Clinical Investigation

Predictive Value of Neutrophils Count for Local Tumor Control After Chemoradiotherapy in Patients With Locally Advanced Pancreatic Carcinoma

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Purpose: Baseline neutrophil count may predict overall survival (OS) in patients with locally advanced pancreatic cancer (LAPC).
Methods and Materials: The international multicenter randomized LAP07 phase 3 trial has enrolled 442 patients with LAPC. We analyzed the prognostic value of both baseline neutrophilia (neutrophil count >7 g/L) and elevated or increasing neutrophil count as (1) neutrophilia or (2) increased absolute neutrophil count after induction chemotherapy versus baseline for OS, progression-free survival, and local control (LC). A Cox proportional hazard model was used to assess elevated or increasing neutrophil count status by randomly assigned treatment interactions for each endpoint.
Results: Among the 442 patients, 47 patients (11%) with baseline neutrophilia had worse OS (median 8.9 vs 13.3 months; $P =$ .01). After induction chemotherapy, among the 235 patients whose blood counts were available, 90 patients (38%) had elevated or increasing neutrophil count associated with poorer OS in univariate (median 14.4 vs 17.9 months; $P =$ .001) and multivariate analysis ($P =$ .004). Elevated or increasing neutrophil count was also predictive of a decreased benefit of chemoradiation therapy on LC. In 126 patients without elevated or increasing neutrophil count, 1-year LC was 80% in the chemoradiation arm versus 54% in the chemotherapy arm ($P <$ .001; interaction test $P =$ .015).
Conclusions: In this study, baseline neutrophilia and increased absolute neutrophil count were associated with worse OS in this large series of patients with LAPC. In addition, the counts were an independent prognosis factor and a strong predictive LC

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biomarker for chemoradiation therapy benefit. An assessment of neutrophils counts can help to improve the selection of patients who might benefit from chemoradiation therapy after induction chemotherapy. © 2021 Elsevier Inc. All rights reserved.

Introduction

Pancreatic cancer (PC) is one of the leading causes of cancer-related mortality worldwide.[1] Still, advances in patient management remain limited. Available data indicate that between 2003 and 2012, death rates from this cancer rose among both sexes.[1] At the time of diagnosis, up to 35% of patients present with locally advanced PC (LAPC)—that is, nonmetastatic but unresectable disease owing to the involvement of the adjacent arteries (TNM stage III).[2]

Despite new, more efficient chemotherapy regimens and advances in radiation therapy techniques, patients with LAPC have high rates of both distant metastatic and local progressions. Induction chemotherapy potentially facilitates the selection of patients with a better prognosis.[3,4] The management of LAPC after induction chemotherapy remains controversial, especially the role of chemoradiation therapy.[4-7] In the LAP07 phase 3 trial, patients without disease progression after 4 months of gemcitabine-based induction chemotherapy were randomized between 2 more cycles of chemotherapy or chemoradiation therapy at a dose of 54 Gy with concurrent capecitabine. Although chemoradiation therapy did not outperform chemotherapy alone in terms of overall survival (OS), chemoradiation therapy was associated with a better local control and a longer delay before reintroduction of chemotherapy at tumor progression.[5] Hence, a subset of patients with LAPC could benefit from chemoradiation, with a rate of secondary resection of 20% in recent series. One should interpret this high percentage with caution; indeed, distinguishing LAPC and borderline PC in some patients is difficult.[6,7] Biomarkers to predict OS, which help identify patients who require intensified induction regimens and those who could benefit from radiation therapy, are necessary.

Cancer-related inflammation enhances tumor initiation, proliferation, angiogenesis, and metastatic process while decreasing response to treatments.[8] It is also suspected to be a barrier to immune surveillance, particularly in PC.[9] This phenomenon is partially induced by tumor-derived granulocyte-macrophage colony-stimulating factor secretion. This secretion reduces the migration of $CD8^+$ T cells to cancer cells.[9,10] Each bone marrow−derived cell type (macrophages, mast cells, neutrophils, and lymphocytes) is involved in the tumor invasion process.[11] Being the most frequent type of white blood cells, neutrophils influence tumorigenesis and progression through secretion of cytokines, including interleukin (IL) 1, IL-8, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor α.[12]

A common pathway for PC development, progression, and chemotherapy resistance is a chronic inflammatory process that includes stroma formation.[13,14] Circulating blood neutrophils are reported to play a major role in tumor inflammation and immunologic reaction.[15] Until recently, the role of baseline and longitudinal changes in absolute neutrophil count in predicting sensitivity to chemotherapy has not been evaluated in patients with LAPC.

The present study aimed (1) to assess whether neutrophil count is able to predict OS in LAPC by analyzing the largest cohort of LAPC patients included in the LAP07 phase 3 study and (2) to evaluate the effects of elevated or increasing neutrophil count on the success of chemoradiation in terms of progression-free survival (PFS) or local control (LC).

