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# Neural invasion severity is a strong predictor of local recurrence in pancreatic ductal adenocarcinoma

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ABSTRACT

*Background:* In pancreatic ductal adenocarcinoma, neural invasion is being increasingly recognized as an unfavorable predictor of patient outcomes. Neural invasion severity seems to have a stronger clinical impact on patient prognosis than neural invasion status alone. Therefore, this study aims to assess the impact of severity of neural invasion on overall survival and disease-free survival in pancreatic ductal adenocarcinoma.
*Materials:* To assess the impact of intrapancreatic neural invasion severity, tumor specimens resected from patients with pancreatic ductal adenocarcinoma between 2007 and 2014 were systematically re-evaluated, and neural invasion severity was determined using the standardized neural invasion severity score.
*Results:* In our cohort ($n = 216$), an increased neural invasion severity score was associated with markedly shorter overall survival in pancreatic head ductal adenocarcinoma (neural invasion severity score low: 22.8 months vs neural invasion severity score high: 17.6 months: $P = .001$). An external European validation cohort confirmed these results and showed significantly better survival of patients with lower neural invasion (20.5 vs 15.4 months, $P = .026$). The disease-free survival time was also substantially decreased in patients with pancreatic head pancreatic ductal adenocarcinoma and increased neural invasion severity (neural invasion severity score low: 19.1 months vs neural invasion severity score high: 10.4 months; $P = .004$). Moreover, the neural invasion severity score was an important independent factor influencing overall survival (hazards ratio 1.024, $P = .04$) and disease-free survival (hazards ratio 1.03, $P = .01$) using an adjusted Cox proportional hazards model. Importantly, higher neural invasion severity score leads to significantly more and earlier local recurrence than to distant tumor recurrence.
*Conclusion:* Neural invasion severity is a powerful independent factor influencing overall survival and local recurrence in patients with pancreatic ductal adenocarcinoma. Therefore, individuals with high neural invasion severity score values should be regarded as a specific subgroup of pancreatic ductal adenocarcinoma patients and may benefit from more tailored postoperative oncologic therapy.



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## Background

Despite being the focus of intensive research, the prognosis of patients suffering from pancreatic ductal adenocarcinoma (PDAC) remains dismal; only 8% of all patients survive the first 5 years after diagnosis.[1] This abysmal prognosis is attributable to the low number of cases that can undergo curative resection and the high rates of local recurrence.[2–6] Moreover, death rates have not changed meaningfully over recent decades, underlining the urgent requirement for new therapeutic options and diagnostic markers to enhance patient survival.[1]

We extensively characterized neural invasion (NI) as a valuable histopathologic hallmark of PDAC.[7] Depending on the exact localization of PDAC cells around intrapancreatic nerves, NI can be stratified into *epineural association* (tumor cells located close to nerves, without making direct contact), *perineural invasion* (tumor cells in broad contact with the epineurium, encircling the nerve), or *endoneural invasion* (tumor cells encountered inside the nerve).[8,9] Although NI is also observed in other tumors, such as colorectal, gastric, or prostate cancer, the reported incidence of NI in PDAC surpasses that in any other known solid tumor.[9] To assess the true incidence of NI in gastrointestinal (GI) malignancies, we systematically screened tumor specimens from almost 2,000 patients with various GI cancers and identified the strongest prevalence of NI in PDAC at 100%, which implies that NI is an omnipresent feature of PDAC.[9] In contrast, NI was less frequent in other GI tumors, including hepatocellular cancer (6%); cholangiocellular carcinoma (58%); squamous cell carcinoma of the esophagus (37%); adenocarcinoma of the esophagogastric junction type I (36%), type II (36%), and type III (65%); gastric cancer (38%); colon cancer (28%); and rectal cancer (34%).[9] Because every patient with PDAC exhibited NI, it was striking that the severity of NI could be identified as an independent predictor that could stratify patients with dismal overall survival (OS).

A recent systematic review and meta-analysis on the impact of NI on PDAC-associated survival rates showed increased mortality in patients with NI compared with those without NI.[10] Thereby, a multivariate analysis of 36 HRs confirmed the unfavorable effect of NI by identifying NI as an independent prognostic factor for OS, disease-free survival (DFS), and progression-free survival.[10]

Collectively, these observations suggest that the presence of NI represents a biologically unfavorable factor and indicator of aggressive tumor biology in PDAC. Therefore, we questioned how far the presence and the severity of NI might affect survival and recurrence in patients with PDAC. We expected to potentially stratify patients at high risk with this useful tool. Therefore, we performed a retrospective analysis of pathology specimens resected from patients at our institution between 2007 and 2014 and assessed the correlation of the NI severity score (NI-SSc) with survival and recurrence data. We hypothesized that, more than the presence of NI, it is the quantifiable severity of NI that has a major prognostic impact in resected pancreatic ductal adenocarcinoma.

## Methods

### *Retrospective analysis*

The institutional review board approved the prospective data collection and retrospective review of patient records for this project (434/18s). Analyses were conducted using an anonymized, prospectively collected data set.

