vascular resection (HR = 1.92, 95%CI: 1.27–2.9, p = 0.002), postoperative CA 19–9 level (HR = 1.0001, 95%CI:1–1.001, p < 0.001), tumor size (HR = 1.01, 95%CI: 1.002–1.019, p = 0.02), positive lymph nodes (HR = 1.09, 95%CI: 1.032–1.15, p = 0.002), surgical margins (HR = 1.63, 95%CI: 1.186–2.248, p = 0.003), and TNM stage III (HR = 2.31, 95%CI: 1.14–4.69, p = 0.02). Finally, having completed adjuvant treatment with chemotherapy was a protective factor since it was associated with better survival (HR = 0.43, 95%CI: 0.30–0.62, p < 0.001). It is worth noting that the adjuvant treatment variable had missing values of 26%.

Multivariable Analysis

In the multivariable analysis including the variables which resulted statistically significant in bivariate analysis, the risk factors that remained significantly associated with worse overall survival were the presence of perineural invasion (HR = 1.94, 95%CI: 1.21–3.14, p = 0.006), surgical margin (HR = 1.83, 95%CI: 1.10–3.02, p = 0.019), tumor size (HR = 1.01, 95%CI: 1.003–1.027, p = 0.16), and postoperative CA 19–9 level (HR = 1.001, 95%IC: 1.0003–1.0009, p < 0.001). On the other hand, the protective factor of completion of adjuvant treatment (HR = 0.53, 95%CI: 0.35–0.8, p = 0.002) remained significant. The final model with 110 subjects (132 observations deleted due to missingness of any of the variables) had a c-statistic of 0.69.

Adjuvant Treatment

The most used adjuvant treatment was gemcitabine-based therapies in 86 patients (35.6%), whereas monotherapy or in association with oxaliplatin or capcitabine. FOLFOXIRINOX was used in 13 patients (5.3%). Radiotherapy was used in 33 patients (13.6%). The use of neoadjuvant treatment did not decrease the frequency of PNI in our cohort (OR = 1.2, 95%CI: 0.18–6.5), but due to a low number of subjects (8 patients) in the neoadjuvant group, this result should be taken with caution.

Discussion

Surgical treatment is the only potentially curative treatment for patients with pancreatic cancer that present at a resectable stage, and it may be substantially underutilized even in countries...
with sufficient medical resources [22], hence the importance of reporting long-term results of surgical treatment of this disease. In addition, little evidence is published from Argentina and from Latin America about long-term oncological outcomes of multidisciplinary treatment of pancreatic cancer. When we analyze the overall survival in this cohort of 10 years of consecutive pancreatectomies for PDAC in a single center, we find that results are similar to international standards. For example, in a recent manuscript from Heidelberg University, 937 patients were included that received pancreatic surgery over the first decade of this millennium, and they obtained a median actual overall survival of 22.1 months and 5-year survival rate of 17% [7]. Whereas in our cohort, the estimated overall survival was 22.8 months, and 5-year survival rate was 20.8%.
Perineural invasion is a major pathway by which tumors progress and spread to the adjacent tissue. Furthermore, it seems to be an important prognostic factor in many types of human malignancies [23]. The pancreas is an organ that is highly innervated by sympathetic and parasympathetic nerves from ganglia around the celiac and superior mesenteric artery [24]. As mentioned before, recent studies showed a major role of PNI in cancer progression, to the point that in animal models of PDAC, the ablation of sympathetic nerves resulted in the inhibition of cancer progression [25]. The aggressiveness of PNI cancer cell invasion is related to neuropathic changes, desmoplasia, and pain. Severe and enduring pain has been strongly associated with poor prognosis in PDAC [8, 26]. In our study, we have found that using multivariable analysis, the presence of PNI was an independent prognostic factor for worse OS, with an HR of 1.94. These results are consistent with findings reported by a recent multicenter study which included 778 patients from well-known different worldwide pancreas centers. They found that PNI was an independent predictor of survival with a HR of 1.6, and the median OS was 50 months in patients without PNI compared with 27 months in those with PNI. The authors showed that perineural invasion plays a major role in disease recurrence and survival after pancreatectomy for pancreatic head ductal adenocarcinoma, especially in early-stage disease [27].