Methods and Materials

Patients and tumors

We included the 442 patients with LAPC who were recruited in the LAP07 multicenter randomized phase 3 trial (NCT00634725). The LAP07 study assessed whether chemoradiation administered to LAPC patients whose tumor has been controlled after 4 months of gemcitabine alone or with erlotinib increases OS compared with continuation of the initial chemotherapy regimen (Fig. E1). The complete design and trial procedures of the LAP07 study were described previously.[5] Demographics, cancer history, and clinicopathologic, biologic, and imaging parameters at baseline and at the second randomization, as well as treatment outcomes, were collected.

Complete blood count analysis

In the current analysis, we used blood samples taken at the inclusion of patients and before any chemotherapy to define baseline biological inflammation. We define anemia as hemoglobin count <2 g/dL; thrombocytosis as platelet count >400 g/L; and neutrophilia as neutrophil blood count >7 g/L. To calculate increased absolute neutrophil count (IANC), we subtracted the baseline neutrophil count from the neutrophil count at the second randomization (chemoradiation vs chemotherapy), after induction chemotherapy. We define IANC as an increased absolute neutrophil count after induction chemotherapy, compared with the baseline count. We define elevated or increasing neutrophil count as neutrophilia or IANC, or both, after induction chemotherapy versus baseline.

Relationship between neutrophil counts and endpoints

We proceeded to a 3-steps analysis as follows:

1. Evaluating baseline neutrophilia as a prognostic factor for OS, PFS, LC, and distant metastases control (DMC) in all patients included in LAP 07 trial
2. Evaluating baseline neutrophilia and IANC, distinct and combined as "elevated or increasing neutrophil count," as a prognosis factor for OS, PFS, LC, and DMC in the population of patients selected for the second randomization (nonprogressive tumor after 4 months of induction chemotherapy)
3. Assessing elevated or increasing neutrophil count as a predictive factor for the treatment arm effect (ie, chemoradiation therapy or chemotherapy) on OS, PFS, LC, and DMC in the second randomization population.

Follow-up

Patients were observed at 2, 4, 7, 9, and 11 months after inclusion and every 2 months thereafter. Each follow-up visit included a detailed clinical history and a complete physical examination. The database was locked on February 23, 2014.

Statistical analysis

The characteristics of patients with or without elevated or increasing neutrophil count at baseline were compared using a Fisher test, a Wilcoxon-Mann test, Student t test, and variance analysis. Time-to-event endpoints correspond to the time between the date of the first randomization and the last follow-up or first event (time of death for OS, recurrence or death for PFS, local recurrence for LC, and distant metastasis for DMC) and are estimated using the Kaplan-Meier method. We used the log-rank test to compare time-to-event curves. Hazard ratio (HR) and 95% confidence interval (CI) were estimated with univariate analysis. The inflammation status by randomly assigned treatment interaction was assessed individually for each biomarker using a Cox proportional hazards model. This model was adjusted by randomly assigned treatment, inflammation status, or IANC (positive or negative). To evaluate the predictive association between inflammation and treatment efficacy (chemoradiation therapy vs chemotherapy only), we used an interaction test with a 5% threshold. Factors were considered as predictive for OS, PFS, or LC if the P value for their interaction term with the randomization arms (chemoradiation or chemotherapy) was <.05. $P < .05$ was considered significant.

Competing prognosis factors included in the multivariate analysis were age, pain, albumin, tumor size, and CA 19-9, in accordance with the PROLAP study.[16] The PROLAP nomogram has been developed from 442 patients with LAPC who were enrolled in the LAP07 trial, analyzing 30 baseline parameters, and was externally validated in a retrospective monocentric series including 106 patients. Age, pain, tumor size, albumin, and CA 19-9 were finally included in the nomogram that accurately predicted OS before initiation of induction chemotherapy in patients with LAPC.

We performed multivariate analyses using the variables with $P < .20$ in the univariate analysis, according to the Cox proportional hazards model. We performed the statistical analyses with R (version 3.3.2).

Results

Patients and outcome

We analyzed data from 442 patients with LAPC treated in the LAP07 trial between February 2008 and December 2011. The median follow-up time was 34.3 months (95% CI, 27.6-43.7). Among the 269 patients who underwent the second randomization, 236 patients (88%) had documented tumor progression at the time of the analysis, which was locoregional in 93 patients (39%), metastatic in 122 patients (52%), and of unknown type in 21 patients (9%).

Hemoglobin level and neutrophil and platelet counts at inclusion (baseline) were available in 439 patients (99%). Anemia was reported in 123 patients (28%), thrombocytopenia in 12 patients (3%), and neutrophilia in 47 patients (11%).