### *Perineural invasion and NI-SSc*

A neural invasion severity score was determined for all tumor specimens, as previously described.[11,12] In brief, intrapancreatic NI was classified into the following 3 stages: epineural tumor association (ENA), defined as lesions where the tumor directly touches the epineural sheet but without penetrating into the perineurium; perineural invasion (PNI), defined as tumor cells found within the perineural space; and endoneural invasion (ENI), characterized by the infiltration of cancer cells into the endoneurium, where they are completely contained within the nerve fascicles.[11] All nerves on every histologic slide were scored and categorized as noninvaded (0), ENA (1), PNI (2), or ENI (3). Subsequently, the severity of NI in each case specimen was determined using the NI-SSc, as established previously.[8] Therefore, all nerves in the entire tissue specimen were categorized and scored as follows: noninvaded (0), or ENA (1), PNI (2), or ENI (3) cancer cell invaded. The NI-SSc was computed by adding the number of invaded nerves ($n$) to the abovementioned NI severities using the following standardized formula: individual NI-SSc = $n$ (ENA) × 1 + $n$ (PNI) × 2 + $n$ (ENI) × 3.[12] At least 3 different hematoxylin-eosin–stained samples from different tumor sites from each patient were screened, and the mean NI-SSc was calculated from the 3 sections. The cutoff point for low/high perineural invasion was the median severity score.

### *Patients*

Our prospective institutional database was retrospectively screened and analyzed for potential curative pancreatic resections and 350 patients who underwent elective pancreaticoduodenectomy, distal pancreatectomy/left resection, or total pancreatectomy for histologically confirmed PDAC between July 2007 and October 2014 were identified. The exclusion criteria were as follows: UICC stage IV ($n = 29$), patients treated with neoadjuvant therapy ($n = 24$), in-hospital mortality ($n = 15$), and arterial or R2 resection ($n = 7$). Ten patients were lost to follow-up, and 40 patients had no representative tissue samples; consequently, the NI-SSc could not be assessed. Only 9 patients had no NI, and they were also excluded, as this study aimed to assess the impact of the NI-SSc on tumor recurrence and OS. Therefore, the analyzed cohort included a total of 216 patients (Figure 1).

Patients were followed up until July 2024. The median follow-up duration for 28 patients who survived was 125 (36–177) months, and that for 188 patients who died was 17.6 (2–144) months. OS and DFS were calculated from the date of surgery to the date of death/tumor recurrence or the last follow-up if death/tumor recurrence did not occur. OS was defined as the time between the surgical procedure and death of the patient, whereas DFS was defined as the time between the operation and death or tumor recurrence. Local recurrence was defined as radiologically suspicious tumor formations in the pancreatic bed, among the celiac and/or the superior mesenteric trunk. Data were obtained from hospital/practitioner records, tumor registries, or direct telephone contact with patients and their relatives (Tables I and II). Tumor recurrence was confirmed by re-examination via contrast-enhanced computed tomography scans by the Institute of Radiology at the Technical University of Munich. To stratify tumors of the pancreatic body and the pancreatic tail, the following definition was used in this study: tumors of the pancreatic head were defined as tumors to the right of the mesenterico-portal axis, tumors of the pancreatic body were those located between the mesenterico-portal axis and the left border of the aorta, and tumors of the

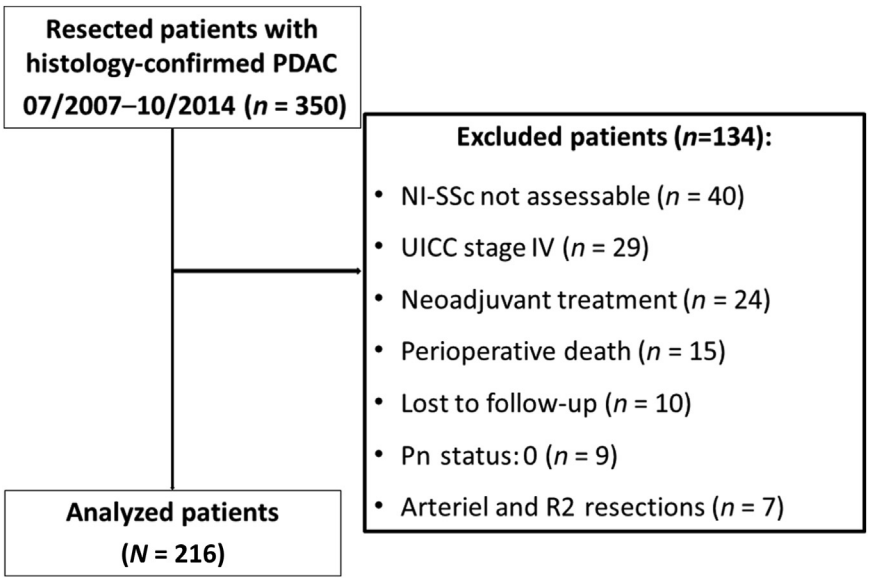


**Figure 1.** Study flow diagram. The number of included patients is shown; a total of 350 patients underwent pancreatic resection between 2007 and 2014 because of pancreatic cancer. After excluding noneligible patients, the NI-SSc and survival were analyzed in 216 patients. *NI*, neural invasion; *NI-SSc*, neural invasion severity score; *PDAC*, pancreatic ductal adenocarcinoma; *Pn*, perineural invasion; *UICC*, Union for International Cancer Control.

distal pancreas were defined as tumors located to the left border of the aorta.

