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Prognostic and diagnostic potential of local and circulating levels of pentraxin 3 in lung cancer patients

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There is a well-established link between inflammation and cancer of various organs, but little data are available on inflammation-associated markers of diagnostic and prognostic clinical utility in pulmonary malignancy. Blood samples were prospectively collected from 75 resectable lung cancer patients before surgery and in a cohort of 1,358 high-risk subjects. Serum levels of long pentraxin 3 (PTX3) were determined by high-sensitivity ELISA. PTX3 immunostaining was evaluated by immunohistochemistry in cancer tissue. Serum PTX3 levels in the high-risk population were not predictive of developing subsequent lung cancer or any other malignancy; however, serum PTX3 values in patients with lung cancer were significantly higher compared with cancer-free heavy smokers. With a cutoff of 4.5 ng/ml, specificity was 0.80, sensitivity 0.69, positive predictive value 0.15 and negative predictive value 0.98. The receiver operating curve (ROC) for serum PTX3 had an area under the curve (AUC) of 83.52%. Preoperative serum PTX3 levels in lung cancer patients did not correlate with patient outcome, but high interstitial expression of PTX3 in resected tumor specimens was a significant independent prognostic factor associated with shorter survival ($p < 0.001$). These results support the potential of serum PTX3 as a lung cancer biomarker in high-risk subjects. Furthermore, PTX3 immunohistochemistry findings support the role of local inflammatory mechanisms in determining clinical outcome and suggest that local expression of PTX3 may be of prognostic utility in lung cancer patients.

Despite advancements in surgery, anesthesiology and the improvement of chemotherapy and radiotherapy regimens, the prognosis for clinically detected lung cancer remains dismal, with overall 5-year survival rates of 5–15%. Even with early-stage disease 30–40% of the patients ultimately relapse and die,[1] suggesting that sophisticated biological mechanisms affect their outcome that are not reflected by pathological stage alone. For such a reason, prognostic markers independent of stage are actively sought.

In the last few years, leukocyte counts and blood levels of several inflammation markers have been correlated with lung cancer prognosis[2] or investigated as lung cancer risk predictors.[3,4]

The role of inflammation in cancer pathogenesis and progression—that has long been investigated—includes the generation of reactive oxygen/nitrogen species and the secretion of cytokines, chemokines and proangiogenic factors.[5–8] In lung cancer, in addition to smoking—the predominant risk factor—inflammatory conditions such as chronic obstructive pulmonary disease,[9] pulmonary fibrosis and chronic lung infections[10,11] as well as polymorphisms of inflammatory genes[12] are all associated with an increased risk.

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What's new?

To examine the relationship between cancer and inflammation, the authors measured serum levels of pentraxin 3, a "cousin" of C-reactive protein, in patients with non-small cell lung cancer. Levels were significantly higher in patients as compared to high-risk cancer-free controls, supporting a role for pentraxin 3 as biomarker in lung cancer. Although serum levels did not correlate with clinical outcome, immunostaining of the inflammatory mediator in lung tissue was associated with shorter patient survival, underscoring the pathogenetic relevance of local inflammation in such disease.

Pentraxin 3 (PTX3) is a member of the pentraxin superfamily which includes C-reactive protein (CRP), involved in innate immune responses and inflammation.[13,14]

PTX3 differs from CRP in several aspects: gene organization, structure (that includes a 174-amino acid-long N-terminal domain coupled to the 200-amino acid-long pentraxin domain), inducing stimuli and recognized ligands.[13] Under physiological conditions, normal PTX3 blood levels are <2 ng/ml.[15]

Unlike CRP that is mainly released by hepatocytes, PTX3 expression is rapidly induced in a variety of mesenchymal and epithelial cell types, including myelomonocytic, endothelial and lung epithelial cells by numerous proinflammatory cytokines (*e.g.*, IL-1β, TNF-α), by tissue damage and by microbial moieties.[16–18]

Besides having an established role in innate immunity and in apoptotic cell removal,[13] PTX3 contributes in regulating inflammation and complement activation, and participates in tissue remodeling and angiogenesis.[16,19]

In the last 15 years, PTX3 has emerged as a candidate new marker of inflammation,[20,21] including cancer-related inflammation[22–24] for clinical use, as it better reflects local and systemic inflammatory processes compared with other inflammation markers.

This study was designed to investigate the possible role of PTX3 as a lung cancer risk–predictor in heavy smokers, and its diagnostic and prognostic value in clinical non-small cell lung cancer (NSCLC) amenable to surgical resection.