Among the 47 patients with baseline neutrophilia, 21 (45%) underwent the second randomization. Blood cell counts at the second randomization were available in 235 patients (87%). Anemia was present in 153 patients (65%), none (0%) had thrombocytopenia, 69 patients (29%) had IANC, and neutrophilia was observed in 7 patients (3%), 6 of whom had IANC and 1 of whom had baseline neutrophilia. Thus, 26 patients (55%) with neutrophilia at diagnosis had progressed during induction chemotherapy. However, neutrophilia was not significantly associated with disease progression after primary chemotherapy ($P = .46$).

At first randomization, 20 of 201 patients (9%) randomized in the chemotherapy arm had neutrophilia, compared with 27 of 191 patients (12%) in the chemotherapy + erlotinib arm ($P = .25$).

Among the patients included in the second randomization, 9 of 111 patients (7.5%) in the chemotherapy arm had neutrophilia at diagnosis, compared with 12 of 106 (10%) in the chemotherapy + erlotinib arm ($P = .46$). In addition, 2 of 117 patients (1.7%) in the chemotherapy group had neutrophilia at second randomization, compared with 5 of 113 (4.2%) in the chemotherapy + erlotinib group

Table 1   Clinical, biological, and histologic characteristics of the 235 patients studied according to baseline and secondary radiation versus chemotherapy randomization

Characteristics	Overall population second randomization* n = 235	Systemic inflammation[†]		
		No (n = 145)	Yes (n = 90)	P value
	n (%) or median [range]			
Patients characteristics at first randomization				
Age (y)	63 [31-81]	63 [31-81]	63 [41-81]	.554
Differentiation				
Poorly	14 (6%)	8 (6%)	6 (7%)	.143
Moderately	41 (18%)	30 (21%)	11 (12%)	
Well	60 (27%)	39 (26%)	21 (23%)	
Missing	115 (49%)	68 (47%)	52 (58%)	
Performance status				
0	113 (48%)	62 (43%)	51 (57%)	.072
1	111 (47%)	74 (51%)	37 (41%)	
2	11 (5%)	9 (6%)	2 (2%)	
Pain				
No	110 (47%)	67 (46%)	45 (50%)	.694
Yes	123 (53%)	78 (54%)	45 (50%)	
Tumor size (RECIST, mm)	40 [0-100]	40 [0-85]	39 [5-100]	.724
Biological characteristics at first randomization				
Neutrophil count (g/dL)	4.1 [2.40-27.9]	4.4 [1.5-6.9]	3.5 [2.4-27.9]	.016
Hemoglobin count (g/dL)	12.90 [9.0-159]	12.90 [9.0-17]	13.25 [9.0-159]	.100
Platelet count (g/L)	258 [100-759]	258 [113-537]	256 [100-759]	.974
Albumin (g/L)	38.9 [23.3-58]	39 [25-58]	38.1 [23.3-49]	.099
Biological characteristics at second randomization				
Neutrophil count (g/dL)	3.1 [0.5-17.3]	2.6 [0.5-5.7]	4.2 [1.9-17.3]	<.001
Difference versus baseline count	1.0 [−14.8 to 23.5]	1.5 [0.0-5.2]	−0.8 [−14.8 to 23.5]	<.001
Hemoglobin count (g/dL)	11.50 [8.5-119]	11.40 [8.6-16.40]	11.60 [8.5-119]	.092
Platelet count (G/L)	199 [9.3-655]	191 [9.3-655]	209 [54-595]	.017
Treatment characteristics				
Randomization set				
CT: gem.	61 (26%)	37 (26%)	24 (27%)	.030
CT: gem/erlo.	61 (26%)	29 (20%)	32 (35%)	
CRT: gem.	57 (24%)	38 (26%)	19 (21%)	
CRT: gem/erlo.	56 (24%)	41 (28%)	15 (17%)	

Abbreviations: CRT = chemoradiation; CT = chemotherapy; erlo. = erlotinib; gem. = gemcitabine.

* Patients with both neutrophil count available at first and second randomization.

[†] Systemic inflammation: baseline neutrophilia (neutrophil count > 7 g/L) or increased absolute neutrophil count between first and second randomization.

(P = .25). Patient baseline characteristics according to the cohort set are summarized in Table 1.

Prognostic value of blood count disorders for OS, PFS, LC, and DMC

Baseline neutrophilia
At the first randomization, patients with baseline neutrophilia had decreased OS (median 13.3 vs 8.9 months; P = .011; Fig. 1A). Baseline neutrophilia was not associated with PFS (P = .203), LC (P = .274), or DMC (P = .684). Anemia or thrombocytosis was not associated with OS (P = .098 and P = .118), PFS (P = .605 and P = .087), or LC (P = .065 and P = .234, respectively).