The presence or absence of lymph node metastases is an established prognostic factor in patients with resected adenocarcinoma of the pancreas. In a reported experience from Johns Hopkins University of 905 patients that underwent pancreateicoduodenectomy for pancreatic adenocarcinoma from 1995 to 2005, they obtained a median survival for all patients of 17.4 months, and the 5-year actuarial survival rate was 16.1%. Demographics, operative data, number of lymph nodes evaluated, number of lymph nodes with metastatic carcinoma, LN ratio, pathologic margin status, and long-term survival were analyzed. They found that LN ratio was one of the most powerful predictors of survival [28]. In our study, LN ratio was also a significant variable in bivariate analysis but was not significant after adjusting for the other factors.

Systemic inflammation is a well-established physiopathological factor in neoplastic condition. Neutrophilia reflects
an underlying neoplastic inflammatory syndrome and is usually accompanied by a variable degree of lymphopenia. Therefore, neutrophil lymphocyte ratio (NLR) is an accessible marker of systemic inflammation. The balance between the negative effects of neutrophilia and the positive effects of lymphocyte-mediated immunity is an interesting line of research. There are meta-analyses that validated pretreatment NLR as a prognostic factor, and high NLR values were linked to poor outcomes in numerous types of solid tumors [29]. In metastatic pancreatic adenocarcinoma, a high neutrophil lymphocyte ratio at diagnosis is a marker of poor prognosis. In addition, a high preoperative NLR indicates a worse prognosis than in patients with a low NLR according to another meta-analysis [30]. Furthermore, the prognostic role of baseline NLR and NLR variation after surgery is a novel approach that, to our knowledge, has not been studied before. Therefore, we included this variable in the analysis with special interest, but an association with survival was not found in this cohort. Nevertheless, prospective studies would be appropriate to validate this finding due to the possibility of information bias related to the retrospective nature of this work.

Different authors found a significantly lower rate of PNI in patients receiving preoperative chemotherapy/chemoradiation (50–70%) compared with those undergoing immediate resection (80–90%) [31, 32]. In our cohort, only 8 patients (3.3%) of the surgically resected patients received neoadjuvant therapy. We could not find a statistically significant difference between groups, but, due to the low number of patients in the neoadjuvant arm, it is not proper to draw conclusions about the effect of neoadjuvant treatment on PNI. Whereby in our institution, neoadjuvant therapy approach is reserved for borderline and locally advanced tumors, previously discussed in a multidisciplinary tumor board. Since in the analyzed period, the gold standard was still upfront surgery, and no protocols of neoadjuvant treatments were in place in our institution; for the vast majority of the patients, surgery was the initial approach. Interestingly, recent evidence on this topic was revealed in the PREOPANC Trial, which was a randomized phase III trial in 16 centers from