Methods

Patients

Three sets of patients were included: a cohort of high-risk, cancer-free male subjects aged 60–74 enrolled in a lung cancer early-detection trial with spiral CT between 2001 and 2006,[25] a group of screening-detected lung cancer patients and a group of consecutive non-small cell lung cancer patients admitted to our Thoracic Surgery Department between January 2009 and June 2010. Patients with small-cell lung carcinoma or carcinoid tumors, synchronous bilateral lung cancers and those who had received preoperative chemotherapy or radiotherapy were excluded.

Patients' demographics, smoking exposure, Charlson comorbidity scores, CT findings, disease stage, type and extent of surgical resection, histology and pathological stage of resected lung cancers, postoperative treatment and outcomes were reported.

Spirometry data were prospectively obtained from a random sample of 730 healthy participants and from all lung cancer patients upon admission for treatment.

Blood testing

In the screening trial population, blood samples were prospectively collected either at the time of enrolment or of subsequent screening rounds. In patients with clinically detected lung cancer, pretreatment blood samples were prospectively collected before surgical resection (Supporting Information file).

Pathology

All cases were reviewed by two experienced pathologists (MN and DR) and histological subtypes were defined according to the 2004 WHO classification.[26] Adenocarcinomas and non-small cell carcinoma cases, not otherwise specified, were reviewed according to the IASLC/ATS/ERS International Classification of Lung Adenocarcinoma.[27] In the case of disagreement, consensus readings were obtained and reported. Pathological stage was determined according to the TNM Staging Manual, 7th Edition.[1]

Lung tissues were fixed in 10% formalin and embedded in paraffin and initial histological diagnoses were performed by routine hematoxylin–eosin staining.

PTX3 immunohistochemistry was evaluated on the area with the most representative histological lesion. PTX3 staining distribution was analyzed both as extracellular stromal expression and cellular positivity. Quantification was performed separately for interstitial and cellular expression by a semiquantitative scale (from 0-negative to 3-high positivity). Normal lung parenchyma was used as control for normal expression (Supporting Information file).

Follow-up and endpoint ascertainment

After surgery, patients were seen on an outpatient basis every 4–6 months and received follow-up telephone interviews. Disease status was assessed by serial CT scans of the chest and other diagnostic testing as needed. Recurrence modality was classified as local, distant, combination of the former or new lung cancer, according to accepted criteria.[28] Causes of death were assessed by examining medical records, by interviewing family doctors or through death certificates. Follow-up cutoff date was 01 February 2015.

Table 1. General features of lung cancer patients

	All LC patients	Screening	Clinical	*p* Values
No. of subjects	110	47	63	
Male sex	99 (90.00%)	47 (100%)	52 (82.54%)	0.002
Age (mean ± SD)	69 ± 6	69 ± 4	69 ± 8	0.527
Never smokers	6 (5.45%)	0	6 (9.52%)	0.037
Pack-years (mean ± SD)	48 ± 26	54 ± 21	44 ± 28	0.063
Respiratory symptoms	77 (70.00%)	30 (63.83%)	47 (74.60%)	0.293
FEV1 [median (IQI)]	2.3 (1.85–2.66)	2.44 (1.97–2.92)	2.16 (1.77–2.58)	0.101
Charlson score [median (IQI)]	4 (3–5)	3 (3–5)	4 (3–5)	0.808
Previous malignancy[1]	15 (100)	4 (8.51)	11 (17.46)	0.262
NCSLC stage[2]				0.016
Stage I	61 (55.45%)	33 (70.21%)	28 (44.44%)	
Stage II	22 (20.00%)	8 (17.02%)	14 (22.22%)	
Stage III	25 (22.73%)	5 (10.64%)	20 (31.75%)	
Stage IV	2 (1.82%)	1 (2.13%)	1 (1.59%)	
NSCLC histology				0.060
AC, lepidic predominant	21 (19.09%)	14 (29.79%)	7 (11.11%)	
AC, nonlepidic	50 (45.45%)	16 (34.04%)	34 (53.97%)	
Squamous	32 (29.09%)	14 (29.79%)	18 (28.57%)	
Other[3]	7 (6.36%)	3 (6.38%)	4 (6.35%)	

[1]Four urinary tract, four prostate, two low-grade hematologic, two early head and neck, one early gastric cancer and two previous lung cancers.[27]
[2]Stage I includes stage IA and IB, stage II includes stage IIA and IIB and so forth.
[3]Adenosquamous carcinoma ($N = 2$), mucoepidermoid carcinoma ($N = 1$), large cell neuroendocrine carcinoma ($N = 3$), NSCLC NOS ($N = 1$).
Abbreviation: AC: adenocarcinoma.