IANC and baseline neutrophilia
At the second randomization, we considered OS in 235 nonprogressive patients randomized in chemoradiation versus chemotherapy arms with available blood cell count.
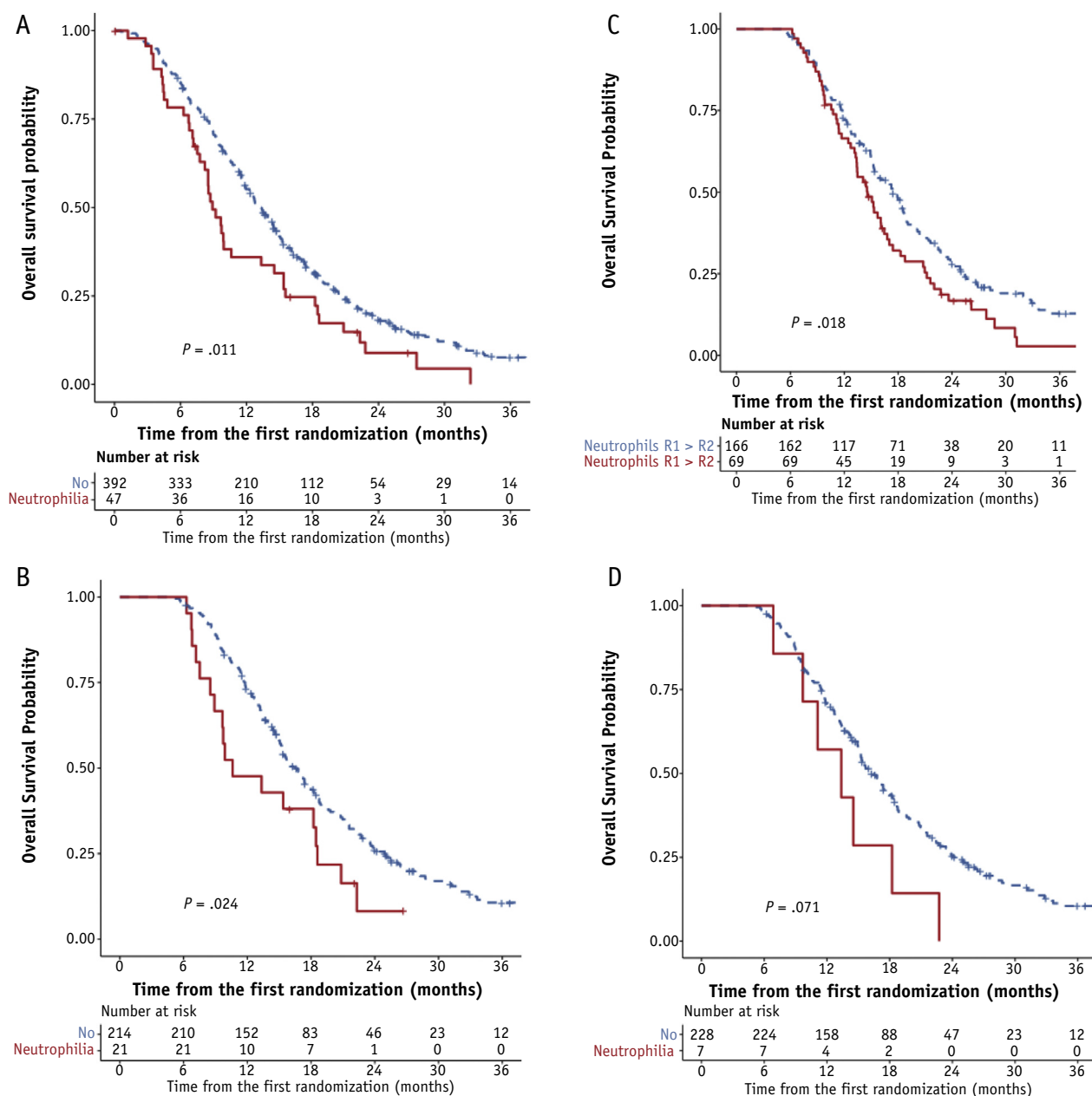
Fig. 1. (A) Estimated overall survival in all patients included according to baseline neutrophilia. (B) Estimated overall survival in patients at second randomization with or without baseline neutrophilia. (C) Estimated overall survival in patients at second randomization with or without increased absolute neutrophil count. Neutrophilia: neutrophil count >7 g/L at second randomization. *Abbreviation:* IANC = increased absolute blood count between first (R1) and second randomization (R2).

Baseline neutrophilia at first randomization still predicted worse OS ($P = .027$; Fig. 1B). Baseline neutrophilia was not associated with PFS ($P = .339$) or LC ($P = .065$) in this population. Neutrophilia at second randomization, present in 7 patients (3%), was not significantly related to OS ($P = .075$; Fig. 1C).

