

Intra-tumoral vascular or perineural invasion as prognostic factors for long-term survival in early stage non-small cell lung carcinoma[☆]

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Abstract

Objective: In recent studies focusing on the prognostic significance of histologic features of NSCLC tumors, vessel invasion was correlated to survival across all surgical stages. We similarly analyzed whether intra-tumoral permeation could affect survival in subgroups of stage I and II NSCLC. **Methods:** A retrospective single institution analysis of a prospectively computed database. Specimens were analyzed for intra-tumoral vascular, lymphatic and nervous permeation. Overall mortality was determined and for each stage, a Cox regression analysis of selected variables was performed. Detailed histologic information was available in all patients. Follow-up was 100% complete (median = 69 months). **Results:** From 1989 to 2004, out of 346 patients with stage I and II NSCLC, 253 patients with p stage I (75.7%) and 81 patients with p stage II (24.3%) underwent surgery with complete resection, for a completeness resection rate of 97% (334/346). We performed 70 pneumonectomies, 255 lobectomies and 9 lesser resections (respectively, 21%, 76.3% and 2.7%). In-hospital mortality was 2.1%. The incidence of intra-tumoral permeation was 14.4% (48/334). Permeation correlated both with T status ($p = 0.04$), grade of differentiation ($p = 0.03$) and stage ($p = 0.02$). Median survival and overall 5-year survival for patients with and without permeation were 42.3 months (95% CI [20–64.6]) and 72.1 months (95% CI [56.9–87.2]), respectively; and 44% and 54%, respectively ($p = \text{NS}$). However, intra-tumoral permeation was not a significant predictor for overall death (HR = 1.1 [95% CI = 0.74–1.66]). **Conclusion:** In this large institutional study of early stage NSCLC, the presence of intra-tumoral permeation was correlated both to T, grade of differentiation, as well as to stage. However, in contrast to recent reports, we did not find that intra-tumoral permeation adversely affects long-term survival.

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1. Introduction

The most recent data available in stage Ib and stage II patients arises from the JBR.10 Trial where 5-year survival rates were 69% and 54%, whether or not cisplatin-based adjuvant chemotherapy was given, in those selected groups of NSCLC patients [1]. Those results have defined the current standard of practice in early stage lung cancer patients. Despite all efforts, there still remains a 30–50% cancer-related death rate that forces us to better understand tumor behavior. From Martini et al.'s [2] studies in the 90s, we have learned that recurrence in early NSCLC

(overall rate of 55%) was mostly due to distant metastasis (79%) while locoregional recurrence was present in only 21% of patients.

Several prognostic factors for recurrence have been identified.

Among others factors that characterized tumor behavior, histological features of tumor 'aggressiveness' (vessel invasion, permeation) have been widely investigated across all stages. Tumor vascular invasion can be venous, arterial or lymphatic, while nervous invasion is most often localized to the perineural area. The prognostic value of tumor permeation has already been demonstrated both in breast [3], colorectal [4] and head and neck cancers [5].

Though sometime contradictory in lung cancer studies, most authors have accepted a positive correlation between those histological features and survival [6–10].

For the very early stage patients, if proven accurate, such postoperative pathological sub staging could help in identifying

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groups of patients most at risk for recurrence or metastasis and therefore might guide clinicians in using adjuvant chemotherapy.

The purpose of this single-center study was to assess the prevalence of tumor permeation at large in a selected subgroup of completely resected patients with pathologically proven stage I or II NSCLC, and then to assess its prognostic significance with respect to cancer recurrence and patient survival.

2. Material and methods

2.1. Patients characteristics

From December 1989 to December 2004, 489 patients were operated on in our institution for primary NSCLC. Out of those, 346 tumors were stage I and II after pathological staging according to the last revisions in the international system for lung cancer staging [11].

Resection was classified R0 (macro- and microscopically complete) in 334 patients (97%), R1 (microscopically incomplete) in 12 patients (2.1%), including five positive bronchial margins. No patient was classified R2 (macroscopically incomplete) [12]. We selected for this survival analysis only the 334 patients who had a complete (R0) resection. There were 55 females and 279 males included in the study. Their clinico-pathological data are summarized in Table 1. For this study, to avoid a potential confounding effect of adjuvant chemotherapy, data inclusion was closed in 2004 since it is only after the publication of the IALT trial results [13] that adjuvant chemotherapy became standard practice in our group for all suitable stage Ib and II patients.

The Committee on Human Rights in Research (Institutional Review Board) of Cliniques Universitaires Saint-Luc approved this study.