Statistical methods

Data are presented as number and percentages, mean and standard deviation (SD), or median and interquartile interval (IQI) as appropriated. Proportion comparisons between groups were made by the χ^2 test, using the Fisher's exact test if necessary. For continuous variable differences in either group, the Wilcoxon test was used. Overall survival (OS) time was calculated from the date of surgery to the date of death or last contact. Disease-free survival (DFS) time was calculated from the date of surgery to the date of recurrence or of last contact. Survival curves were calculated by the method of Kaplan and Meier. In the whole surgical series, potential prognostic factors were analyzed by univariate Cox regression. All independent variables with $p < 0.1$ were included in a multivariate analysis. A $p < 0.05$ was considered significant. For all calculations Stata13 statistical package was used.

Results

Characteristics of the study groups

Cancer-free, high-risk subjects. In the screening group ($n = 1{,}358$), the average age was 64.7 (95% CI: 64.5–64.9), and average smoking exposure was 54.6 pack-years (95% CI: 40.7–68.5). Comorbidity data were available for 1,277 patients. Based on prescreening evaluation data, the predominant comorbidity was chronic lung disease in 427 (33.4%), cardiovascular disease in 227 (17. 8%), other in 82 (6.4%) and none in 541 (42. 4%).

Lung cancer patients. Overall, 110 patients harboring resectable non-small cell lung cancer were included in the analysis, while 32 clinically detected cases were excluded for the following reasons: 11 were eventually not resected, seven did not have primary lung cancer, six had synchronous bilateral cancers and eight had received preoperative chemotherapy. Age, smoking exposure, Charlson comorbidity scores and BMI values were comparable in screening and clinically detected lung cancer patients. All screening-detected patients were males per inclusion criteria.[25] Respiratory comorbidity was slightly more prevalent in the clinically detected group but the difference was not significant (Table 1).

Fifteen patients had a history of previous malignancy deemed cured at the time of inclusion in this study, including two previous lung cancers.[28]

A lobectomy was carried out in 84 cases (76%), while 14 patients (13%) underwent pneumonectomy and 12 patients (11%) underwent segmentectomy.

There was a significantly higher rate of stage I disease ($p = 0.01$) and of lepidic-predominant adenocarcinoma