For the external validation cohort, tumor specimens of 74 patients from the Tissue Biobank of the Institute of Pathology at the University of Mainz (Institut für Pathologie Universitätsmedizin der Johannes Gutenberg-Universität Mainz) were obtained. In these patients, the NI-SSc was independently assessed, and 2 groups, depending on the median NI-SSc, were established. Afterward, OS analysis was performed to assess the impact of the NI-SSc in this group.

### *Statistics*

Continuous variables are reported as medians and ranges and were compared using the Mann-Whitney *U* test. Categorical variables are summarized as frequency counts and percentages and were compared using Fisher exact test or Pearson $\chi^2$ -square test. Correlations were estimated using Spearman ρ, and significant parameters were included in an adjusted logistic regression model. Survival analysis was performed using the Kaplan-Meier method, and differences were evaluated using the log-rank test. The median NI-SSc was used to stratify patients into low and high NI-SSc groups and correlated with OS and DFS times and local recurrence. To estimate predictive parameters, a proportional Cox hazards model was constructed. Statistical analyses were performed using IBM SPSS v23 for Windows (IBM Corp, Armonk, NY).

## Results

### *Patient characteristics*

Patient characteristics are presented in Table I. From a total of 216 included pancreatic resections, 139 patients underwent pylorus-preserving pancreaticoduodenectomy (64.4%), 10 patients underwent classic pancreaticoduodenectomy (4.6%), 35 patients underwent distal pancreatectomy (16.2%), and 32 patients underwent total pancreatectomy (14.8%). In total, 191 patients (88.4%) received adjuvant chemotherapy.

The median tumor size was 3.5 cm. T-stage, according to the new eighth classification (2017), was distributed as follows: T1 stage, $n =$ 22 (10.2%); T2 stage, $n = 133$ (61.6%); T3 stage, $n = 45$ (20.8%); and T4 stage, $n = 16$ (7.4%). There were 62 lymph node–negative resections (28.8%), and 94 patients (43.5%) had an N1 status, with 60 (27.8%) having an N2 status. There were 18 (8.3%) patients with grade 1 disease, 99 (45.9%) with grade 2 disease, 97 (44.9%) with grade 3 disease, and 2 (0.9%) with grade 4 disease (Table I).

### *Perineural invasion*

Initially, specimens from 225 patients were assessed: only 9 patients did not have NI, whereas 216 (95.8%) patients had NI. The median overall NI-SSc was 8.0. A higher grade of NI severity (ie, >median NI-SSc) was significantly associated with tumor-positive lymph nodes ($P = .005$) and positive resection margins ($P = .001$). Tumors of the pancreatic tail had a significantly lower mean NI-SSc than those of the pancreatic body and head (distal pancreas: 3.7 vs pancreatic body: 8.0 vs pancreatic head: 8.3, respectively; $P = .014$; Supplementary Figure S1).

### *Survival*

Overall survival was superior in patients with a low NI-SSc, with a median OS duration of 22.8 months, compared to those with a high NI-SSc, with a median OS duration of 17.5 months ($P = .003$; Figure 2, *A*). Subgroup analyses revealed that a significant survival benefit in the low NI-SSc group was only associated with pancreatic head tumors (22.8 vs 17.6 months, $P = .01$; Figure 2, *B*). No different survival was seen in tumors of the body (17.5 vs 15.7 months, $P =$ .42), whereas there was a nonsignificant better survival in tail tumors (32.2 vs 21.7, $P = .14$). Hence, multivariate analysis of OS were assessed in patients suffering from PDAC of the pancreatic head. Here, bigger tumor size (HR 1.02, $P = .001$), grade G3/G4 (HR 1.90, $P < .001$), tumor-positive lymph nodes (N1: HR 1.90, $P = .006$; N2: HR 2.33, $P = .002$), tumor-positive resection margin (HR 1.57, $P =$ .02), no chemotherapy (HR 4.38, $P < .001$), and a higher Ni-SSc (HR 1.024, $P = .042$) were independent factors for OS (Table III, Supplementary Figure S3).