Patients with IANC had worse OS: median 14.6 months (95% CI, 13.4-16.8) in patients with IANC versus 17.4 months (95% CI, 15.3-18.9 months) in patients without IANC ($P = .018$; Fig. 1D). IANC was not associated with

PFS ($P = .281$) or LC ($P = .532$). Anemia at the second randomization was not related to OS, PFS, LC, or DMC ($P = .998$, $P = .528$, $P = .295$, and $P = .950$, respectively). No patient had thrombocytosis on the second randomization's blood count analysis.

In patients without IANC, PFS was not significantly improved in any treatment arm ($P = .052$; interaction $P = .343$; Fig. E2A). Considering the 166 patients without IANC at the second randomization, with LC evaluated in 145 patients, chemoradiation therapy significantly

improved LC compared with the chemotherapy arm ($P <$ .001, with an interaction term between IANC and the randomization arm $P =$ .014; Fig. E2).

In multivariate analysis, using prognostic factors identified in the PROLAP nomogram, elevated or increasing neutrophil count was independently associated with worse OS (HR, 1.59; 95% CI, 1.16-2.18; $P =$ .004; Table 2).[16]

Predictive value of elevated or increasing neutrophil count for chemoradiation versus chemotherapy on OS, PFS, and LC

In the population included in the second randomization, patients with neutrophilia or IANC were defined as having elevated or increasing neutrophil count, in addition to patients with baseline neutrophilia. Ninety patients (38%) had elevated or increasing neutrophil count, and 145 patients (62%) had none.

In the 235 patients with blood counts available, there was no significant difference between chemoradiation therapy versus chemotherapy alone in terms of OS or PFS ($P =$ .753 and $P =$ .053, respectively).

Elevated or increasing neutrophil count at the second randomization was related to a worse OS ($P <$ .001). Estimated 2-year OS was 31% (95% CI, 24%-40%) in patients without elevated or increasing neutrophil count versus 15% (95% CI, 9%-26%) in those with it ($P <$ .001; Fig. E3A). This result remained significant in the chemoradiation therapy arm ($P =$ .004), but not in the chemotherapy arm ($P =$ .054; Figs. E3B, E3C). Still, the interaction between elevated or increasing neutrophil count status and the randomization arm was not significant considering OS ($P =$ .266). There was no association between the randomization arm and survival in patients regarding elevated or increasing neutrophil count ($P =$ .276 and $P =$ .696, respectively).

Elevated or increasing neutrophil count at the second randomization was not significantly associated with PFS ($P =$ .123); this also holds when restricting the analysis to the chemoradiation therapy arm ($P =$ .055) and to the chemotherapy arm ($P =$ .961). In patients without elevated or increasing neutrophil count, PFS was significantly improved in the chemoradiation therapy arm: 10.3 months (95% CI, 9.2-12.9) versus 8.3 months in the chemotherapy arm (95% CI, 7.7-9.6; $P =$ .043; Fig. 2A). In patients exhibiting elevated or increasing neutrophil count, however, there was no significant difference in PFS between the 2 arms ($P =$ .930; Fig. 2B). Considering PFS, the interaction between elevated or increasing neutrophil count and the randomization arms was not significant ($P =$ .175).

In the overall population after the second randomization, elevated or increasing neutrophil count was not significantly related to LC ($P =$ .096). The absence of elevated or increasing neutrophil count, however, predicted superior efficacy of chemoradiation therapy compared with chemotherapy on LC (treatment by inflammation status interaction test $P =$ .015). In addition, elevated or increasing neutrophil count was associated with a poor LC

in the chemoradiation arm ($P =$ .021; Fig. E3D), but it had no influence on LC in the chemotherapy arm ($P =$ .640; Fig. E3E). In 126 patients without elevated or increasing neutrophil count, chemoradiation therapy significantly improved LC compared with only chemotherapy: 1-year LC was 80% in the chemoradiation therapy arm versus 54% in the chemotherapy arm ($P <$ .001; interaction between elevated or increasing neutrophil count and randomization arm, $P =$ .015; Fig. 2C). Conversely, in the 80 patients with elevated or increasing neutrophil count, there was no significant difference in LC between the chemoradiation therapy and chemotherapy treatments. DMC was not related to treatment arm ($P =$ .726) or elevated or increasing neutrophil count ($P =$ .883).

Discussion

Our results show an association between elevated or increasing neutrophil count (through neutrophilia) and worse OS in patients with LAPC. Combined with a prospective randomized phase 3 study, our results strongly suggest that an elevated or increasing neutrophil count has a predictive value for LC. Indeed, we observe an increased benefit from chemoradiation in patients without elevated or increasing neutrophil count.

