







# Impact of microvascular invasion on 5-year overall survival of resected non-small cell lung cancer

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## ABSTRACT

**Objectives:** Non-small cell lung cancer (NSCLC) is an incidental and aggressive type of cancer. Although curative treatment can be offered, the recurrence rate is relatively high. Identifying factors that have a prognostic impact may guide changes in the staging system and recommendations for adjuvant therapy. The aim of this study was to evaluate the impact of microvascular invasion on the 5-year overall survival (OS) of patients with resected NSCLC treated at a reference cancer center. **Methods:** This retrospective, observational cohort study included patients diagnosed with early-stage NSCLC (clinical stages I-IIIa), treated with curative-intent surgery at the Brazilian National Cancer Institute between 2010 and 2016. **Results:** The dataset comprised 91 surgical patients, mostly females and white, with a mean age of 62 years (range between 29-83). Cases were distributed as stages I, II, and III in 55%, 29%, and 16%. Adenocarcinoma was the predominant histological subtype (67%), and microvascular invasion was present in 25% of the patients. The 5-year OS probability was 60% (95% CI, 48.3-68.9). Among all characteristics, advanced stages ( $p = 0.001$ ) and the presence of microvascular invasion ( $p < 0.001$ ) were related to a worse 5-year OS. After adjusting for age group and pathological stage, the presence of microvascular invasion was associated with a 4-fold increased risk of death (HR 3.9, 95% CI, 1.9-8.2). **Conclusion:** The presence of microvascular invasion was an independent factor related to worse survival and, therefore, should be routinely assessed in resected specimens.

**Keywords:** non-small cell lung cancer, thoracic surgery, survival analysis, microvascular invasion.

## INTRODUCTION

Lung cancer is the most frequent malignancy among men and the third most frequent among women, with an estimated 2 million new cases worldwide in 2020.<sup>(1)</sup> The five-year overall survival (OS) is considered low (10-20%), especially when compared to other frequent malignant tumors, such as colon (60-69%), prostate (70-100%), and breast cancer (85%).<sup>(2)</sup> The extent of the disease at diagnosis influences both the treatment decision and the prognosis. In less than 20% of cases, the diagnosis is performed when the tumor is still localized, a fact that greatly limits the number of patients who can be treated primarily with curative-intent surgery.<sup>(3,4)</sup> It is estimated that this percentage will rise in upcoming years as a result of the increased use of lung cancer screening.<sup>(5)</sup> Even though curative treatment can be offered, the recurrence rate is relatively high (30-70%) and, in most cases (80%), it occurs within the first 2 years of follow-up.<sup>(6)</sup>

Some characteristics have been associated with a better prognosis, including non-advanced disease stages, good performance status (PS), the absence of weight loss (< 5% of body weight), and being of the female

sex.<sup>(7,8)</sup> The identification of factors that impact the prognosis can guide changes in the staging system and recommendations for adjuvant therapy, improving the quality of treatment and the outcome.<sup>(7)</sup> The description of microvascular invasion, determined by the presence of malignant cells within the vessel lumens, has been associated with lower disease-free survival and OS of operated patients for over a decade. Some authors have proposed adjuvant therapy in the presence of this finding, even in the absence of lymph node involvement or advanced primary tumors,<sup>(7)</sup> as is already practiced in other cancer types.

The aim of the present study was to evaluate the impact of microvascular invasion on the 5-year overall survival (OS) of patients with resected non-small cell lung cancer (NSCLC) treated at the Brazilian National Cancer Institute (INCA).

## METHODS

### Study Design

This was a retrospective, observational cohort study of patients diagnosed with early-stage NSCLC (clinical

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stages I-IIIa) treated with curative-intent surgery at INCA between January 2010 and December 2016. The exclusion criteria were: ages less than 18 years, prior treatment at other institutions, other malignant tumors in the preceding 5 years, and atypical lung cancer histological subtypes: sarcomatoid carcinoma, mucoepidermoid carcinoma, neuroendocrine tumors, and salivary gland tumors. Hospital medical records were the primary source for data collection. Patient screening was carried out using the hospital database system and the thoracic surgery database. A list of all potentially eligible patients was provided by the institution's cancer registry.

An electronic clinical research form was created to annotate all relevant information, including patient and tumor characteristics and the outcomes. Former smoker status was defined as patients who had quit smoking at least 1 year before diagnosis. The Eastern Cooperative Oncology Group PS scale was used.<sup>(9)</sup> The maximum standardized uptake value (SUV<sub>max</sub>) was selected to determine tumor avidity through F18-fluorodeoxyglucose (FDG) positron emission tomography (PET). Staging was established according to the seventh edition of the UICC/IASLC/AJCC (Union for International Cancer Control/International Association for the Study of Lung Cancer/American Joint Committee on Cancer).<sup>(10)</sup> Pathological surgical reports were standardized as an institutional routine protocol during the study period, including systematic reports of microvascular invasion. Briefly, the surgical specimens were fixed in 10% formalin and embedded in paraffin. Serial sections were stained with hematoxylin-eosin (H&E), and microvascular invasion was defined as the presence of intravascular cancer cells within the blood vessels. The analysis was exclusive for blood vessel invasion, and lymphatic invasion was not routinely annotated.

