Significance of the Presence of Microscopic Vascular Invasion After Complete Resection of Stage I–II pT1-T2N0 Non-small Cell Lung Cancer and Its Relation with T-Size Categories

Did the 2009 7th Edition of the TNM Staging System Miss Something?

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Introduction: The aim of this study was to assess the significance of microscopic vascular invasion (MVI) in a population of resected patients with early-stage non-small cell lung cancer (NSCLC), along with an analysis of the effect of the combination of MVI and tumor size for the T-size categories T1a-T2b according to the 2009 7th edition of the tumor, node, metastasis (TNM) classification.

Methods: From January 1993 to August 2008, 746 patients with pT1-T2N0 NSCLC received resection at our institution. MVI was ascertained using histopathological and immunohistochemical techniques.

Results: MVI was observed in 257 patients (34%). Prevalence was higher in adenocarcinoma (ADK) than in squamous cell carcinoma ($p = 0.002$). A significant correlation was found between MVI and ADK ($p = 0.03$), increased tumor dimension ($p = 0.05$), and the presence of tumor-infiltrating lymphocytes ($p = 0.02$). The presence of MVI was associated with a reduced 5-year survival overall ($p = 0.003$) and in ADK ($p = 0.0002$). In a multivariate survival analysis, MVI was an indicator of poor survival overall ($p = 0.003$) and in ADK ($p = 0.0005$). In each T category (T1a-T2b) of the 2009 TNM staging system, survival of MVI+ patients was significantly lower than the corresponding MVI− patients; T1a and T1b MVI+ patients had a survival similar to MVI− T2 patients.

Conclusions: The finding of MVI in pT1-T2N0 NSCLC is frequent. MVI correlates with adenocarcinoma histotype, increased tumor dimensions, and tumor-infiltrating lymphocytes. The presence of MVI is an independent negative prognostic factor. In our experience, MVI was a stronger prognostic indicator than T size in T1a-T2b categories according to the 2009 TNM staging system.

Key Words: Lung cancer, Vessel invasion, Surgery, Pathology, Early stage.

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Lung cancer is the leading cause of cancer-related deaths among men and women. Despite recent improvements in early diagnosis and treatment, the overall 5-year survival rate is a dismal 15%.[1] Even patients at stage I disease have a 5-year survival rate ranging from 65 to 73%, well below that of most other solid organ tumors, and about two-third of stage I patients eventually die of distant metastases. For this reason, many authors have looked for clinicopathologic markers that can reliably be used as prognostic indicators, as well as a guide to identify patients who are most likely to benefit from adjunct therapies. Among others, microscopic vascular invasion (MVI), including intratumoral blood vessel invasion (BVI) and lymphatic vessel invasion (LVI), has been reported to be important prognostic factors in early stages[2,3] or in all stages[4,5] of non-small cell lung cancer (NSCLC). Furthermore, tumor size has recently been identified as a significant prognosticator, and in the most recent 7th edition of the tumor, node, metastasis (TNM) staging system of lung cancer,[6] several subgroups of T categories by size at 2, 3, 5, 7, and >7 cm have been introduced, showing definite survival stratification.

Surprisingly, despite MVI defined as BVI, LVI, or a combination of both has been found to represent a major determinant of poor prognosis in most surgical series since the 1960s; it has received little interest in all the TNM editions, and even the last 2009 7th edition indicates MVI

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among the "optional descriptors," which deserve further investigation.

Therefore, the aim of this study was to assess, in a surgical population of resected patients with NSCLC at stage I–II pT1-T2N0M0, prevalence, correlation with other clinicopathologic variables, and prognostic significance of MVI, along with an analysis of the effect of the combination of MVI and tumor size for the T-size categories T1a-T2b using the 2009 7th edition of the TNM classification.