| Table 2  | Bivariate and multivariate analysis results |
|---------------------------------|---------------------------------|
| **Factors**                     | **Bivariate**                   | **Multivariate**               |
|                                 | HR IC 95% p value               | HR (adjusted) IC 95% p value   |
| Age (years)                     | 1.004 0.99–1.02 0.6            |                                |
| Sex (man)                       | 1.224 0.90–1.67 0.2            |                                |
| Preoperative NLR                | 0.98 0.86–1.1 0.69             | 1.06 0.45–2.45 0.89            |
| Postoperative NLR               | 1 0.89–1.1 0.9                 | 0.83 0.41–1.69 0.61            |
| Delta NLR                       | 1.14 0.77–1.68 0.5             |                                |
| Surgical resection              | 1.095 1.03–1.16 0.005          |                                |
| Vascular resection              | 1.915 1.26–2.9 0.002           |                                |
| Preoperative CA19-9 (U/ml)      | 1 1                             | 0.08                            |
| Postoperative CA19-9 (U/ml)     | **1.001** **1–1.001** <0.0001 | **1.0006** **1.0003–1.0009** 0.00039 |
| Tumor histology                 | 0.54 0.22–1.33 0.2             |                                |
| Differentiation (baseline = well-differentiated) | 1.12 0.9–1.4 0.3 |                                |
| **Tumor size (mm)**             | **1.01** **1.002–1.019** 0.02 | **1.015** **1.0027–1.027** 0.016 |
| Lymph nodes harvested           | 1.01 0.98–1.03 0.9             |                                |
| Positive lymph nodes            | 1.09 1.03–1.15 0.002           | 0.96 0.81–1.14 0.68            |
| Lymph node ratio                | 1.66 1.21–2.26 0.001           | 1.11 0.61–2.01 0.74            |
| R1 resection                    | **1.63** **1.19–2.25** 0.003 | **1.83** **1.1–3.03** 0.019    |
| **Perineural invasion**         | **1.54** **1.06–2.22** 0.02 | **1.94** **1.21–3.14** 0.006   |
| Perivascular invasion           | 1.263 0.89–1.8 0.2             |                                |
| IA stage                        | 0.6 0.32–1.15 0.1             |                                |
| IB stage                        | 0.8 0.56–1.16 0.2             |                                |
| IIA stage                       | 0.56 0.27–1.14 1              |                                |
| IIB stage                       | 1.22 0.89–1.67 0.2            |                                |
| III stage                       | 1.55 1.07–2.26 0.02           | 1.57 0.62–3.97 0.34            |
| Complete adjuvant chemotherapy  | **0.43** **0.31–0.62** <0.0001 | **0.53** **0.35–0.798** 0.002 |

Bold emphasis the variables that were statistically significant in multivariate analysis

CA 19–9 carbohydrate antigen 19–9, NLR neutrophil–lymphocyte ratio
Netherlands where they compared patients with resectable or borderline resectable pancreatic cancer that were randomly assigned to receive preoperative chemoradiotherapy versus immediate surgery and 6 courses of adjuvant gemcitabine. The patients that underwent upfront surgery showed a median overall survival of 16 months vs 14.3 months for the neoadjuvant arm \((p = 0.096)\). Even though they did not reach statistical significance in the primary endpoint that was overall survival, a significantly higher proportion of patients reached R0 resections in the neoadjuvant arm \((71\% \text{ vs } 40\%, p < 0.001)\) and also a lower rate of perineural invasion [33]. In a posterior long-term analysis from this trial, 3- and 5-year overall survival (intention-to-treat) was 27.7% and 20.5% after preoperative chemoradiotherapy (CRT) versus 16.5% and 6.5% after immediate surgery (HR 0.73; 95% CI 0.56 to 0.96; \(p = 0.025\)), which becomes an important evidence towards neoadjuvant approach in this group [34].

This study is not free from limitations. Its retrospective nature makes it susceptible to information bias. Some of the follow-up data is also a problem with these patients, especially the loss of some oncological outcomes such as recurrence or adjuvant treatment completion. One explanation for the 26% of missing data about adjuvant treatment is the population of patients that are treated in our center; since it has become a referral center for pancreatic diseases in Argentina, many patients come for the surgical treatment of pancreatic cancer but complete oncological treatment in their hometown. Another reason is healthcare systems and health insurance in our country that sometimes cover surgical treatment but not chemotherapy treatment which have to be completed in other centers. Therefore, precise information about the adjuvant chemotherapy of some of those patients is missing in our electronic records. On the other hand, information about death was recovered by different means, such as telephonic interviews and public registries making practically a complete registry of this outcome. Furthermore, to the best of our knowledge, there is no previous evidence of the study of variation of neutrophil–lymphocyte ratio in pancreatic cancer surgery survival. Finally, the main use of these results for our daily practice is related to the

![Kaplan–Meier survival estimates by perineural invasion](image-url)
awareness of physicians and patients about the prognostic factors that may lead to long-term survival after surgery.

**Conclusion**

Neutrophil–lymphocyte ratio and delta NLR were not associated with OS in a 10-year cohort of patients with PDAC surgically treated. The presence of perineural invasion was clearly associated with worse OS. Other risk factors such as surgical margins, CA19-9 level, and tumor size also showed worse survival in our cohort, whereas completing adjuvant treatment was a protective factor.