Systemic inflammation is a significant indicator of poor prognosis in various types of cancers.[12] Their response markers have previously been studied in PC. One retrospective study including 321 patients with LAPC or metastatic PC correlated baseline leukocyte, neutrophil, and monocyte counts in addition to the neutrophil-to-lymphocyte ratio (NLR) with OS.[17] Another study retrospectively associated NLR and eosinophil-to-lymphocyte ratio with prognosis in patients with early-stage PC undergoing chemoradiation therapy.[18] Albumin-to-lymphocyte ratio and NLR were also retrospectively associated with lower OS in patients with LAPC treated with stereotactic body radiation therapy.[19] Still, the optimal NLR cutoff varies in these studies, typically from 2.5 to 5. NLR can be related to increased neutrophil count, decreased lymphocyte count, or both. A comparison with NLR in the LAP07 study was not possible because lymphocyte count was not available. Our current work on 439 patients settles baseline neutrophil count as a prognostic biomarker for OS in LAPC. It also shows that an increase in neutrophil count after 4 gemcitabine cycles is associated with a reduced OS in the 235 patients who had no evidence of tumor progression after this induction chemotherapy. Finally, we found a predictive association between absolute neutrophil count and local resistance to chemoradiation in patients with LAPC. This association was significant considering IANC ($P <$ .001; interaction $P =$ .014) and a composite score, "elevated or increasing neutrophil count," including patients with baseline neutrophilia or IANC ($P <$ .001; interaction $P =$ .015).

Table 2 Results of univariate and multivariate (Cox) analyses for overall survival regarding prognosis factors

	Overall Survival (235 patients after second randomization)					
	Univariate Cox analysis			Multivariate Cox analysis		
Variable	HR	95%CI	P	HR	95%CI	P
Chemoradiation (vs chemotherapy)	—	—	.754	—	—	—
Systemic inflammation (vs absence)*	1.65	1.23-2.21	.001	1.59	1.16-2.18	.004
Tumor size	—	—	.656	—	—	—
Pain (vs absence)	—	—	.966	—	—	—
Age	—	—	.224	—	—	—
Albumin	0.95	0.02-0.98	<.001	0.95	0.90-0.99	.035
CA 19.9	—	—	.255	—	—	—

Abbreviations: CI = confidence interval; HR = hazard ratio.

* Systemic inflammation: baseline neutrophilia (neutrophil count >7 g/L), neutrophilia or increased absolute.

PC has a unique and complex microenvironment consisting of fibroblasts and stellate, endothelial, endocrine, and immune cells.[17] Approximately 30% of patients with PC die of locally aggressive disease associated with the somatic *SMAD4/DPC4* genes status.[20] Smad proteins play a major role in the development of tumors, through the induction of angiogenesis and immune suppression, and are associated with poor OS.[21,22] A paradigm of antitumoral "N1 neutrophils" versus protumoral "N2 neutrophils" has been proposed, in which transforming growth factor β (TGF-β) blocks the switch from the "N2" to the "N1" antitumoral phenotype.[23,24] TGF-β signaling results in nuclear accumulation of active Smad complexes, which regulate transcription of target genes.[25] In addition to Smad4, expression of CD15$^+$ neutrophils in the immune profile within the microenvironment of pancreatic ductal adenocarcinoma has been associated with poor outcome after surgery.[26] Combining the findings of previous studies and our current work, "local resistance" to radiation therapy seems to be associated with neutrophilia, which suggests TGF-β as a potential target in patients with LAPC who are displaying systemic inflammation.

A number of tumors are known for aberrant production of growth factors, such as the granulocyte colony-stimulating factor (G-CSF), which includes PC. These tumors are more aggressive because of cytokine-mediated immune suppression and angiogenesis.[27] In PC patients, high expression of G-CSF has been associated with worse prognosis (pas de virgule) and early recurrence.[28] In addition, a significant correlation was observed between a high G-CSF expression and neural invasion. Elevated concentrations of G-CSF in PC stimulate myeloid cells (pas de virgule) and decrease T cell proliferation.[29] Therefore, neutrophilia could be an easily measurable reflection of a G-CSF−secreting tumor phenotype.