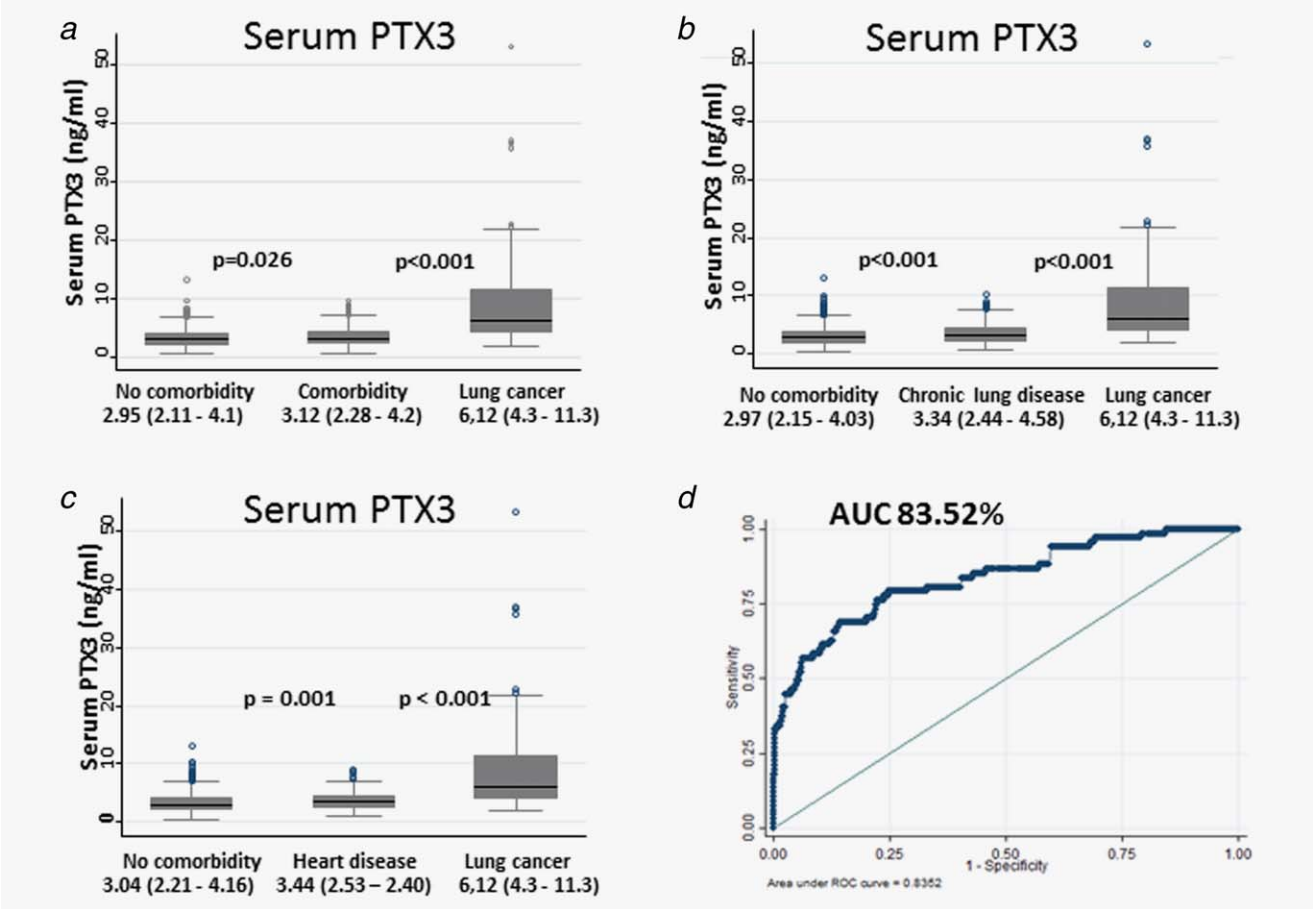

Figure 1. Circulating levels of PTX3 in high-risk cancer-free subjects and in NSCLC patients before surgical resection. (*a*) Lung cancer patients had significantly higher levels of PTX3 compared to cancer-free subjects, both with and without comorbidity. Cancer-free subjects with pulmonary (*b*) or cardiovascular (*c*) comorbidity had significantly higher circulating levels of PTX3 compared with subjects with no known comorbidity. Results are measured in ng/ml and are expressed as median values (interquartile interval). (*d*) Receiver operating curve (ROC) for PTX3. The AUC is 81.93%. With a cutoff value of 4.5 ng/ml, specificity for lung cancer is 0.80, sensitivity 0.67, negative predictive value 0.97 and positive predictive value 0.157. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

($p = 0.02$) in the screening group compared with the clinically detected cases, while nonlepidic adenocarcinoma was slightly more prevalent in the clinical series (Table 1), but no significant difference was observed in the prevalence of other histotypes. Lepidic-predominant adenocarcinomas were stage I disease in 86% of the cases.

Serum levels of PTX3 in cancer-free subjects compared with lung cancer patients

Serum levels of PTX3 were measured in 75 NSCLC patients before resection and in 1,358 cancer-free screening trial participants. We could not detect any significant relationship between smoking exposure and PTX3 serum levels in such a population (Pearson's correlation coefficient = 0.00032, $p = 0.992$).

Median preoperative serum PTX3 levels in lung cancer patients were significantly higher compared with cancer-free subjects, both with and without comorbidity ($p < 0.0001$, Figs. 1*a*–1*c*). The odds ratio for lung cancer with increasing serum PTX3 levels was 1.75 (95% CI: 1.56–1.97). The ROC curve for PTX3 had an AUC of 83.52% (Fig. 1*d*). With a cutoff value of 4.5 ng/ml, specificity for lung cancer was 0.80, sensitivity 0.69, negative predictive value 0.98 and positive predictive value 0.15.

There was no significant difference between serum levels of PTX3 according to histology ($p = 0.800$, Table 2) and pathological stage ($p = 0.918$).

PTX3 expression in lung cancer tissues

Immunohistochemical analysis was performed in 106 tumor samples (Table 2 and Fig. 2). In normal lung parenchyma, immunostaining for PTX3 was virtually absent, with only scattered weak staining in the interstitium of alveolar septa and perivascular spaces (Figs. 2*a* and 2*b*). PTX3 expression was rarely observed in the cytoplasm of metaplastic bronchial cells; no other cellular staining was found.