**Table I**
Patient and clinical characteristics ($N = 216$)

| Patient/clinical parameters | $n$ (%) or median (range) |
|---|---|
| Sex | |
| Male | 116 (53.7) |
| Female | 100 (46.3) |
| Age, y, median (range) | 67.1 (31.8–93.4) |
| Operation | |
| ppWhipple* | 139 (64.4) |
| Classic Whipple† | 10 (4.6) |
| Total pancreatectomy | 32 (14.8) |
| Distal resection | 35 (16.2) |
| Adjuvant chemotherapy | |
| No | 34 (15.7) |
| <3 cycles | 15 (7.0) |
| Gemcitabine, mono/erlotinib/paclitaxel | 128 (59.3) |
| Multiple chemotherapy (eg, FOLFIRINOX) | 34 (15.7) |
| Unknown | 5 (2.3) |
| Tumor characteristics UICC (2017, 8th edition) | |
| Tumor size | |
| pT1 | 22 (10.2) |
| pT2 | 133 (61.6) |
| pT3 | 45 (20.8) |
| pT4 | 16 (7.4) |
| Tumor size, mm, median (range) | 35 (14–150) |
| Lymph node metastasis | |
| pN0 | 62 (28.7) |
| pN1 | 94 (43.5) |
| pN2 | 60 (27.8) |
| Histological grade | |
| G1 | 18 (8.3) |
| G2 | 99 (45.9) |
| G3 | 97 (44.9) |
| G4 | 2 (0.9) |
| Resection margin (R0 >1 mm) | |
| R0 | 113 (52.3) |
| R1 | 91 (42.1) |
| Unknown | 12 (5.6) |
| Tumor localization | |
| Head | 171 (79.2) |
| Body | 26 (12.0) |
| Tail | 19 (8.8) |
| Follow-up | |
| Survival | 216 |
| Survived | 28 (15.3) |
| Died | 188 (84.7) |
| Survival time, mo, median (range) | |
| Survived | 125 (36–177) |
| Died | 17.6 (2–144) |
| Overall survival of pancreatic head PDAC | |
| Low NI-SSc, mo, median | 22.8 |
| 1-y survival, % | 77.5 |
| 3-y survival, % | 40.0 |
| 5-y survival, % | 27.5 |
| High NI-SSc, mo, median | 17.6 |
| 1-y survival, % | 68.1 |
| 3-y survival, % | 24.2 |
| 5-y survival, % | 14.6 |

*FOLFIRINOX*, leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, and oxaliplatin; *Ni-SSc*, neural invasion severity score; *PDAC*, pancreatic ductal adenocarcinoma; *UICC*, Union for International Cancer Control.
* Pylorus-preserving pancreaticoduodenectomy.
† Pancreaticoduodenectomy.

**Table II**
Recurrence site and neural invasion severity

| Tumor recurrence | NI-SSc, median (min-max) | $P$ value* |
|---|---|---|
| No metastasis, $n = 40$ | 5.0 (0.7–24.3) | |
| Local recurrence only, $n = 10$ | 15.33 (2.7–25.3) | .001† |
| Peritoneal carcinosis only, $n = 5$ | 14.0 (0.3–24.3) | .07 |
| Liver metastasis only, $n = 57$ | 8.0 (0.3–54.7) | .09 |
| Pulmonal only, $n = 3$ | 4.0 (2.0–5.0) | .34 |
| Multiple only, $n = 78$ | 8.6 (0.3–49.0) | .022† |
| Unspecific, $n = 6$ | 8.0 (2.0–19.7) | .41 |
| Unknown, $n = 17$ | 7.0 (2.3–47.7) | .52 |

*Ni-SSc*, neural invasion severity score.
* Mann-Whitney *U* test, compared with no metastasis.
† Statistically significant.

### *Tumor recurrence*

Patients with a low NI-SSc had a median DFS duration of 18.6 months, whereas those with a high NI-SSc had a median DFS duration of 10.4 months ($P < .001$; Figure 3, *A*). Accordingly, a subgroup analysis of tumor location revealed significantly decreased DFS in tumors of the pancreatic head with a high NI-SSc (10.4 months) compared to those with a low NI-SSc (19.1 months; $P = .004$ Figure 3, *B*). Analog to OS Analysis tumors of the body showed no difference (9.6 vs 10.0 months, $P = .49$), whereas low Ni-SSc leads to improved DFS in tail tumors (22.3 vs 9.4 months, $P = .06$). Multivariate DFS analysis indicates same independent predictors as for OS, but not R1 status ($P = .23$): tumor size (HR 1.015, $P = .004$), tumor-positive lymph nodes (N1: HR 2.03, $P = .007$; N2: HR 2.65, $P < .001$), tumor grade G3/G4 (HR 2.19, $P < .001$), no chemotherapy (HR 3.23, $P < .001$), and higher NI-SSc (HR 1.03, $P = .01$) were associated with worse DFS (Table IV).

A more detailed analysis disclosed that higher NI-SSc leads to more often and earlier local recurrence (LR) but not distant metastasis (Table II). These patients have a 2.4 times higher risk suffering LR compared with lower NI-SSc. Multivariate logistic regression revealed Ni-SSc as the strongest predictor for LR (OR 1.066, $P = .001$). Additional independent risk factors for LR were positive lymph nodes (N1: OR 2.13, $P = .04$; N2: OR 2.27, $P = .04$) and no chemotherapy (OR 2.65, $P = .008$). Moreover, time to LR is significant 5 months earlier with higher NI-SSc (9.1 vs 14.1 months, $P = .002$; Figure 4).

### *Validation cohort*

To validate the impact of the NI-SSc in patients with pancreatic cancer, a validation cohort was obtained from the Institute of Pathology of the University of Mainz (Institut für Pathologie Universitätsmedizin der Johannes Gutenberg-Universität Mainz). This cohort included 74 patients with confirmed PDAC who underwent resection between March 1997 and December 2013 with a minimum survival time of 6 months. After assessing the NI-SSc from representative PDAC tissue samples, patients were stratified according to their median NI-SSc into 2 subgroups, and Kaplan-Meier analysis was performed. The median OS duration was 15.4 months in patients with a high NI-SSc and 20.5 months in patients with a low NI-SSc, with a clinically relevant increase in overall survival in patients with a low NI-SSc (log-rank test: $P = .026$; Supplementary Figure S2).