To our knowledge, no prospective study has yet evaluated the association between baseline neutrophilia and survival after gemcitabine induction chemotherapy in LAPC. Although other regimens are now often considered for LAPC, gemcitabine-based chemotherapy is frequently evaluated as a treatment option, making biomarker development in this setting clinically relevant.[14] FOLFIRINOX (5-fluorouracil [5-FU], irinotecan, and oxaliplatin) and the combination of gemcitabine and nab-paclitaxel are now standard chemotherapy regimens in metastatic PC. Only patients without cholestasis, however, are eligible for both these regimens.[30-32] FOLFIRINOX is currently compared with gemcitabine in patients with LAPC in the PRODIGE 29−UCGI 26(NEOPAN) phase 3 trial.[33] The results of the LAPACT phase 2 study are in favor of a good tolerance of the combination gemcitabine and nab-paclitaxel for patients with LAPC with an interesting efficacy.[34] In addition, a post hoc study revealed that the combination of gemcitabine and nab-paclitaxel versus gemcitabine alone improves OS, even in patients with high NLR.[35] A meta-analysis including 355 patients with LAPC treated with the FOLFIRINOX regimen reported a median OS of 24.2 months, longer than that described with gemcitabine (6-13 months).[32] In the LAP07 study, the chemotherapy regimen was gemcitabine based, with or without erlotinib. Among the 439 patients with blood count available, baseline neutrophilia was present in 11% and predicted poor OS. These findings suggest that patients with baseline neutrophilia require more intensive induction chemotherapy regimens when possible.

Inflammation, mediated by cytokines, the reactive oxygen species, plays a key role in the early development of PC.[36] PC risk factors such as diabetes, cigarette smoking, and obesity are also associated with systemic inflammation.[37] Chronic pancreatitis is a well-known risk factor for PC.[38] In addition, during the history of their disease, 70% to 90% of patients with LAPC will develop malignant distal biliary obstruction, transient cholecystitis, or jaundice, associated with poor short-term prognosis.[39] These elements could suffice to explain an increase in inflammation biomarkers, and a rise in circulating white blood cell count;
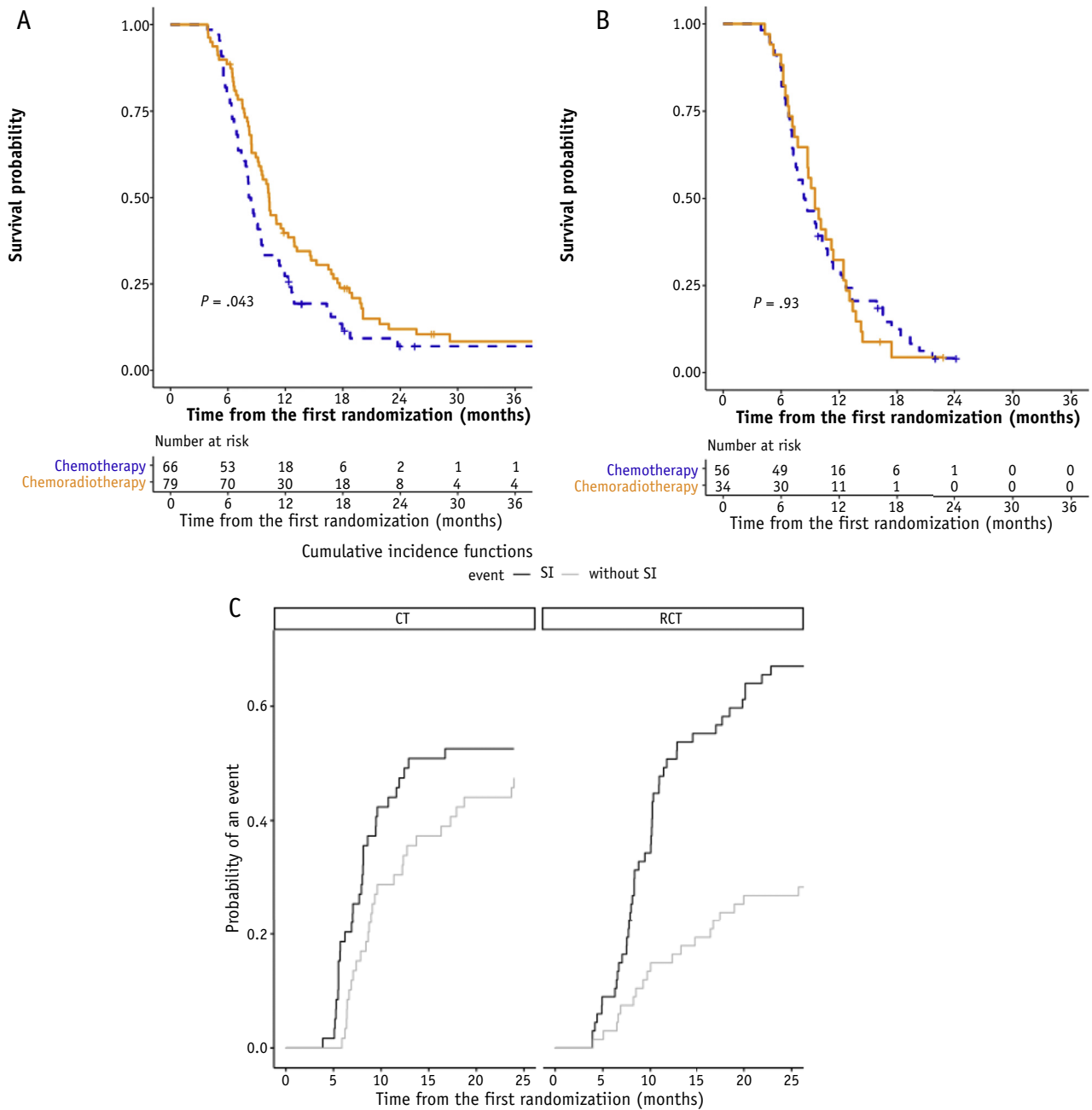
Fig. 2. (A) Kaplan-Meier curves of progression-free survival, according to the second randomization, in patients without systemic inflammation. (B) Kaplan-Meier curves of progression-free survival, according to the second randomization, in patients with neutrophilia or increased absolute neutrophil count. (C) Cumulative incidence curves of local relapses, according to the second randomization, in patients with or without systemic inflammation. Systemic inflammation: baseline neutrophilia (neutrophil count >7 g/L) at first randomization, or neutrophilia at second randomization, or increased absolute neutrophil count, after induction chemotherapy (between first and second randomization). *Abbreviations:* CT = chemotherapy arm; RCT = chemoradiation therapy arm; SI = systemic inflammation.