### Statistical Analysis

In order to describe the study population, tables including absolute and relative frequencies were elaborated. Descriptive statistics (minimum, maximum, mean, median, and standard deviation) were calculated for age and tumor SUV. The staging group was used as a single variable instead of each TNM descriptor for the survival analysis. To estimate the probability of 5-year OS, the Kaplan-Meier estimator was used. OS was defined as the time interval between the date of surgery and death. The log-rank hypothesis test was used to determine the existence of differences between the estimated survival curves. Variables that presented p-values lower than 0.20 in this test were included in Cox proportional risk models. Those that represented less than ten patients were not shown or analyzed, as was the case for other histological subtypes. All the analyses were conducted using the Stata 15 software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX, USA: StataCorp LLC).

### Ethical Considerations

This research project was approved by the local Research Ethics Committee at INCA. A waiver

for informed consent was also approved since no interventions were planned.

## RESULTS

### Patient and Sample Characteristics

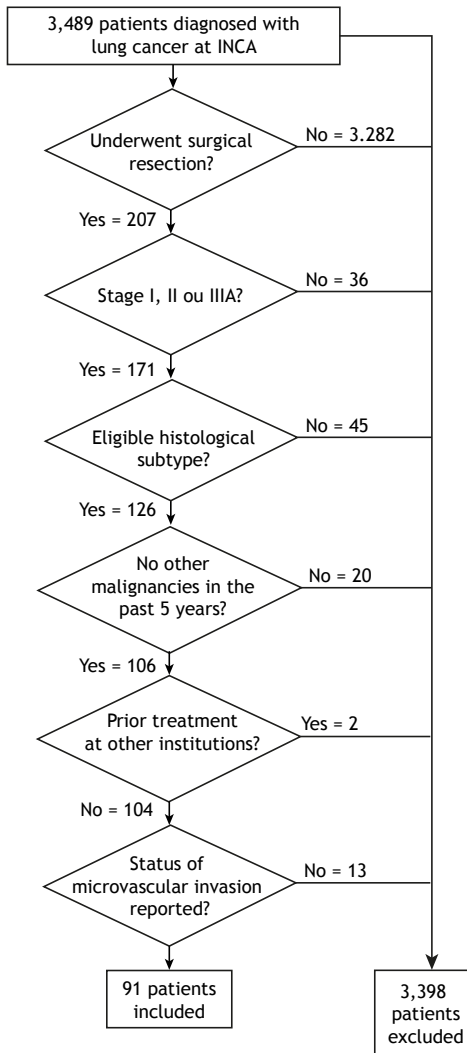
From January 2010 to December 2016, a total of 3,489 patients were diagnosed with lung cancer at INCA. Among these, 207 were NSCLC patient cases that had undergone surgical resection (6%). Thirty-six patients were excluded from the study analysis due to disease stage (IIIB or IV), 45 due to histological subtype, 20 had other malignancies in the past 5 years, 2 underwent prior treatment at other institutions, and 13 had insufficient pathological records to determine the status of microvascular invasion (Figure 1).

Ninety-one patients were included in the study, most of whom were females and white, with a mean age of 62 years (range between 29-83). Approximately 85% had a history of smoking, and in 70%, the smoking load was greater than 40 pack-years. The PS was 0 or 1 in all cases, with 64% classified as mildly symptomatic (PS of 1). Seventy-nine patients were staged using PET-CT, and the mean SUV<sub>max</sub> was 10. The cases were distributed as stages I, II, and III in 55%, 29%, and 16%. Adenocarcinoma was the predominant histological subtype (67%), and microvascular invasion was present in 25% of the patients (Table 1). The occurrence of microvascular invasion was associated with a more advanced pathological nodal stage ( $p < 0.001$ ) and staging group ( $p = 0.003$ ). Surgical resections included lobectomy in 75 cases (82%), while pneumectomy was performed in 9 (10%), bilobectomy in 5 (5%), and segmentectomy or wedge in 1 case each. Chemotherapy was performed in 48 patients, 10 (11%) as neoadjuvant and 38 (42%) as adjuvant treatment.