PATIENTS AND METHODS

This retrospective study included 746 patients with pathologic T1-T2N0 NSCLC who underwent resection at the Section of Thoracic Surgery of the University of Torino, Italy, between January 1993 and August 2008, and who represent the study population. In the same period, a total of 1515 patients received resection for NSCLC. In the study population, the presence of MVI was investigated on the surgical specimen, and the patients were divided into two different groups, MVI+ and MVI−. None of the patients received induction chemotherapy or radiotherapy. Routine preoperative workup included pulmonary function tests with diffusion capacity (DLCO) and blood gas analysis, chest x-rays, computed tomography (CT) of the chest and upper abdomen, bronchoscopy, and, since 2000, positron emission tomography (PET) scan (recently integrated PET-CT scan). Mediastinoscopy was performed in the presence of enlarged (>15 mm) lymph nodes at CT scan or, more recently, positive at PET scan. Operative procedure included in all cases pulmonary resection (wedge, segmentectomy, lobectomy, bilobectomy, or pneumonectomy) and systemic lymphadenectomy. All patients were staged according to the 7th edition of the TNM staging system.[6]

Follow-up information on all patients was obtained through clinic follow-up notes, direct patient or family contact, or contact with the patient's primary care physician.

For analysis, the following histopathologic variables were considered in the two population groups, MVI+ and MVI−: histology, histologic grading of differentiation (well, moderately, and poorly differentiated, respectively, G1, G2, and G3), tumor size, microscopic perineural invasion, and the presence of tumor-infiltrating lymphocytes (TIL).

Histopathological Evaluation

The surgical specimens were immediately fixed in 10% formalin and underwent routine histopathological workup with paraffin embedding. A sampling of the tumor mass at every centimeter was undertaken, and a 1.5 × 2 × 0.5 cm (0.5-cm width) slice was obtained. For a mean tumor diameter of 36 mm (range, 0.9–7 cm), a mean of 4.5 slices (range, 2–7) were undertaken. Routine hematoxylin–eosin stain was used for all slices.

MVI was defined as the presence of neoplastic structures inside the lumen of a vessel, either blood or lymphatic vessel. In most cases, it was characterized by neoplastic cells embedded in organized vascular thrombosis. If there was any doubt whether the neoplastic cells could represent artifacts, the specimen underwent three to four consecutive serial sections, documenting the presence or absence of infiltration of the vascular wall; furthermore, an immunohistochemical staining with antibody anti-CD34 (Monoclonal Mouse Anti-Human CD34 Class II, clone QBEnd 10, DAKO, Milan, Italy) was performed to evaluate blood vessels.

The presence or absence of TIL was defined as CD8+ intraepithelial lymphocytes morphologically identified within the cancer cell nests, and patients were collected in two different groups, TIL-positive and TIL-negative, as described in our previous study.[7] The presence of perineural invasion was defined to be the tumoral involvement of epineurium in the peritumoral tissue.

Statistical Analysis

Comparison between proportion differences was undertaken using χ^2 test (Fisher's exact test when appropriate). To investigate the relationship between some possible causal (independent) variables and the presence/absence of MVI, considered as a binary variable, a logistic regression model was used,[8] with the assumption that the events were independent and the relationship plausibly log-linear. The probability value was calculated on the Wald statistic, and 95% confidence intervals (CIs) were also provided. When the outcome variable was ordinal (such as in case of the T-size descriptors), ordinal regression was used, and the cumulative logit model was employed.[9]

Cumulative survival rates were calculated by the Kaplan-Meier method, using the date of surgery as the starting point and the date of death or the latest follow-up date as the end point. The survival differences were determined by log-rank analysis. Calculation of the relative hazards and the relative 95% confidence intervals using the Cox proportional hazard model was used. A p value less than 0.05 was considered statistically significant. A formal test of interaction was performed before proceeding with the subgroup analysis for the variables of interest. All statistical analysis was undertaken using software packages (STATISTICA, release 7.1, 2005, Statsoft, Italy).

The study was approved by our institutional review board, and individual patient consent was waived because of the retrospective nature of the study.

RESULTS

Table 1 illustrates the patients characteristics. The patients were stratified according to the newest TNM edition (7th) into T1a (≤2 cm, $N = 173$), T1b (>2 but not >3 cm, $N = 238$), T2a (>3 but not >5 cm, $N = 263$), and T2b (>5 but not >7 cm, $N = 72$). The corresponding stages were stage IA (T1a + T1b), stage IB (T2a), and stage IIA (T2b).