Table 1
Characteristics of patients with complete resection ($n = 334$)

	N patients
Mean age (range)	63.7 (35–88)
Male–female	279–55
p stage	
Ia	128
Ib	125
IIa	25
IIb	56
Surgical resection	
Pneumonectomy	70
Lobectomy/bilobectomy	255
Segmentectomy/wedge	9
Mean number of LN	14.1
Histology	
Squamous	168
Adenocarcinoma	152
Undifferentiated carcinoma	14
Tumor permeation	
Vascular	48
Lymphatic	35
Perineural	10
	9

2.2. Surgical strategies

The surgical procedures consisted of 237 lobectomies (70.9%), 18 bilobectomies (5.4%), and 70 pneumonectomies (21%). Segmentectomy was performed in one patient and wedge resection was performed in eight patients. Indications for lesser resection (2.7%) were limited pulmonary reserve in all cases.

Complete homolateral mediastinal lymph node dissection was performed in all cases and node stations were labelled according to the American Thoracic Society guidelines [14]. There were 4430 lymph nodes available for pathological examination with a mean number of 14.1 resected lymph nodes per patient (SD 9.9).

2.3. Pathologic evaluation

Tumor was evaluated in all 334 patients according to the World Health Organization 1999 classification for NSCLC both for histology and grade by one of the authors (B.W.) [15]. After localization and size measuring, the specimens were initially planed with a cryostat, serially sectioned (3–4 mm) and embedded, followed by standard hematoxylin and eosin staining. All resected lymph nodes were either formalin fixed (later period) or Bouin fixed (earlier period). The sections were then analyzed with special attention given to intra-tumoral evidence of tumor invasion to vascular vessels, lymphatics, and neural structures. Tumor vascular invasion (artery, vein or lymphatic) was defined as tumor cells infiltrating the vessels directly or neoplastic thrombosis of the vessel. The presence of neural invasion was defined as tumoral involvement of the epineurium at least.

2.4. Selection of predictor variables

Predictor variables studied for their potential impact on prognosis were age, sex, the histology of the tumor, the grade of differentiation, T status, N status, disease's pathological stage, the presence or absence of vessel and/or perineural permeation and the type of resection.

2.5. Data collection and patient follow-up

All the information necessary for the study was collected from the patient operative reports, the hospitalization charts and our thoracic surgery database. Follow-up was completed from 09/2006 until 05/2007 and was done through contacts with the referring pulmonary physician, the primary care physician or patient's family when appropriate. Survival data were cross-checked with the national registry database. As for survival, follow-up was 100% complete until closure of the study. However, a precise cause of death was only available in 119/185 reported deaths and only those patients were analyzed in term of cancer-free survival.

2.6. Statistical analysis

Survival was calculated from the date of the first surgery to the date of follow-up (or death). For patients presenting recurrences, the number of days was calculated from the date of pulmonary resection to the first documentation of

either locoregional or distant recurrence. For cancer-free survival, patients still alive free from cancer and patients who died from cancer-unrelated causes were censored at the time of either follow-up or death.

For analysis of descriptive statistics and categorical variables, Chi-square or Fisher's exact test were used as appropriate whereas for analysis of continuous variables, Student's *t*-test was used. Survival analysis was performed according to Kaplan–Meier method. Univariate analysis by the log rank test and Cox regression model were used to compare survival, identify predictors of death and calculate hazard ratio. The level of statistical significance was set at a *p* value < 0.05. All statistical analyses were performed with SPSS version 14.0 software (SPSS, Inc., Chicago, IL)

3. Results

3.1. In-hospital mortality and 90-day mortality

Overall 30-day mortality was 2.1%, causes of death were cardiac (*n* = 2), ALI/ARDS (*n* = 3), sepsis (*n* = 2, including one BPF). Extending our short-term follow-up to report our 90-day mortality, we encountered 11 additional deaths, for an overall 90-day mortality of 5.4%. Again, patient demise was attributed to BPF in four patients, to pneumonia in three patients, to pulmonary embolism in two patients and to cardiac failure and to sepsis in one patient each.

As described in Section 2, only completely resected patients were selected for prognostic factor analysis.

Histology revealed squamous cell carcinoma in 168 patients (50.3%), adenocarcinoma in 152 patients (45.4%) and undifferentiated carcinoma in 14 patients (4.3%). According to the grade of differentiation, there were 115 well differentiated (34.4%), 162 moderately (48.5%) and 57 poorly (17.1%) differentiated tumors.