## Discussion

The current study demonstrates that NI severity is the most important factor unfavorably influencing local recurrence. The degree of NI severity is associated with inferior OS and DFS in patients with PDAC.

Our analyses emphasize that patients with a high NI-SSc have a shorter OS and DFS than patients with a low NI-SSc. The observed differences in DFS are mainly attributable to the major influence of NI on local recurrence, whereas there was no significant association with the development of distant metastases.

In 2014, we demonstrated that PDAC cells have a special affinity for nerves, as PDAC patients had the highest incidence of NI in the entire GI tract. However, in contrast to the study by Liebl et al in

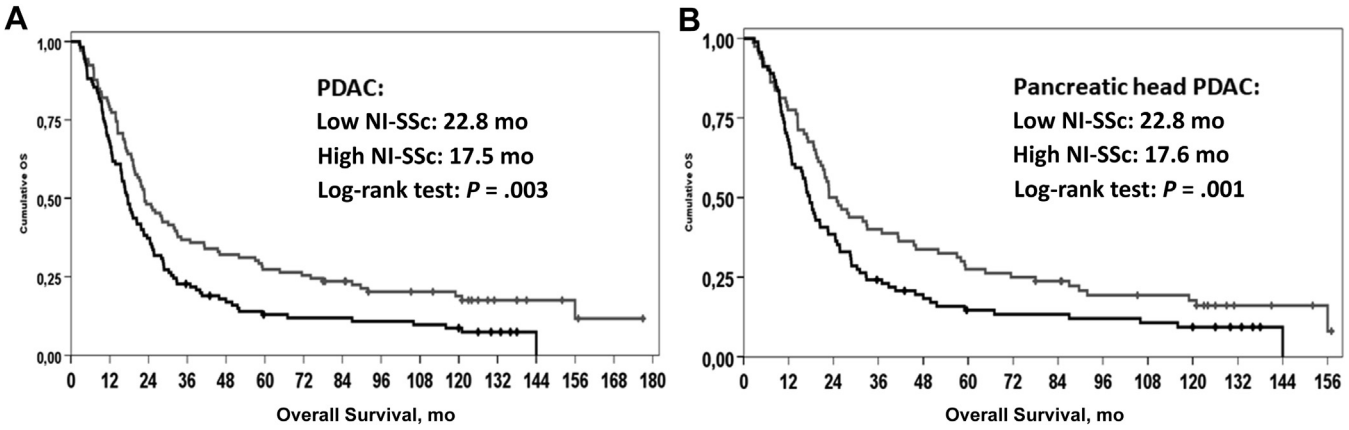


**Figure 2.** Increasing neural invasion severity is associated with decreased OS in the cohort and in patients with PDAC in the pancreatic head. A high NI-SSc was markedly associated with decreased survival in patients with PDAC. (A) Patients with a high NI-SSc (red) had a median OS duration of 17.0 months, whereas those with a low NI-SSc (blue) had a median OS duration of 22.0 months. (B) OS was also strongly decreased in patients with a high NI-SSc (17.0 months) relative to those with a low NI-SSc (22.0 months) among patients with pancreatic head PDAC. *NI-SSc*, neural invasion severity score; *OS*, overall survival; *PDAC*, pancreatic ductal adenocarcinoma. Color version of figure is available online.

**Table III**
Univariate and multivariate analysis for OS in pancreatic head PDAC

| Tumor characteristics | Univariate analysis, HR | *P* value | Multivariate analysis, HR | *P* value |
|---|---|---|---|---|
| Tumor size | 1.03 | <.001 | 1.02 | .001 |
| T status | | .005 | | |
| T2 | 2.32 | .005 | | |
| T3 | 3.83 | <.001 | | |
| T4 | 8.69 | <.001 | | |
| N1 | 2.39 | <.001 | 1.90 | .006 |
| N2 | 2.90 | | 2.33 | .002 |
| G3/4 | 1.98 | <.001 | 1.90 | <.001 |
| R1 (1 mm) | 2.19 | <.001 | 1.57 | .002 |
| NI-SSc | 1.04 | <.001 | 1.02 | .04 |
| No adjuvant chemotherapy | 1.49 | .133 | 4.38 | <.001 |

*HR*, hazard ratio; *NI-SSc*, neural invasion severity score; *PDAC*, pancreatic ductal adenocarcinoma.