Tumor cell PTX3 staining was generally absent or weak, with low expression in 24 cases (23%) and moderate

Table 2. Serum levels of PTX3 and PTX3 immunostaining according to tumor histology

	All	AC, lepidic	AC, nonlepidic	Squamous	Other[1]
N	75	10	41	20	4
Serum PTX3 (ng/ml)[2]	5.3 (3.3–10.36)	6.07 (3.81–11.7)	5 (3.4–8.9)	5.75 (3.19–10.66)	5.13 (2.24–30.57)
Stromal staining					
N	106	20	48	31	7
0	38 (38.85%)	11 (55.00%)	23 (47.92%)	2 (6.45%)	2 (28.57%)
1	36 (33.96%)	6 (30.00%)	15 (31.25%)	11 (35.48%)	4 (57.14%)
2	21 (19.81%)	3 (15.00%)	6 (12.50%)	11 (35.48%)	1 (14.29%)
3	11 (10.09%)	0	4 (8.33%)	7 (22.58%)	0
Tumor cell staining					
N	106	20	48	31	7
0	79 (74.53%)	18 (90.00%)	40 (83.33%)	16 (51.61%)	5 (71.43%)
1	24 (22.64%)	1 (5.00%)	6 (12.50%)	15 (48.39%)	2 (28.57%)
2	1 (0.94%)	0	1 (2.08%)	0	0
ND	2 (1.89%)	1 (5.00%)	1 (2.08%)	0	0

[1]Adenosquamous carcinoma ($N = 2$), mucoepidermoid carcinoma ($N = 1$), large cell neuroendocrine carcinoma ($N = 3$), NSCLC NOS ($N = 1$).
[2]Median (interquartile interval, IQI).
Abbreviation: AC: adenocarcinoma.

expression in one case. Stromal PTX3 immunostaining of neoplastic areas was instead found in 68/106 cases (64%), with high expression in 11 cases (10%) and low-intermediate expression in 57 cases (54%; Table 2).

Stromal PTX3 expression and distribution varied according to tumor histotype. In lepidic-predominant adenocarcinomas ($n = 20$) stromal PTX3 staining was found in nine cases (45%), none of whom had high expression (Figs. 2*c* and 2*d*). Nonlepidic adenocarcinomas expressed PTX3 in a more variable fashion: 49% were negative on immunostaining, 33% expressed low or intermediate levels but four (8%) had high expression (Figs. 2*e* and 2*f*). In squamous carcinomas, PTX3 staining in the stroma was instead present in almost all cases (29 of 31), and it was low or moderate in 22 (71%) and high in seven (21%) (Table 2, Figs. 2*g* and 2*h*).

Survival analysis—PTX3 expression in lung cancer tissues independently correlates with treatment outcome

As of February 2015, median follow-up time was 49 months (range 0–164) for all lung cancer patients, 84 months (1–164) for screening-detected cases and 44 months (0–71) for clinically detected cases. Fifty-eight patients experienced lung cancer recurrence, 30 of whom died of cancer progression. In addition, six patients died of perioperative complications, six of other cancers and 12 of other causes.

Median DFS was 53 months for all patients, 113 months for screening cases and 27 for clinically detected patients, while median OS was 88 months, 113 for screening patients and 47 for clinical cases.

At univariate analysis, the Charlson comorbidity index, percent forced expiratory volume in 1 sec (FEV1%), circulating hemoglobin levels, disease stage, nonlepidic-predominant histology, tumor grade and interstitial PTX3 expression significantly correlated with DFS, while respiratory comorbidity, Charlson index, circulating hemoglobin levels, tumor stage and grade, nonlepidic-predominant histology, preoperative serum levels of PTX3 and high interstitial PTX3 expression significantly correlated with OS.

At multivariate analysis only the Charlson index, disease stage and tumor stromal expression of PTX3 were significantly related with DFS, while respiratory comorbidity, Charlson score, stage and interstitial PTX3 expression retained a significant correlation with OS (Figs. 3*a* and 3*b* and Table 3).

Lack of predictive potential of PTX3

As of May 2013, after a median FU of 106 months (range 3–140), 79 high-risk subjects had developed lung cancer and 127 had developed a nonpulmonary cancer. No significant association was found between PTX3 serum levels and the risk of subsequently developing lung cancer or any other malignancy (Supporting Information Figs. 1A and 1B).