3.2. Intra-tumoral permeation

Overall, 48 patients (14.4%) were diagnosed to have intra-tumoral vessel or perineural permeation and 286 patients had none. The most frequent type of permeation found was vascular permeation (*n* = 35), followed by lymphatic permeation (*n* = 10) and perineural (*n* = 9). A few patients had more than one type of intra-tumoral permeation. We tried to identify clinico-pathological factors that positively correlated to the presence of intra-tumoral permeation. As shown in Table 2, neither the mean age nor the mean tumor diameter of the group of patients with permeation significantly differed from the 286 patients without permeation. No significant correlation was found between tumor permeation and sex, or between node-positive and node-negative patients.

Analyzing the T factor, we found that a much higher percentage of patients had tumor diameter greater than 3 cm in the intra-tumoral permeation group (62.5%) than in the group without permeation (47.1%) (*p* = 0.04).

Other statistically significant positive correlations were found for tumor pathological stage (*p* = 0.02) and for the grade of differentiation (*p* = 0.03). Indeed, the higher the stage or the lower the tumor differentiation, the higher the prevalence of intra-tumoral permeation.

Table 2
Correlation between clinico-pathological data and tumor permeation

	Permeation group (<i>n</i> = 48)	No permeation group (<i>n</i> = 285)	<i>p</i> value
Age (Mean ± SD)	63.6 ± 9.2	63.7 ± 11.2	
% Male	81.3	83.9	
Mean tumor diameter	4.1 ± 2	3.8 ± 2.4	
Less or equal to 3 cm	18	153	0.04
Greater than 3 cm	30	133	
Nodal status			
N0	34	223	0.14
N1	14	55	
Histology			
SCC	25	143	0.72
AdC	22	130	
Undifferentiated	1	13	
Grade of differentiation			
Well	10	105	0.03
Moderate/poor	38	181	
Stage			
I	30	223	0.02
II	18	63	

3.3. Predictors of overall survival (Table 3)

At a median follow-up time of 69 months, a total of 149 patients were still alive, whereas 185 patients had died.

By univariate analysis, we found that sex, T factor (both with cut-off of 3 cm and 2 cm), N factor, p stage, and type of resection were significant prognostic factors of survival.

The 5-year actuarial survival for female and male were 61.6% and 50.6%, respectively. Node-negative and node-positive (as stage I and II) patients had a 5-year survival of 56.2% and 39.9%. Finally, patients who underwent a lobectomy had a better 5-year survival than those with pneumonectomy (58.3% vs 31.5%).

As shown in Fig. 1, the 3- and 5-year overall survival were 64.5% and 53.7% for those patients without permeation, and

Table 3
Hazard ratio for overall mortality by univariate analysis

	β	H.R.	95% CI		<i>p</i> value
			Low	Up	
Sex (male relative to female)	0.441	1.55	1	2.41	0.048
Histology (relative to SCC)					
Adenocarcinoma	−0.040	0.96	0.71	1.29	0.79
Undifferentiated carcinoma	0.322	1.38	0.69	2.74	0.35
Grade of differentiation					
Moderate/poor	0.02	1.02	0.75	1.38	0.89
T factor					
Greater than 3 cm	0.606	1.83	1.37	2.45	<0.001
Greater than 2 cm	0.674	1.96	1.35	2.84	<0.001
N factor					
Node positive	0.423	1.53	1.09	2.13	0.01
Stage (stage II relative to stage I)	0.409	1.5	1.09	2.06	0.01
Intra-tumoral permeation	0.103	1.11	0.74	1.66	0.61
Type of parenchymal resection					
Pneumonectomy (relative to lobectomy)	0.738	2.09	1.52	2.86	<0.001

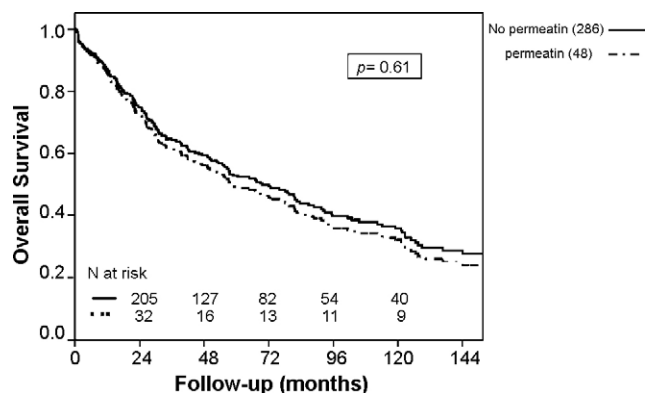


Fig. 1. Overall survival in patients with (dotted line) and without (plain line) intra-tumoral permeation ($n = 334$).

60.3% and 44% for patients with tumor permeation. The median survival time for the former (72.1 months) was nearly twice as long as the one for patient with permeation (42.3 months). However, by Cox univariate analysis, tumor permeation was not found to be a significant factor of survival (HR 1.11, 95% CI [0.74–1.66]).