they were not recorded in the LAP-07 trial, however, thus preventing us from evaluating these confounding factors in the present study.

It is challenging to translate a given neutrophilia into a personalized prognosis or treatment plan.[40] Prospective longitudinal measurements of white blood count to an individual scaler is mandatory to maximize the clinical

usefulness of neutrophil scores.[40] Understanding how neutrophils are polarized and how they can be reprogrammed will be crucial in improving cancer therapies.[41] Neutrophil-targeting agents are being developed for the treatment of inflammatory and autoimmune diseases.[40] In patients with chronic obstructive pulmonary disease, CXCR2 antagonist decreases absolute neutrophil counts

and reduces biological inflammation and disease symptoms.[42] Inhibition of CXCL8−CXCR1/2 signaling by CXCL8 antibodies, or small molecules targeting CXCR1 and/or CXCR2, also decreases tumor growth and progression in tumor mouse models.[41] Clinical trials that assess reparixin, a CXCR1-CXCR2 inhibitor, in cancer treatment are ongoing.[40] Similarly, the CCL2−CCR2 chemokine axis is targeted to recruit tumor-associated macrophages to build an immunosuppressive tumor microenvironment.[43] CCR2-targeted drugs have been shown to be safe and efficient when used in combination with FOLFIRINOX in patients with PC.[43] Considering responses to radiation therapy, preclinical models reported both anti-Ly6G antibody-mediated neutrophil depletion associated with improved radiation therapy efficacy, whereas antibody-mediated depletion of $Gr1^+$ cells was not.[40] Thus, combining targeted radiation therapy with a neutrophil agonist can enhance antitumor immunity, triggering neutrophil-mediated tumor cell death.[24]

The strength of this study is the size of the sample with baseline and postinduction neutrophil counts available for analysis. The prognosis value of neutrophil count evolution after induction chemotherapy has not been evaluated previously. This is a valuable approach to understand the role of the neutrophil to stratify patients who should be treated with highly intensive induction regimens rather than gemcitabine alone. This work also shows a significant interaction between elevated or increasing neutrophil count and LC, with improved local outcome after chemoradiation in about two thirds of patients who had limited or no elevated or increasing neutrophil count after induction chemotherapy. Thus, this finding could help with selecting patients who might benefit from a secondary chemoradiation. Our study, however, has several limitations. First, it is a retrospective analysis from prospectively collected data. In addition, neither NLR nor genomic stratification could be assessed.[44] In addition, the absence of a validation cohort is a limitation. The number of patients included in the LAP07 trial did not allow us in this post hoc analysis to separate a derivation cohort and a validation cohort or to adjust for multiple comparisons, with Bonferroni type correction; this presents methodological limitations. Validation in a larger cohort of patients should be performed with the International Pancreas Database Program ARCAD metabase, which is currently under development. Moreover, despite a trend to a PFS benefit of chemoradiation in patients without elevated or increasing neutrophil count ($P = .043$), the nonsignificant interaction between elevated or increasing neutrophil count and the randomization arm ($P = .175$) prevents us from drawing conclusions on this point. Finally, despite a strong relationship between elevated or increasing neutrophil count and worse OS, there was no trend of survival benefit of using chemoradiation in patients without elevated or increasing neutrophil count.

Conclusion

This study assessed the prognostic value of neutrophilia at baseline on OS in patients with LAPC. Moreover, elevated or increasing neutrophil count can help to predict efficacy or resistance to chemoradiation in patients with LAPC, as well as local control of tumor. This routinely available biomarker could help with the decision to administer intensified chemotherapy schemes and to optimize chemoradiation indications.

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