Discussion

PTX3 has been identified in the cancer microenvironment where it plays an antitumor role by counteracting tumor-promoting inflammation.[16,22,24,29]

In this study, we have investigated a possible role of PTX3 as a candidate biomarker in NSCLC, both for risk prediction

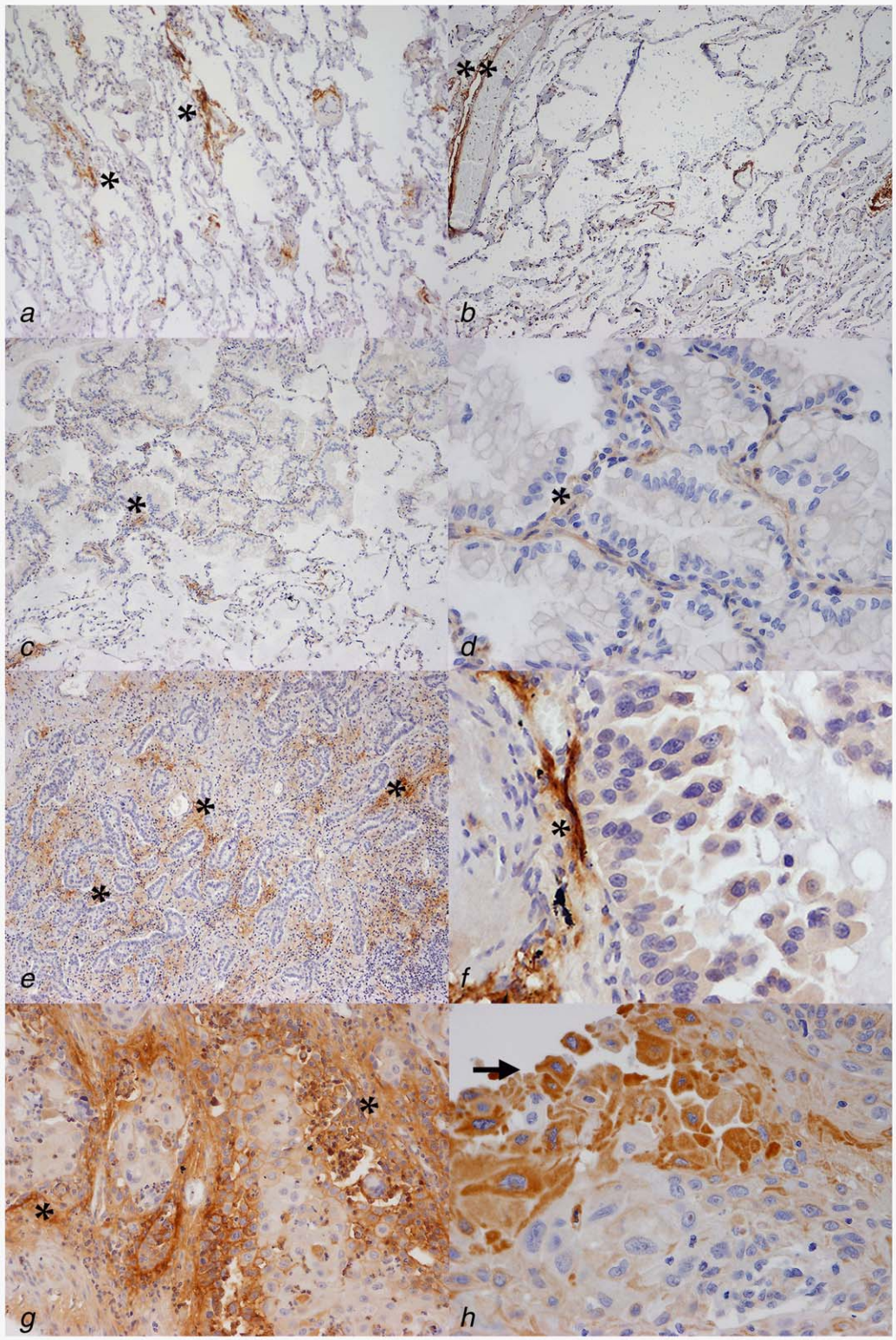

Figure 2. PTX3 immunostaining (brown color). PTX3 extracellular expression in the interstitium (*) and perivascular spaces (**) of normal lung parenchyma (*a* and *b*), lepidic-predominant adenocarcinoma (*c* and *d*), nonlepidic adenocarcinoma (*e* and *f*) and squamous carcinoma (*g*). PTX3 expression in the cytoplasm of neoplastic cells in a case of squamous cell carcinoma (arrow, *h*). (*a*, *c*, *e*, *g*) ×10 OM; (*b*, *d*, *f*, *h*): ×40 OM. PTX3, immunohistochemistry; DAB, hematoxylin counterstaining.