3.4. Predictors of cancer-free survival (Table 4)

Among the 334 patients, 149 patients were alive at completion of follow-up. Detailed cause of death was available in 119 patients out of the 185 deaths (64%) that were recorded through the national registry database. Analysis of cancer-free survival focused on those 268 patients (80.2%) for which complete information on the cause of death was available.

By univariate analysis, we found that T factor (both with cut-off of 3 cm and 2 cm), N factor, p stage were significant prognostic factors of cancer-free survival.

As shown in Fig. 2, tumor permeation was again not a significant factor of cancer-free survival, with 3- and 5-year disease-free survival of 81.4% and 77.9% for those without

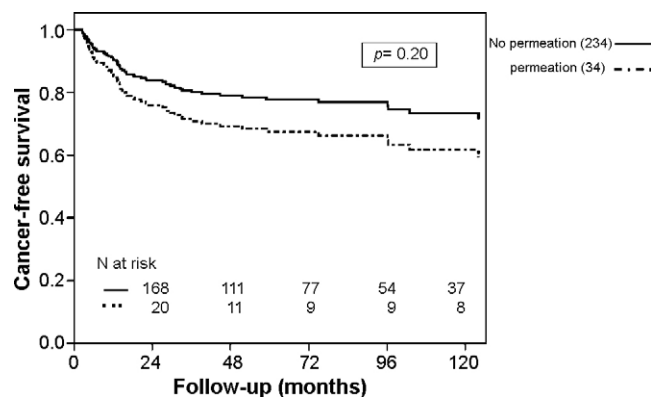


Fig. 2. Cancer-free survival in patients (dotted line) and without (plain line) intra-tumoral permeation ($n = 268$).

permeation, and 66.1% at 3- and 5-year for patients with tumor permeation. The median cancer-free survival time was 46 months for patients without permeation and 30 months for those with permeation. Analysis of the subgroup with stage I disease ($n = 208$) revealed a median cancer-free survival time of 48 and 31 months, respectively ($p = 0.29$).

4. Discussion

In this study, the overall prevalence of intra-tumoral vessel permeation was found to be 14.4%, mainly represented by vascular permeation (10.5%), followed by lymphatic and perineural permeation (about 3% each). This prevalence is in agreement with the one found in a recent study by Khan et al. [10] (10.2%), but much lower than other published studies in which prevalence of 25% [6,9,16,17] or even as high as 40% were reported [18].

Thus the literature review reveals that a wide variation in prevalence still persists and a clear explanation for those discrepancies is still lacking, though subjective histological assessment and the absence of objective qualitative and quantitative methods can be hypothesized.

Few studies have focused on clinico-pathological factors that correlate with the presence of vessel's tumor permeation. In our study, we found that permeation was positively correlated to the T factor, the grade of tumor differentiation as well as the stage. Those findings are in agreement with both the Pechet et al. [18] and Mineo and al. studies where both tumor diameter and differentiation were correlated with permeation [19].

In the present study, which is one of the largest reporting on stage I patients, we could not demonstrate a statistically significant prognostic impact of intra-tumoral permeation either on overall survival or on cancer-free survival. However, a 10% overall 5-year survival between patients with and without tumor permeation could well be seen as clinically relevant, even though statistical significance was not reached in this moderately-sized study. With respect to cancer-free survival, we should raise a word of caution in interpreting our results as a detailed cause of death was only available for 2/3 of the patients.

There are at least two hypotheses for this negative study. Firstly, our prevalence of permeation was mainly attributed

Table 4
Hazard ratio for cancer-related mortality by univariate analysis

	β	H.R.	95% CI		p value
			Low	Up	
Sex (male relative to female)	-0.13	0.99	0.51	1.9	0.97
Histology (relative to SCC)					
Adenocarcinoma	0.25	1.28	0.77	2.15	0.34
Grade of differentiation					
Moderate/poor	0.08	1.08	0.63	1.88	0.77
T factor					
Greater than 3 cm	0.798	2.22	1.31	3.74	0.003
Greater than 2 cm	0.631	1.88	1	3.55	0.05
N factor					
Node positive	0.79	2.2	1.26	3.85	0.005
Stage (stage II relative to stage I)	0.964	2.62	1.55	4.44	<0.001
Intra-tumoral permeation	0.443	1.56	0.79	3.08	0.20
Type of parenchymal resection					
Pneumonectomy (relative to lobectomy)	0.595	1.81	0.98	3.37	0.06

to vascular permeation and several reports have emphasized the lack of prognostic significance in NSCLC studies [6,9]. Secondly, this retrospective study spans over more than 20 years, and even though we selected only patients with complete resection and systematic mediastinal lymph node sampling, the fact that PET FDG scanning was only introduced in the second half of the study period might have precluded us from detecting unforeseen metastatic disease which could have masked the potential prognostic impact of tumor permeation.