MVI Prevalence

Overall, MVI was observed in 257 patients (34%). In 77 cases (77 of 257 cases, 30%), immunohistochemical staining with CD34 was necessary for the final diagnosis of MVI. MVI prevalence was significantly higher in adenocarcinoma (159 patients, 44%) than in squamous cell carcinoma (81 patients, 27%) ($p = 0.002$) and large cell carcinoma (7 patients, 32%).

TABLE 1. Patients Characteristics of the Study Population

	N	%
Age, mean (range)	65 (37–82)	
M/F	612/134	82/18
Histology		
Adenocarcinoma	359	48
Squamous cell	295	39
BAC	55	7
Large cell	22	3
Others	15	2
Resection		
Wedge/segment	80/21	13
Lob/bilobectomy	557/12	76
Pneumonectomy	76	10
Grading[a]		
G1	109	15
G2	342	49
G3	247	35
T size, cm, mean (range)	3.6 (0.9–7)	
T categories[b]		
T1a (<2 cm)	173	
T1b (2–3 cm)	238	
T2a (3–5 cm)	263	
T2b (5–7 cm)	72	

[a]Available for 698 patients.
[b]According to the 2009 TNM staging system.
BAC, bronchioloalveolar carcinoma; TNM, tumor, node, metastasis.

Correlations of MVI with Clinicopathologic Variables

Using logistic regression model, the presence of MVI was tested against different clinicopathologic variables, including age, gender, grading, TIL, histology, and tumor size. Among all the variables, MVI was significantly associated with the presence of TIL (odds ratio [OR] 1.54, 95% CI 1.09–2.24, $p = 0.02$), an increased tumor size (OR 1.13, 95% CI 1.01–1.24, $p = 0.05$), and adenocarcinoma histotype (OR 1.20, 95% CI 1.08–2.48, $p = 0.03$).

The Association Between T-Size Categories and MVI

A dedicated analysis was undertaken to look at the association between the T-size categories (T1a through T2b) according to the 2009 7th edition of the TNM staging system and the presence of MVI. Prevalence of MVI increased with the T predictor from T1a (49 patients, 28%) to T2b (29 patients, 40%) (Table 2). When using an ordinal regression model with T-size categories as dependent variable and the following independent variables (histology, MVI, perineural invasion, TIL, and grading), histology (adenocarcinoma type, $p = 0.03$), MVI ($p = 0.04$), and grading ($p = 0.00003$) all significantly correlated with increasing T size (Table 3).

Univariate and Multivariate Survival Analysis

Follow-up with vital status was available for all patients. Mean follow-up time was 53 months.

TABLE 2. MVI Prevalence According to Different T-Size Categories of the 2009 7th Edition of the TNM Staging System for Lung Cancer

T Status	MVI+, *n* (%)	MVI−, *n* (%)
T1a	49 (28)	124 (72)
T1b	76 (32)	162 (68)
T2a	109 (41)	154 (59)
T2b	29 (40)	43 (61)

MVI, microscopic vascular invasion; TNM, tumor, node, metastasis.

TABLE 3. Ordinal Regression Analysis

	Wald Statistic	*p*
Perineural invasion	0.1903	0.662
MVI	4.1181	0.004
TIL	0.0073	0.931
Grading	17.113	0.00003
Histology (adenocarcinoma type)	4.4520	0.003

Dependent variable: T-size determinant T1a through T2b according to the 2009 7th Edition TNM staging system for lung cancer.
MVI, microscopic vascular invasion; TIL, tumor-infiltrating lymphocytes.

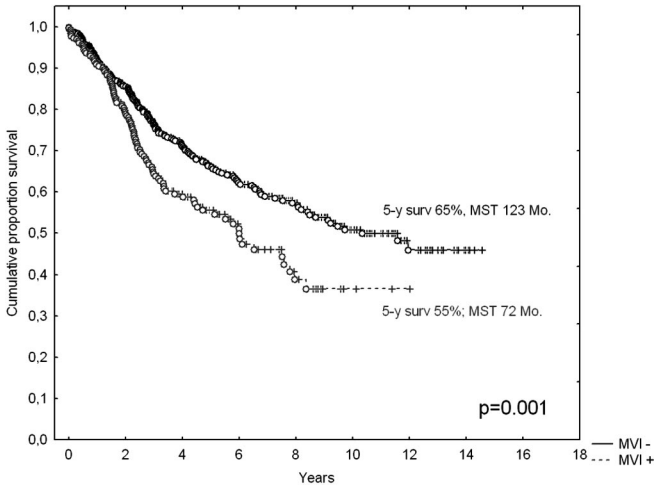

FIGURE 1. Overall survival of the study population according to the presence/absence of microscopic vascular invasion. MST, mean survival time.