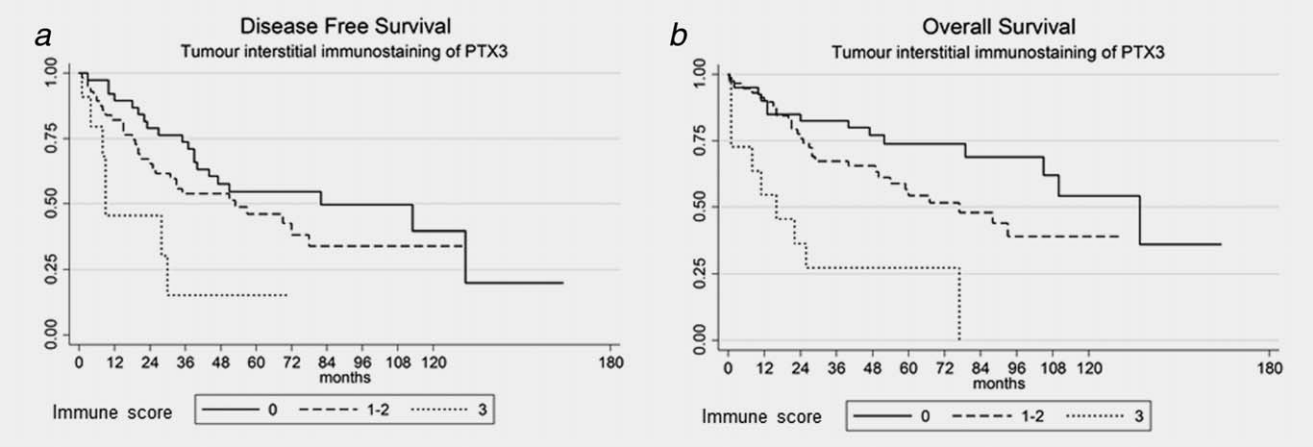

Figure 3. Tumor interstitial immunostaining of PTX3 correlates with patient survival. High expression of PTX3 immunostaining (score 3) is significantly associated with: (*a*) shorter disease-free survival ($p < 0.001$) and (*b*) shorter overall survival ($p < 0.006$).

and for clinical purposes, and we show that both systemic and local levels of PTX3 are increased in lung cancer patients.

In our control group of high-risk cancer-free subjects as well serum mean values of PTX3 were higher than normal values,[15] possibly reflecting highly prevalent smoking-related comorbid conditions such as chronic bronchitis and peripheral vascular disease in such a population. Indeed, a statistically significant correlation was observed between elevated PTX3 serum levels and chronic respiratory and cardiovascular diseases, confirming the results obtained in previous studies.[30–33]

Interestingly, we could not detect any significant relationship between smoking exposure and PTX3 serum levels; with a median age of 64 years and a median smoking exposure of 45.0 pack-years[25] our male-only screening trial cohort is however not fully representative of all smokers, and a correlation might be identifiable by including younger subjects of either sex and wider variations of smoking exposure levels in future studies.

As only the main comorbidities were specifically recorded in the high-risk cohort, some subjects may have harbored rheumatoid arthritis or other chronic inflammatory diseases that could not be investigated as to their relationship with circulating PTX3 levels. However, their number would be very small, as the prevalence of rheumatoid arthritis in the general population is below 1%.[34]

Our data show for the first time that intratumor high expression of PTX3 independently correlates, in a multivariate analysis, with DFS and OS after potentially curative resection of NSCLC.

On the other hand, our data do not support this biomarker as a lung cancer predictor in high-risk cancer-free subjects, as there was no difference in serum PTX3 levels between subjects who eventually developed a pulmonary malignancy and those who did not.

The systemic increase of PTX3 in lung cancer patients has been previously described. In one study by Diamandis *et al.*,[23] 203 lung cancer patients with any disease stage and 223 high-risk controls were included. The AUC for the ROC curve was 0.67. In the study by Zhang *et al.*,[35] performed in a larger cohort, the AUC for the ROC curve was 0.823. In our study, the AUC for the ROC curve was 0.8352. A cutoff value of 4.5 ng/ml effectively ruled out lung cancer in 97.7% of the cases, supporting the value of PTX3 as a potential lung cancer biomarker. If confirmed, such findings may also be of clinical use when dealing with CT-detected undetermined pulmonary nodules.