**Author Contribution**

(I) Conception and design: Martín de Santibañes, Ignacio G. Merlo. (II) Administrative support: Juan Pekolj. (III) Provision of study materials or patients: Oscar Mazza, Rodrigo Sanchez Claria, Juan Pekolj, Martín de Santibañes, Eduardo de Santibañes. (IV) Collection and assembly of data: Ignacio G. Merlo, Eugenia Fratantoni. (V) Data analysis and interpretation: Ignacio G. Merlo, Victoria Ardiles. (VI) Manuscript writing: All authors. (VII) Final approval of manuscript: All authors.

**Data Availability**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Declarations**

**Conflict of Interest**

The authors declare no competing interests.

**References**

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. PMID: 30207593.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Marias LN. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913–21. PMID: 24804067.
3. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Widwoski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA - J Am Med Assoc. 2013;310(14):1473–81. PMID: 24104372.
4. Neoptolemos JP, Kleeff J, Michl P, Costello E, Greenhal P, Palmer DH. Therapeutic developments in pancreatic cancer: current and future perspectives. Nat Rev Gastroenterol Hepatol. 2018;15(6):333–48. PMID: 29717230.
5. Klaiber U, Hackert T, Neoptolemos JP. Adjuvant treatment for pancreatic cancer. Transl Gastroenterol Hepatol. 2019;4(April). PMID: 31143848.
6. Conroy T, Hammel P, Hebbel M, Ben Abdelghani M, Wei AC, Raoul J-L, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379:2395–406. PMID: 30575490.
7. Strobel O, Lorenz P, Hinz U, Gaida M, Konig AK, Hank T, et al. Actual five-year survival after upfront resection for pancreatic ductal adenocarcinoma. Ann Surg. 2020. PMID: 32649469. https://doi.org/10.1097/SLA.0000000000004147.
8. Liebl F, Demir IE, Mayer K, Schuster T, D’Haese J, Becker K, et al. The impact of neural invasion severity in gastrointestinal malignancies: a clinicopathological study. Ann Surg. 2014;260(5):900–8. PMID: 25379860.
9. Luchini C, Veronese N, Nottega A, Riva G, Pilati C, Mafficini A, et al. Perineural invasion is a strong prognostic moderator in ampulla of vater carcinoma: a meta-analysis. Pancreas. 2019;48(1):70–6. PMID: 30451797.
10. Gasparrini G, Pellegatta M, Crippa S, Schiavo M, Belloni G, et al. Nerves and pancreatic cancer: new insights into a dangerous relationship. Cancers (Basel). 2019;11(7):1–24. PMID: 31248001.
11. Faulkner S, Jobling P, March B, Jiang CC, Hondermark H. Tumor neurobiology and the war of nerves in cancer. Cancer Discov. 2019;9(6):702–10. PMID: 30944117.
12. Roxburgh CSB, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Futur Oncol. 2010;6(1):149–63. PMID: 20021215.
13. Luo G, Guo M, Liu Z, Xiao Z, Jin K, Long J, et al. Blood neutrophil–lymphocyte ratio predicts survival in patients with advanced pancreatic cancer treated with chemotherapy. Ann Surg Oncol. 2015;22(2):670–6. PMID: 25155401.
14. 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(1-January):181–9. PMID: 29407690.
15. Malleo G, Maggino L, Capelli P, Gulino F, Segattini S, Scarpa A, et al. Reappraisal of nodal staging and study of lymph node station involvement in pancreaticoduodenectomy with the standard international study group of pancreatic surgery definition of lymphadenectomy for cancer. J Am Coll Surg. 2015;221(2):367–379. e4. PMID: 26081176.
16. You MS, Lee SH, Cho YH, Shin BS, Paik WH, Riu JK, et al. Lymph node ratio as valuable predictor in pancreatic cancer treated with R0 resection and adjuvant treatment. BMC Cancer. 2019;19(1):1–8. PMID: 31615457.
17. Merlo I, Fratantoni E, de Santibañes M, Ardiles V, Sanchez Clariá R, Pekolj J, de Santibañes E, Mazza O. Long-term survival after pancreatic cancer surgery. Medicina (B Aires). 2021;81(5):800–802. PMID: 34633955.
18. Cong L, Liu Q, Zhang R, Cui M, Zhang X, Gao X, et al. Tumor size classification of the 8th edition of TNM staging system is superior to that of the 7th edition in predicting the survival outcome of pancreatic cancer patients after radical resection and adjuvant chemotheraphy. Sci Rep. 2018;8(11):10383. PMID: 29991730.
19. Aoyama T, Yamamoto N, Kiami M, Murakawa M, Tamagawa H, Sawasaki S, et al. The lymph node ratio is an independent prognostic factor in pancreatic cancer patients who receive curative resection followed by adjuvant chemotherapy. Anticancer Res. 2018;38(8):4877–82. PMID: 30061263.
20. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGIPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery. 2017;161:85–91. PMID: 28040257.
21. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187–96. PMID: 19638912.
22. Swords DS, Mulvihill SJ, Skarda DE, Finlayson S, Stoddard GJ, Ott MJ, et al. Hospital-level variation in utilization of surgery for clinical stage I-II pancreatic adenocarcinoma. Ann Surg. 2019;269(1):133–42. PMID: 28700442.
23. Chatterjee D, Katz MH, Rashid A, Wang H, Iuga AC, Varadachary GR, et al. Perineural and intraneural invasion in posttherapy
pancreaticoduodenectomy specimens predicts poor prognosis in patients with pancreatic ductal adenocarcinoma. Am J Surg Pathol. 2012;36(3):409–17. PMID: 22301497.