2014,[9] we decided to perform a detailed oncologic analysis of the impact of the severity of NI, focusing not only on OS but also on disease-free survival (DFS). Moreover, to present a homogenous cohort, subgroup analysis was performed on patients with tumors of the pancreatic head.[9] To our knowledge, this is also the first study to show that the severity of neural invasion seems to differ between PDAC of the pancreatic tail versus PDAC of the pancreatic head and body. Although the exact mechanism of NI is not yet known, one could assume that the different neural invasion severities might be due to different patterns of innervation. Accordingly, in a recent study published by Mota Reyes et al,[13] crucial differences in the microenvironment between PDAC of the pancreatic head, body, and tail could be observed. Here, PDAC of the pancreatic head showed increased intratumoral CD45 leucocytes, cytotoxic T cells, and antitumor immune cells, such as dendritic cells and M1 macrophages. Additionally, tumors of the pancreatic body and the tail had a pronounced immunosuppressive environment, with a higher number of regulatory T cells.[13]

In accordance with our findings, Crippa et al[14] presented, in 2020, one of the largest cohort studies (778 patients) of the impact of NI on OS and DFS. In their cohort, NI was present in 87% of patients, underlining the extremely high incidence of NI in PDAC. Here, the presence of NI was also linked to decreased DFS, ie, 20 months in patients without NI and 15 months in patients with NI

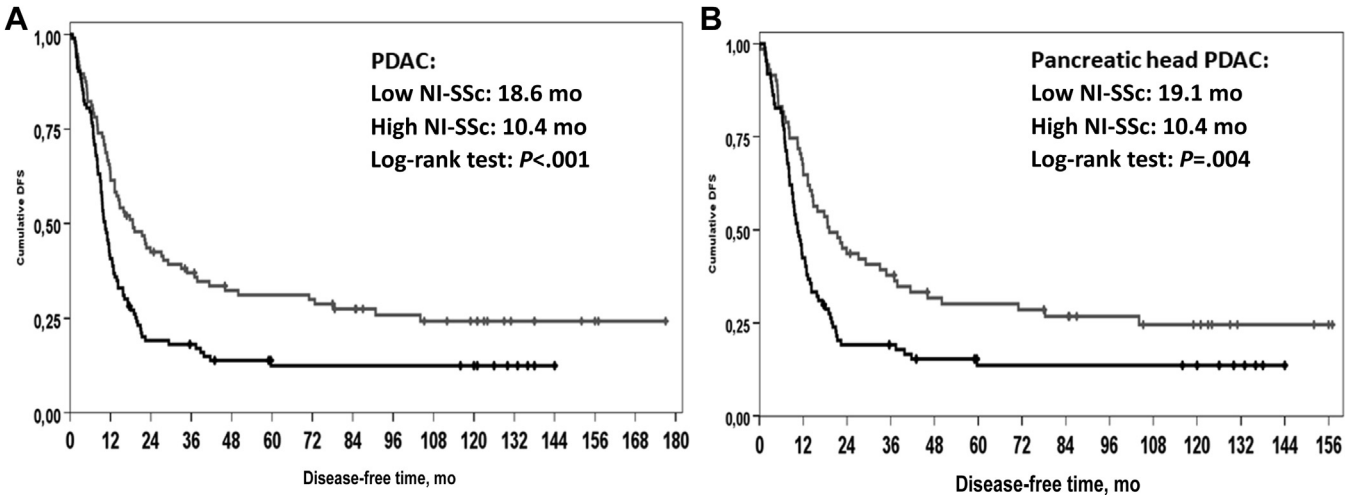


**Figure 3.** Increasing neural invasion severity is associated with decreased DFS in the cohort and in patients with PDAC in the pancreatic head. DFS was also strongly decreased in patients with a high NI-SSc (12.5 months) relative to those with a low NI-SSc (18.6 months). The decreased DFS was also detectable in patients with pancreatic head PDAC (low NI-SSc: 18.6 months vs high NI-SSc: 11.0 months; $P = .004$). *DFS*, disease-free survival; *PDAC*, pancreatic ductal adenocarcinoma; *NI-SSc*, neural invasion severity score.

**Table IV**
Univariate and multivariate analysis for DFS in pancreatic head PDAC

| Tumor characteristics | Univariate analysis, HR | *P* value | Multivariate analysis, HR | *P* value |
|---|---|---|---|---|
| Tumor size | 1.02 | <.001 | 1.01 | .004 |
| T status | | .02 | | |
| T2 | 2.40 | .009 | | |
| T3 | 4.40 | <.001 | | |
| T4 | 8.12 | <.001 | | |
| N1 | 2.52 | <.001 | 2.03 | .007 |
| N2 | 3.37 | <.001 | 2.65 | <.001 |
| G3/4 | 2.26 | <.001 | 2.19 | <.001 |
| R1 (1 mm) | 2.04 | <.001 | 1.83 | .23* |
| NI-SSc | 1.05 | <.001 | 1.03 | .01 |
| No adjuvant chemotherapy | 2.43 | <.001 | 3.23 | <.001 |

*HR*, hazard ratio; *NI-SSc*, neural invasion severity score; *PDAC*, pancreatic ductal adenocarcinoma.
* Not in final model.