Patients at risk (Yrs)	0	2	4	6	8	10	12	14
MVI -	489	350	245	160	106	53	22	1
MVI +	257	162	80	40	13	3	1	-

In univariate survival analysis, the presence of MVI on the overall patient population was associated with a significant decreased survival (65% versus 55% at 5 years for MVI+ and MVI− populations, respectively; $p = 0.001$) (Figure 1).

We further analyzed the study population by histology considering the two histotypes, adenocarcinoma and squamous cell carcinoma.

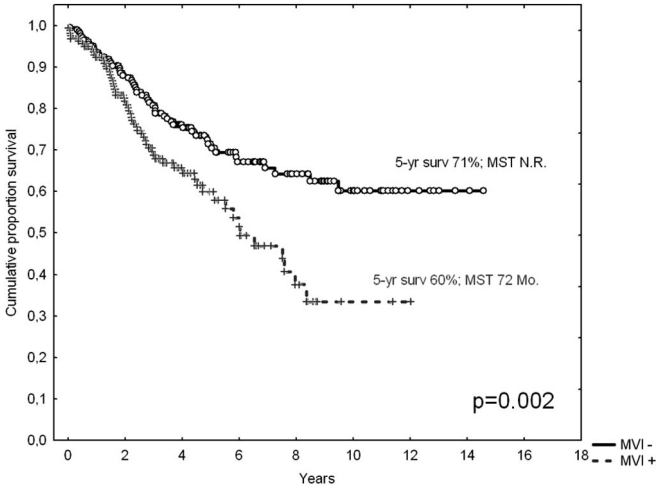

FIGURE 2. Survival of the study population according to the presence/absence of microscopic vascular invasion and adenocarcinoma histotype. MST, mean survival time; N.R., not reached.

Patients at risk (Yrs)	0	2	4	6	8	10	12	14
MVI -	200	136	97	56	42	18	7	1
MVI +	159	104	51	23	11	2	1	-

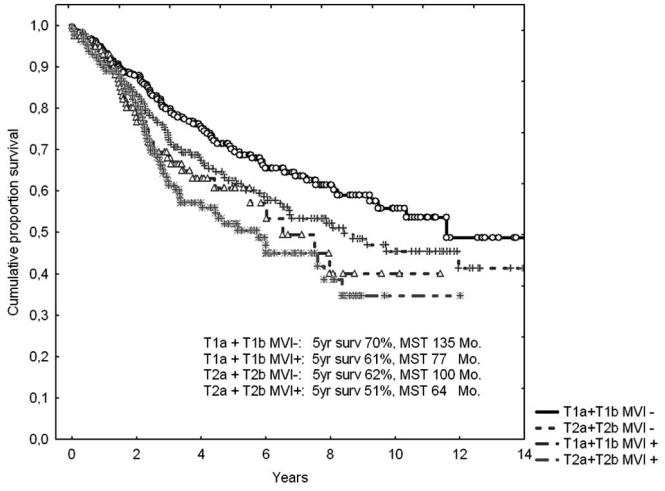

FIGURE 3. Survival curves stratified by T-size categories T1a-T2b according to the 2009 7th edition of the tumor, node, metastasis (TNM) staging system for lung cancer and the presence/absence of microscopic vascular invasion in the study population overall. MST, mean survival time.