Pathologically, PTX3 expression, which was virtually absent in the normal lung interstice, was also absent or low in lepidic-predominant adenocarcinomas, in which tumor cells initially line the alveoli with little or no stromal invasion and present as subsolid nodules on CT. These tumors tend to have a relatively unaggressive clinical course and have very high cure rates after surgery.[36]

Instead, nonlepidic-predominant adenocarcinomas that behave more aggressively expressed stromal PTX3 in a variable fashion, and squamous cell carcinomas that tend to have the fastest growth rate among non-small cell lung cancers[37] very often expressed stromal PTX3 at moderate or high levels in our series (Fig. 2 and Table 2).

The preferential expression of PTX3 in the stroma, rather than in neoplastic cell components, is in agreement with recent findings indicating that PTX3 gene is epigenetically modified and silenced in cancer cells.[29] In conclusion, it can be hypothesized that PTX3 immunostaining in the stroma reflects the activation of an inflammatory program associated with tumor expansion, and that high PTX3 expression is associated with a more aggressive clinical course and may be prognostically useful.

Our data also suggest that low circulating levels of PTX3 are associated with a very low risk of harboring lung cancer;

Table 3. Univariate and multivariate Cox analysis

	Disease-free survival				Overall survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*p* Values	HR (95% CI)	*p* Values	HR (95% CI)	*p* Values	HR (95% CI)	*p* Values
Sex (M)	1.943 (0.605–6.240)	0.265	–		1.053 (0.375–2.951)	0.922	–	
Age	0.997 (0.953–1.043)	0.901	–		1.065 (1.013–1.121)	0.014	–	
Respiratory comorbidity	1.494 (0.827–2.698)	0.184	–		2.181 (1.087–4.376)	0.028	2.134 (1.004–4.537)	0.049
FEV1%	0.986 (0.973–0.998)	0.024	–		0.988 (0.976–1.000)	0.051	–	
Circulating hemoglobin	0.832 (0722–0.958)	0.011	–		0.831 (0.718–0.962)	0.013	–	
Charlson index	1.253 (1.080–1.453)	0.003	1.239 (1.056–1.454)	0.008	1.358 (1.204–1.533)	<0.001	1.479 (1.258–1.738)	<0.001
Subsolid nodule density	0.497 (0.243–1.014)	0.055	–		0.176 (0.055–0.567)	0.004	–	
Tumor histology								
AD, lepidic predominant	1				1			
AD, nonlepidic	2.749 (1.210–6.247)	0.016	–		3.234 (1.1083–9.446)	0.032	–	
Squamous	2.342 (0.960–5.718)	0.062	–		4.886 (1.662–14.36)	0.004	–	
Other	1.706 (0.439–6.630)	0.441	–		4.952 (1.325–18.50)	0.017	–	
Tumor grade								
1	1				1			
2	1.761 (0.793–3.989)	0.164	–		1.870 (0.775–4.516)	0.164	–	
3	2.430 (1.141–5.178)	0.021	–		2.559 (1.101–5.945)	0.029	–	
Tumor Stage								
Stage I	1		1		1		1	
Stage II	3.801 (1.995–7.240)	<0.001	3.515 (1.808–6.832)	<0.001	3.035 (1.468–6.279)	0.003	2.582 (1.165–5.723)	0.019
Stage III	3.909 (2.031–7.523)	<0.001	4.068 (2.078–7.965)	<0.001	4.607 (2.326–9.126)	<0.001	6.419 (2.966–13.89)	<0.001
Stage IV	4.560 (1.060–19.61)	0.041	5.241 (1.136–24.18)	0.034	4.555 (1.044–19.85)	0.044	6.892 (1.331–35.69)	0.021
Serum CRP	0.968 (0.904–1.035)	0.341	–		0.998 (0.948–1.050)	0.925	–	
Serum PTX3	1.009 (0.977–1.042)	0.580	–		1.034 (1.003–1.065)	0.003	–	
Interstitial PTX3 score								
0	1		1		1		1	
1 + 2	1.345 (0.758–2.388)	0.311	1.363 (0.744–2.497)	0.317	1.869 (0.929–3.760)	0.079	1.840 (0.846–4.004)	0.124
3	3.464 (1.428–8.402)	0.006	4.386 (1.738–11.07)	0.002	5.940 (2.425–14.55)	<0.001	8.534 (3.145–23.16)	<0.001

Abbreviations: FEV1%: percent forced expiratory volume in 1 sec; AD: adenocarcinoma.

measurements of systemic PTX3 levels may be a useful complement in LDCT screening. Further research will help establish its clinical utility in such a setting.

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