($P < .01$). Although NI was not an independent factor for DFS in the entire cohort (HR 1.3, $P = .07$), NI was shown to be an independent factor for DFS in R0/N0 PDAC patients (HR 2.2, $P < .01$) and in PDAC patients with a resection margin $\leq$20 mm (HR 1.8, $P = .02$). Importantly, the presence of NI was associated with worse survival in the multivariate analysis of the entire cohort (NI: 27 months vs no NI: 50 months; $P = .01$).[14] Although these findings are in line with our current data, Crippa et al investigated only the effect of NI *incidence* in patients with PDAC, whereas the current authors applied the NI-SSc system to analyze both the incidence and severity of NI by stratifying patients according to their *neural invasion capacity*. In particular, NI severity is more accurate for estimating the risk of local recurrence after curative resection, as almost all patients develop recurrence in their tumor specimens,[9] and the incidence of extrapancreatic, extratumor cells is correlated with NI severity.[15,16] To assess the impact of NI degree on patient outcome, Takahashi et al[15] correlated the presence of extrapancreatic neural plexus invasion by PDAC cells with the degree of intratumoral NI. Strikingly, whereas the extrapancreatic neural plexus of patients without NI was tumor-free (0%), one third of patients with a low degree of NI had a tumor-positive extrapancreatic neural plexus (33.3%), rising to 78.3% and 85.7% in patients with moderate or high degrees of NI, respectively.[15] Therefore, it is logical to infer that PDAC cells use the intratumoral/intrapancreatic nerves to spread toward the retroperitoneal space and may thus be unreachable using routine surgical procedures. Hence, the greater risk of extrapancreatic neural plexus invasion may also account for the reduced OS and DFS in patients with a high NI-SSc following curative surgery. Moreover, the clinical consequence, namely, the presence of residual tumor cells in the extrapancreatic neural plexus, highlights the advantages of our NI-SSc, because this score is based on a combined assessment of the amount and severity of NI and, therefore, may predict residual tumor cells within the extrapancreatic nervous plexus and thus the risk of local recurrence more accurately than merely the presence of NI.

The impact of NI severity on OS and DFS raises the question of how far an adjusted adjuvant therapy, based on the NI severity score, could prolong OS and DFS in patients with PDAC. The effect of adjuvant therapy on PDAC characteristics, including NI, is difficult to evaluate; however, the effect of neoadjuvant chemotherapy (NTx) on PDAC is currently the focus of ongoing research. In a recently published systematic review with meta-analysis, NTx was also associated with a decreased NI.[17] Interestingly, this effect of NTx is not limited to PDAC as a decrease of NI after NTx could also be seen in patients with rectal cancer.[12] Accordingly, tumor recurrence after curative resection was strongly decreased in patients with a high NI-SSc in the RCTx group ($P < .01$), as well as in the upfront surgery group ($P < .001$).[12] Regarding the limitation of the assessment and reproducibility of the NI-SSc preoperatively using core needle biopsies to stratify patients who would benefit from NTx, further radiologic or serological biomarkers are urgently needed and should be focused on in future studies. Nevertheless, a more aggressive chemotherapy might be offered postoperatively to those patients with a high NI-SSc.

Although results were in line with the literature, some limitations must be discussed. Because of its retrospective character, the

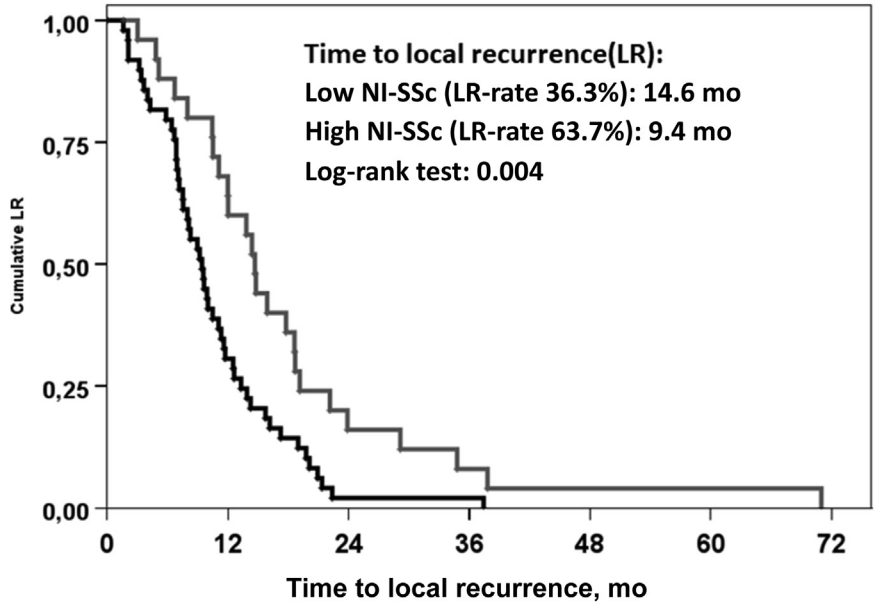


**Figure 4.** Increasing neural invasion severity is associated with decreased time from surgery until local recurrence. Patients with a high NI-SSc (green) showed a decreased time until local recurrence relative to those with a low NI-SSc (blue) (low NI-SSc: 14.1 months vs high NI-SSc: 9.1 months). *LR*, local recurrence; *NI-SSc*, neural invasion severity score. Color version of figure is available online.

NI-SSc was not assessable in 40 patients because of insufficient tumor specimens, and an additional 9 patients showed no NI in their specimens. Moreover, survival and recurrence data of 10 patients (2.9%) were not available, leading to their exclusion because of loss to follow-up. Nevertheless, this small number of patients excluded because of loss to follow-up and the systematic processing of tumor specimens also underline the quality of the results, which minimized the risk of relevant bias. Moreover, regarding the validation cohort, one should mention that these analyses were limited by the small number of patients ($n = 84$) and by the treatment interval, as these patients were treated because they were diagnosed with PDAC between March 1997 and December 2013. Moreover, tumor specimens consist of any kind of PDAC, with no further possibility to stratify according to the exact tumor location.