Patients at risk (Yrs)	0	2	4	6	8	10	12	14
T1a+T1b MVI -	275	186	138	98	56	26	12	1
T2a+T2b MVI -	190	164	102	64	47	36	11	1
T1a+T1b MVI +	118	68	28	14	6	1	-	-
T2a+T2b MVI +	129	89	45	20	13	1	1	-

In patients with squamous cell carcinoma, the presence of MVI was not associated with a significant 5-year survival difference versus patients without MVI (59% versus 49% in MVI+ and MVI−, respectively; $p = 0.25$). Conversely, in patients with adenocarcinoma, the presence of MVI was significantly associated with a poorer 5-year survival (71% versus 60% in MVI+ and MVI−, respectively; $p = 0.002$) (Figure 2). In the subgroup analysis, the interaction between MVI and histology was assessed using a test of interaction, by including in the multivariate Cox method an additional variable of interaction defined as the product of the two variables, MVI and histology (adenocarcinoma versus squamous cell carcinoma).

The test of interaction provided a marginal level of significance ($p = 0.06$). Therefore, we may suggest that the survival differences by histology in the MVI− and MVI+ groups are important, although we cannot draw any conclusion from a statistical point of view that the relationship between MVI and survival is different in adenocarcinoma versus squamous cell types. A possible explanation may be that the study had no statistical power to detect survival differences at the conventional ($p = 0.05$) level of significance because of the sample size or limitations in the study design.

We then performed a multivariate survival analysis using different covariates, including age, sex, grading, tumor size, MVI, perineural invasion, TIL, histology, and stage. The presence of MVI was an independent prognostic factor either overall (HR 1.61, 95% CI 1.30–2.15, $p = 0.003$) or in adenocarcinoma histotype (HR 2.02, 95% CI 1.36–3-02, $p = 0.0005$) but not in squamous cell type (HR 1.21, 95% CI 0.82–1.80, $p = 0.59$).

A dedicated survival analysis was undertaken, exploring the prognostic significance of MVI in four different T-size categories (T1a through T2b) according to the 2009 7th edition of the TNM staging system along with the combination of the effects of MVI and T-size determinant. In each T-size category, and when grouping T-size categories into T1a + T1b and T2a + T2b, the presence of MVI had a negative prognostic impact overall (Figure 3, Table 4), and this was more evident in adenocarcinoma (Figure 4). Survival in MVI+ patients was similar among the four T size groups, T1a, T1b, T2a, and T2b ($p = 0.90$) either overall or in adenocarcinoma ($p = 0.72$). Interestingly, T1a and T1b MVI+ patients had a survival similar to T2a and T2b MVI− patients (5-year survival: 61% versus 62%, respectively, $p = 0.46$; Table 4). Therefore, our results seem to suggest that MVI is a more powerful prognostic indicator than size in early-stage pT1-T2N0 NSCLC patients.

DISCUSSION

This study was aimed at investigating the role of MVI in the clinical presentation and outcome of early-stage NSCLC along with the analysis of the effect of the combination of MVI and tumor size for the T-size categories T1a through T2b using the 2009 7th edition of the TNM classification.

The results of the study indicate that (1) MVI is frequent in resected patients with NSCLC; (2) MVI correlates with the tumor size, the presence of TIL, and the adenocar-

TABLE 4. Median Survival Time and 5-yr Survival Rates for the Four T-Size Categories T1a through T2b in the Two Population Groups MVI− and MVI+

T-Size Category	Median Survival	5-yr Survival (%)
T1a (≤2 cm)		
MVI−	NR	75
MVI+	91	61
T1b (>2 but not >3 cm)		
MVI−	116	66
MVI+	68	61
T2a (>3 but not >5 cm)		
MVI−	103	64
MVI+	69	52
T2b (>5 but not >7 cm)		
MVI−	86	61
MVI+	55	50
T1a + T1b		
MVI−	135	70
MVI+	77	61
T2a + T2b		
MVI−	100	62
MVI+	64	51

MVI, microscopic vascular invasion; NR, not reached.