24. Yi SQ, Miwa K, Ohta T, Kayahara M, Kitagawa H, Tanaka A, et al. Innervation of the pancreas from the perspective of perineural invasion of pancreatic cancer. Pancreas. 2003;27(3):225–9. PMID: 14508126.

25. Renz BW, Takahashi R, Tanaka T, Macchini M, Hayakawa Y, Dantes Z, et al. β2 adrenergic-neurotrophin feedforward loop promotes pancreatic cancer. Cancer Cell. 2018;33(1):75-90.e7. PMID: 29249692.

26. Ceyhan GO, Bergmann F, Kadihasanoglu M, Altintas B, Demir IE, Hinz U, et al. Pancreatic neuropathy and neoplastic pain—a comprehensive pathomorphological study of 546 cases. Gastroenterology. 2009;136(1):177-186.e1. PMID: 18992743.

27. Crippa S, Pergolini I, Javed AA, KC. Honselmann, M. J. Weiss, F. Di Salvo, et al., “Implications of perineural invasion on disease recurrence and survival after pancreatectomy for pancreatic head ductal adenocarcinoma,” Ann. Surg., vol. Publish Ah, Oct. 2020. PMID: 33086324.

28. Pawlik TM, Gleisner AL, Cameron JL, Winter JM, Assumpcao L, Lillemoe KD, et al. Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer. Surgery. 2007;141(5):610–8. PMID: 17462460.

29. Choi N, Kim JH, Chie EK, Gim J, Kang HC. A meta-analysis of the impact of neutrophil-to-lymphocyte ratio on treatment outcomes after radiotherapy for solid tumors. Med (United States). 2019;98(18):1–8. PMID: 31045780.

30. McLellan P, Henrques J, Ksontini F, Doat S, Hammel P, Desrme J, et al. Prognostic value of the early change in neutrophil-to-lymphocyte ratio in metastatic pancreatic adenocarcinoma. Clin Res Hepatol Gastroenterol. 2021;45(3):101541. PMID: 33055007.

31. Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EL, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg. 2015;261(1):12–7. PMID: 25599322.

32. Barnes CA, Chavez MI, Tsai S, Aldakkak M, George B, Ritch PS, et al. Survival of patients with borderline resectable pancreatic cancer who received neoadjuvant therapy and surgery. Surg (United States). 2019;166(3):277–85. PMID: 31272811.

33. Versteijne E, Suer M, Grootenhuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC trial. J Clin Oncol. 2020;38(16):1763–73. PMID: 32105518.

34. Van Eijck CHJ et al. Preoperative chemoradiotherapy to improve overall survival in pancreatic cancer: long-term results of the multicenter randomized phase III PREOPANC trial. J Clin Oncol. 2021;39(15_suppl):4016–4016. https://doi.org/10.1200/JCO.2021.39.15_suppl.4016.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.