In conclusion, we clearly show that the incidence and degree of NI are associated with decreased OS and DFS in patients with PDAC. Moreover, we implemented the NI-SSc as a valuable oncologic tool for identifying patients with more unfavorable tumor biology. To what extent patients with a high NI-SSc benefit from more aggressive and individual-based adjuvant therapy must be evaluated in future trials.

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## Conflict of Interest/Disclosure

All authors declare that there were no conflicts of interest.

## Availability of data

Data, analytic methods, and study materials will be available through contacting the corresponding author.

## CRediT authorship contribution statement

**Stephan Schorn:** Writing – original draft, Validation, Supervision, Software, Formal analysis. **Anouk Brock:** Writing – original draft, Investigation, Formal analysis, Data curation. **Georgios Kaissis:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Data curation. **Matthias M. Gaida:** Writing – review & editing, Supervision, Resources, Data curation. **Katja Steiger:** Writing – review & editing, Supervision, Data curation. **Carsten Jäger:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Investigation, Formal analysis, Data curation. **Anna Melissa Schlitter:** Writing – review & editing, Supervision, Data curation. **Rickmer Braren:** Writing – review & editing, Validation, Supervision. **Helmut Friess:** Writing – review & editing, Supervision, Resources, Project administration. **Ihsan Ekin Demir:** Writing – review & editing, Supervision, Project administration. **Güralp Onur Ceyhan:** Writing – review & editing, Supervision, Project administration.

## Supplementary materials

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## References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:7–30.
2. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. *World J Surg*. 1997;21:195–200.
3. Gebhardt C, Meyer W, Reichel M, Wunsch PH. Prognostic factors in the operative treatment of ductal pancreatic carcinoma. *Langenbecks Arch Surg*. 2000;385:14–20.
4. Bradley 3rd EL. Long-term survival after pancreatoduodenectomy for ductal adenocarcinoma: the emperor has no clothes? *Pancreas*. 2008;37:349–351.
5. Hohenberger W, Kastl S. Neoadjuvant and adjuvant therapy of ductal pancreatic carcinoma. *Zentralbl Chir*. 2000;125:348–355.
6. Barbier L, Turrini O, Gregoire E, Viret F, Le Treut YP, Delpero JR. Pancreatic head resectable adenocarcinoma: preoperative chemoradiation improves local control but does not affect survival. *HPB (Oxford)*. 2011;13:64–69.
7. Bockman DE, Buchler M, Beger HG. Interaction of pancreatic ductal carcinoma with nerves leads to nerve damage. *Gastroenterology*. 1994;107:219–230.
8. Ceyhan GO, Bergmann F, Kadihasanoglu M, et al. Pancreatic neuropathy and neuropathic pain–a comprehensive pathomorphological study of 546 cases. *Gastroenterology*. 2009;136:177–186.e1.
9. Liebl F, Demir IE, Mayer K, et al. The impact of neural invasion severity in gastrointestinal malignancies: a clinicopathological study. *Ann Surg*. 2014;260:900–907;discussion 907-8.
10. Schorn S, Demir IE, Haller B, et al. The influence of neural invasion on survival and tumor recurrence in pancreatic ductal adenocarcinoma - a systematic review and meta-analysis. *Surg Oncol*. 2017;26:105–115.
11. Liebl F, Demir IE, Rosenberg R, et al. The severity of neural invasion is associated with shortened survival in colon cancer. *Clin Cancer Res*. 2013;19:50–61.
12. Ceyhan GO, Liebl F, Maak M, et al. The severity of neural invasion is a crucial prognostic factor in rectal cancer independent of neoadjuvant radiochemotherapy. *Ann Surg*. 2010;252:797–804.
13. Mota Reyes C, Teller S, Muckenhuber A, et al. Neoadjuvant therapy remodels the pancreatic cancer microenvironment via depletion of protumorigenic immune cells. *Clin Cancer Res*. 2020;26:220–231.
14. Crippa S, Pergolini I, Javed AA, et al. Implications of perineural invasion on disease recurrence and survival after pancreatectomy for pancreatic head ductal adenocarcinoma. *Ann Surg*. 2020;276:378–385.
15. Takahashi T, Ishikura H, Motohara T, Okushiba S, Dohke M, Katoh H. Perineural invasion by ductal adenocarcinoma of the pancreas. *J Surg Oncol*. 1997;65:164–170.
16. Takahashi T, Ishikura H, Kato H, Tanabe T, Yoshiki T. Intra-pancreatic, extratumoral perineural invasion (nex). An indicator for the presence of retroperitoneal neural plexus invasion by pancreas carcinoma. *Acta Pathol Jpn*. 1992;42:99–103.
17. Schorn S, Demir IE, Reyes CM, et al. The impact of neoadjuvant therapy on the histopathological features of pancreatic ductal adenocarcinoma – a systematic review and meta-analysis. *Cancer Treat Rev*. 2017;55:96–106.