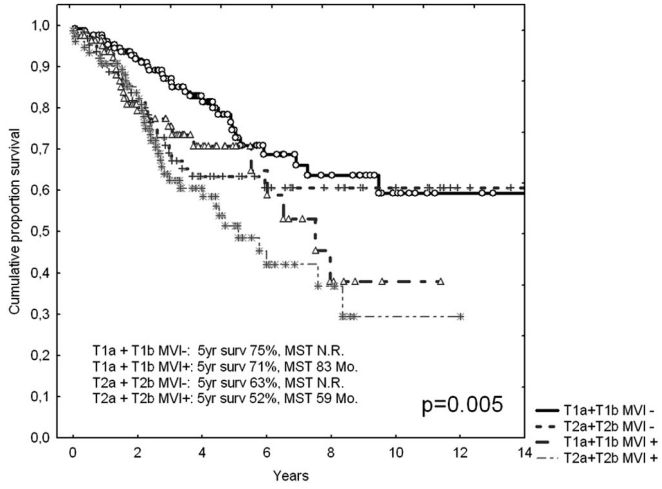

FIGURE 4. Survival curves stratified by T-size categories T1a-T2b according to the 2009 7th edition of the tumor, node, metastasis (TNM) staging system for lung cancer and the presence/absence of microscopic vascular invasion in the study population, adenocarcinoma histotype. MST, mean survival time; N.R., not reached.

Patients at risk (Yrs)	0	2	4	6	8	10	12	14
T1a+T1b MVI -	130	98	67	30	24	7	2	1
T2a+T2b MVI -	63	44	30	21	16	9	3	1
T1a+T1b MVI +	82	49	22	10	4	2	-	-
T2a+T2b MVI +	75	55	29	10	6	1	1	-

cinoma type; (3) MVI is an independent negative prognostic factor; (4) the new 2009 7th edition of the TNM staging system underestimates the presence of MVI, which, at least in T1a through T2b size categories, has a greater prognostic impact than size.

BVI is one of the steps leading to metastatic diffusion. It has been demonstrated that during the early stages of tumor growth, angiogenesis is required to foster tumor progression. Tumor cells from the primary neoplasm may penetrate these new vessels and escape from the primary site to distant organs.[4] The relationship between tumor vessels, intravascular tumor cell invasion, and metastases has been studied in animal models. The first studies about the prognostic role of MVI in lung cancer date back to the late 1950s. Since then, numerous studied have investigated the importance of MVI in the progression of lung cancer.

Surprisingly, no TNM staging system of lung cancer so far has incorporated MVI in the determinants of prognosis, and even the 2009 7th edition of the TNM staging includes lymphatic and venous invasion as "optional descriptors,"[6] which deserve further investigation. Studies investigating the importance of MVI in relation to stage and T determinant have been published in the past decades. Back in the mid-1990s, Kessler et al.[4] suggested that vascular invasion should be considered superior to T descriptor as a prognostic factor. Macchiarini et al.[10] observed that in tumor with a high degree of angiogenesis, MVI was significantly more frequent. As a consequence, it has been speculated that the presence of MVI is an indicator for the presence of occult metastases and therefore these patients might be considered candidates to a postoperative chemotherapy. More recently, Tsuchiya et al.[3] observed on a large series of 322 stage IA patients, staged according to the 6th TNM edition, that the overall 5-year survival rate of patients with MVI+ stage IA was similar to that of MVI− stage IB patients. Similarly, MVI+ stage IB patients had similar survival rates as MVI− stage IIA patients. Therefore, they recommended to upgrade MVI+ stage IA and IB patients to stage IB and IIA, respectively. The only report published so far about MVI, using the newest TNM staging system, from a Japanese series[11] clearly confirms that in pathologic stage IA NSCLC, disease-free survival in MVI + T1a (<2 cm) and T1b (2–3 cm) was significantly poor. In our series, T1a through T2b size categories, patients with MVI had nonsignificantly different survival rates, although significantly lower than the corresponding MVI− categories, thus demonstrating that MVI was a far more powerful prognostic indicator than size in T1-T2 size categories NSCLC. Therefore, there are numerous reports, including ours, indicating that at least in early-stage NSCLC, MVI is a far more important determinant than size and should therefore be taken into account for staging.