On the other hand, studies that only focused on either vascular or lymphatic permeation might have failed to clearly ascertain which of those components might have an undisputable impact on survival.

Finally, current positive studies still present with several weaknesses: in the one from Tsuchiya et al. [16], no data is given on completeness resection rate, the type of parenchymal resection is not analyzed and no information is given on cancer-free survival. In the study from Saijo et al. [20], stages I–III were all included and in their multivariate analysis, the pN factor was by far the most powerful predictor of death in the overall survival and recurrence-free survival analysis. Moreover, in the stage I subgroup analysis, the authors compared the only nine patients with extra-tumoral lymphatic tumor permeation. No information was given for stage I patients when lymphatic permeation (extra- and intra-tumoral) was analyzed.

In conclusion, in this large institutional study of early stage NSCLC, the presence of intra-tumoral permeation was correlated both to T, grade of differentiation, as well as to stage. However, in contrast to recent reports, we did not found that intra-tumoral permeation adversely affected long-term survival.

Further large-scale studies with recent patient cohorts and refined histological techniques will hopefully shed some light on this debated topic.

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Appendix A. Conference discussion

Dr R. Rami-Porta (Barcelona, Spain): You have concluded that whereas intra-tumoral permeation is associated to larger tumors, high undifferentiated grade and high pathologic status, it is not, by itself, prognostic of survival.

However, there are really striking differences in survival when we compare overall survival and also cancer-free survival. In the overall survival, there is a 16% 5-year survival difference between those patients with tumors with those pathologic features and those patients without the pathologic features that you have studied, and the difference in median survival is 30 months. When we look at cancer-free survival, the difference in 5-year survival is 12% and the difference in median survival is 16 months.

The curves that I've seen in the paper, both for overall survival and cancer-free survival, separate very nicely. The graph that you showed on overall survival is slightly different from the graph I've seen in the text. In the one you showed, both curves seemed to get together at the very end of the follow-up. It's not so in the graph that's in the paper. But anyway, it seems that the difference is consistent along all follow-up and is more evident in the cancer-free survival graph.

Why these differences are not statistically significant, I don't know. You mentioned the scarce number of patients with these pathologic features. And although, you had a large series of patients compared with the series that you have mentioned in the discussion of your paper, when we start breaking down, the figures go smaller, and you only had 48 cases with these pathologic features.

And also when we analyze a single risk factor or a single potential risk factor, I think we may find this sort of discrepancy between your series and others reported. I imagine, for example, that maybe you have a cluster of patients with tumors that have a certain negative prognostic factor that has

not been determined or it is still unknown, or maybe those tumors without pathologic features that you have studied have a higher SUV uptake as you showed this morning. Anyway, there may be other factors that have not been determined in the series.

In any case, I think that because these differences may be clinically relevant, even if there is not enough ground to recommend adjuvant therapy, perhaps, at least, these patients should be closely followed up after surgery just to see if you can pick up early recurrences or not.

As the authors concluded, I think that we still need larger series, maybe multi-institutional and prospective, with standardized pathologic study, to clarify the impact of these pathologic features in early stage non-small cell lung cancer.

I only have one question. You have not mentioned, and I have not seen it in the paper, whether these patients received adjuvant therapy after surgery.

Dr Poncelet: To answer easily to the last question, none of those patients had adjuvant chemotherapy since we only started adjuvant chemotherapy in 2004 in our university.

The main point I made from this study and working with our data, we have obviously one pathologist who is devoted to the lung, and so that person, who is the last author, I think really at each time has really made its best in diagnosing permeations. But when I saw our prevalence of 14.4%, I really felt that we may just increase the threshold of sensitivity by adding new detection techniques, such as elastin staining, for example. Because even though she's the only one to have concluded on the permeation, I think that we are lacking patients here and probably the group would be differently separated if we had done better immunohistochemistry studies. That would be my conclusion, I think.

Appendix B

Members of the 'Groupe d' oncologie thoracique des Cliniques universitaires Saint-Luc, Université Catholique de Louvain' and cooperating in the study are E. Coche, Ph. Collard, Y. Humblet, F. Mazzeo, G. Liistro, M. Lonneux, Ph. Noirhomme, Th. Pieters, A.J. Poncelet, D. Rodenstein, P. Scalliet, and B. Weynand.