As a consequence, most authors recommend to use adjuvant chemotherapy in MVI patients irrespective of the stage. Several recent trials have shown that cisplatin-based chemotherapy after resection of NSCLC may be beneficial. The Lung Adjuvant Cisplatin Evaluation meta-analysis[12] found an overall hazard ratio (HR) of 0.89, thus demonstrating a proven benefit of adjuvant chemotherapy. The same meta-analysis, however, failed to demonstrate a survival advantage (HR 1.40) in pathologic stage IA. Therefore, the current practice is not to administer postoperative chemotherapy in stage IA NSCLC patients. The results

TABLE 5. Results About MVI in the Literature

Author (Year)	*N*	Stages	MVI Prevalence (%)	Prognostic Significance	Correlations
Rigau (2002)	86	All stages	29	No	NS
Mineo (2004)	51	IB–IIA	25	Yes	Grading, tumor size
Khan (2004)	98	T1–T2N1	10	Yes	NS
Kessler (1996)	593	All stages	NS	Yes	NS
Tsuchiya (2007)	995	I–II	50	Yes	NS
Tsuchiya (2007)	322	IA	26	Yes	CEA, tumor size
Gabor (2004)	72	T1–T3N0	32	Yes	No
Poncelet (2008)	346	I–II	14	No	T, grading
Bodendorf (2008)	112	All stages	45	Yes	Tumor size, ADK
Brechot (1996)	96	All stages	52	No	Tumor size
Shoji (2010)	217	IA	9	Yes	No
This Study	746	I–II	34	Yes	Tumor size, ADK, TIL
Mean MVI prevalence			29		

MVI, microscopic vascular invasion; NS, not stated; ADK, adenocarcinoma; TIL, tumor-infiltrating lymphocytes.

obtained so far about the role of MVI in early-stage lung cancer, including stage IA, may change the scenario. The finding of MVI has been discussed extensively in the literature as an indication for adjuvant chemotherapy,[9,10,13–15] although this continues not to be recognized as a standard treatment according to European guidelines. A recent Japanese study[3] using oral uracil-tegafur chemotherapy demonstrated an increased 5-year survival in stage IA MVI+ patients by more than 25%. Other authors[13] found that MVI significantly correlated with vascular endothelial growth factor (VEGF) expression, and oral uracil-tegafur or other VEGF inhibitors may be effective in these high-risk patients.

The implications of a correct staging for patients with clinicopathologic prognosticators including MVI is of utmost importance in early-stage NSCLC, where the chance of cure is high and the potential benefits of multimodality treatment have been demonstrated. The issue is of primary importance because the frequency of detecting stage IA NSCLC has been increasing over the recent years due to refinement and improvement in diagnostic techniques and mass screening programs. Watanabe et al.[16] reported that the proportion of patients with stage IA NSCLC has increased from 19% in 1991 to 26% in 1998, and it is steadily increasing in the more recent years. The more precise the identification of prognostic subgroups in these early stages, the more "targeted" would be optimal treatment to these patients. Therefore, the literature and our own work support the hypothesis that MVI should be incorporated in the TNM staging system, as it is currently being adopted for liver, testicular, and breast carcinoma.[17]

Table 5 summarizes the results of the major series published so far about the role of MVI in NSCLC. Although the study populations were different, comprising different stages and different number of patients, the majority of the studies indicate that MVI is a significant prognostic indicator. Some authors differentiate between blood vessel and LVI,[18,19] whereas others tend to consider the MVI irrespective of the type of vessel (blood or lymphatic). Some authors reported that only LVI but not BVI is significantly related to a decreased survival,[2,20,21] whereas other reports stated the opposite[12] and indicated that cells from early-stage NSCLC metastasize preferentially via the blood vessels, and thus MVI is a more reliable prognosticator.[9,10,14,22–24] Finally, some reports indicate that both blood and lymphatic invasion were significantly associated with a poor prognosis.[3,25] Studies that only focused on either vascular or lymphatic permeation failed to reach an agreement about which of the two components has an impact on survival. A further confusion in the interpretation of the results arises because of the debate of the significance of large vessels (arteriolar or venous) or small vessels (primarily lymphatic) invasion. Also, it is often impossible to identify the vessel type (arterial or venous) in the tumor. We, as other authors,[3] decided to consider MVI as a combination of blood and LVI to reduce the pathologic confusion and to limit the number of subgroups. Another source of confusion stems from the lack of standardized criteria among the pathologists for the definition of MVI, and each pathologist has his or her own subjective diagnostic criteria, which may explain the difference in the results among the reported series; theoretically, the frequency of MVI is proportional to the number of slides examined, and for this reason, the best method to identify MVI in a tumor is to examine all serial sections prepared from the tumor material. Some authors[3] recommend to examine at least two slides per tumor and two blocks per centimeter (5-mm slices) of the tumor. The same authors suggest to use specific markers for normal and tumor-associated lymphatics, such as Ab antiD2-40. Because of the importance of MVI in the prognosis of patients with NSCLC, an agreement among the pathologists regarding tissue sampling, examination protocols, and the use of specific immunohistochemical markers is strongly needed.

Prevalence of MVI is extremely variable in the reported series, depending on the care of the pathologist to look for it and the different stages examined, ranging from as low as 9%

to as high as 60% (Table 4). Our prevalence of 31% is in accordance with that of the literature. Few studies have looked for possible correlations between MVI and different clinicopathologic variables. Poncelet et al.,[26] in a patient population of more than 300 stage I–II NSCLC patients, found a correlation between MVI and T factor and grading. Tsuchiya et al.[3] in stage I patients correlated MVI with serum CEA levels and tumor size, and Bodendorf et al.[5] in NSCLC from all stages found a correlation between MVI and tumor size and adenocarcinoma type. In this series, using a logistic regression model, we found that MVI significantly correlates with tumor size, adenocarcinoma type, and the presence of TIL. The correlation with tumor size has been confirmed when we performed an ordinal regression model using the T-size descriptors of the newest edition of TNM (T1a through T2b) as the dependent variable and the presence/absence of MVI as independent variable, and the correlation was highly significant. Therefore, we may have hypothesized that as the tumor increases, new vessels are formed, and the permeation by tumor cells through the neovessels is increased. In our previous study investigating the role of TIL in lung neoplasms,[7] a significant correlation emerged between TIL and MVI, grading, and tumor dimension. This suggests that immune cell reactions are more pronounced, as the tumor dedifferentiation and biologic malignant behavior (including vascular permeation by tumor cells) progress. Similar results were obtained in NSCLC by other authors[27,28] and in other human solid organ tumors.[29,30] Therefore, it seems hypothesized that a complex inter-relationship takes place in the tumoral and peritumoral microenvironment where neoangiogenesis, immunogenicity, and intrinsic characteristics of the tumoral cell lines (histotype and the degree of differentiation) all have a role in determining tumor progression. We are just starting to understand these complex interactions, which may profoundly influence our treatment strategies with targeted therapies.

This study has some limitations including the retrospective nature of the study design and the long time interval of the patient series, both of which should surely be taken into account for the interpretation of the results. However, we would point out that, despite the relatively long time period (15 years), the surgical team has remained the same over the whole period, and the surgical techniques have been maintained basically constant, and this may partly offset the aforementioned limitations. An additional point to be considered is that the outcome measure adopted in this study was the all-cause mortality. Although it may be argued that this might have excluded noncancer-related deaths, it is worth noticing that in our country, like in other countries,[31] patients with a diagnosis of lung cancer will have this condition listed on the death certificate irrespective of the actual cause of death. This makes the identification of noncancer-related deaths very difficult. Also, as pointed out elsewhere,[32] such an attempt may itself introduce a potential bias by excluding the contribution of an undiagnosed recurrent malignancy in an apparently noncancer-related death.

We conclude that in resected patients with pT1-T2N0 NSCLC, the finding of MVI in the surgical specimen is frequent, occurring in up to one-third of the cases. MVI correlates with important clinicopathologic variables, including tumor size, adenocarcinoma type, and TIL. MVI represents a poor prognostic factor, which in our experience was a more important prognostic determinant than size in T1a through T2b size categories according to the 2009 TNM staging system. Patients with MVI are therefore to be considered a high-risk group among patients with early-stage NSCLC. We recommend that pathologists dealing with NSCLC need to perform a meticulous search for MVI in every patient operated on for NSCLC, and the presence of MVI in the surgical specimen should be emphasized and reported to the surgeon and the medical oncologist. As a final consequence, our study suggests that upstaging of patients with MVI is strongly recommended as well as consideration for adjuvant chemotherapy in this high-risk group of patients.

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