### Survival Analysis

The median follow-up was 83 months (95% CI, 54-97 months), and the probability of 5-year OS was estimated at 60% (95% CI, 48.3-68.9). There was no difference in survival between age groups ( $p = 0.211$ ), men and women ( $p = 0.683$ ), and between white and non-white individuals ( $p = 0.618$ ). Smoking history, as well as higher smoking loads, did not interfere in the 5-year OS ( $p = 0.997$  and  $p = 0.456$ , respectively). There were no statistically significant differences in 5-year OS according to the PS ( $p = 0.188$ ), the SUV<sub>max</sub> ( $p = 0.588$ ), tumor size ( $p = 0.093$ ), and histological subtype ( $p = 0.878$ ). Among all the analyzed characteristics, only advanced stages ( $p = 0.001$ ) and the presence of microvascular invasion ( $p < 0.001$ ) were related to a worse probability of survival at 60 months (Table 2).

As the disease stage becomes more advanced, the likelihood of long-term survival decreases. The greatest difference in 5-year OS was observed in stage IIIa when compared to the other stage groups and was more pronounced after the first year of follow-up (Figure 2). Patients whose tumors presented microvascular



**Figure 1.** Flow diagram of patient enrollment and analysis.

invasion evolved with lower rates of survival compared to those without microvascular invasion. Again, the magnitude of the difference was mainly observed after the second year of follow-up (Figure 3).

The results obtained with the Cox model, adjusted for age group, pathological stage, and presence of microvascular invasion, indicated that patients aged 60 years or older had twice the risk of death at 60 months when compared to younger patients (HR 1.9, 95% CI, 0.9-3.9). Individuals with pathological stage IIIA disease also presented a higher risk of death at 60 months when compared to those with stage I tumors (HR 2.8, 95% CI, 1.2-6.5), while no difference was observed between stages I and II (HR 0.8 95% CI, 0.3-1.8). The presence of microvascular invasion increased the risk of death 4-fold in relation to patients without microvascular invasion (HR 3.9, 95% CI, 1.9-8.2). The magnitude of the risk caused by the presence of microvascular invasion increased and maintained statistical significance after the adjustment in the complete model (Table 3).

## DISCUSSION

The present study was carried out to evaluate the influence of microvascular invasion on the survival of patients undergoing surgery to treat lung cancer. We analyzed a total of 91 locally operated patients and observed a lower 5-year OS rate associated with the presence of microvascular invasion. A 4-fold increased risk of death was estimated, even after adjustment for age and pathological stage.

While surgery represents the greatest chance of cure, less than 20% of NSCLC cases are resectable at diagnosis.<sup>(4)</sup> The identification of prognostic factors could allow for more customized treatment decisions, for instance, to help define whether adjuvant chemotherapy is required.<sup>(11)</sup> The presence of microvascular invasion is considered a strong negative prognostic indicator, regardless of the histological subtype.<sup>(7,12-15)</sup> In 2011, a meta-analysis concluded that the risk of recurrence in patients with microvascular invasion was 4 times higher compared to patients without microvascular invasion, and the risk of death was 2 times greater.<sup>(7)</sup> In addition, microvascular invasion has also been related to an increased risk of late recurrence.<sup>(13,16)</sup>

In 2014, another meta-analysis showed that the presence of lymphovascular invasion increased the risk of recurrence and death, even at stage I.<sup>(17)</sup> Microvascular and lymphatic invasion have been described as a single pathological factor (lymphovascular invasion), but the two findings seem to have different weights.<sup>(11)</sup> Hishida et al. (2013) analyzed 1,039 patients operated on at stages T1A-3N0M0 and found microvascular and lymphatic invasion in 34% and 20%, respectively.<sup>(18)</sup> According to the authors, patients with recurrence and microvascular invasion had more distant metastases than those with lymphatic invasion alone, indicating that microvascular invasion had a worse impact on the prognosis.<sup>(18)</sup> Miyoshi et al. (2009) noted a worse prognosis in patients with microvascular and pleural invasion within the same pathological stage, suggesting that prospective studies should be carried out to evaluate adjuvant chemotherapy for stage I cancer with microvascular or pleural invasion.<sup>(19,20)</sup> In the present study, lymphatic invasion was not systematically annotated; only microvascular invasion was assessed.

The authors of the United States National Comprehensive Cancer Network (NCCN) consensus recommended that adjuvant chemotherapy be considered in high-risk patients, even at stage IB (eighth edition of the staging system).<sup>(21)</sup> High-risk features include poorly-differentiated tumors, microvascular invasion, wedge resection alone, tumors larger than 4 cm, visceral pleural involvement, and unknown lymph node status.<sup>(21)</sup> Of note, the eighth edition of the staging system, which was published in December 2016 and is currently in use worldwide, should not be replaced with the ninth edition until 2024.<sup>(22)</sup>

The fact that one-fifth of cancer patients submitted to curative-intent surgery, with free margins and without lymph node involvement, may still recur indicates that it

**Table 1.** Distribution of patients with non-small cell lung cancer treated surgically at INCA from 2010 to 2016.

Characteristics	Microvascular invasion				p-value	Total	
	Absent		Present			N	%
	N	%	N	%			
Total	68	74.7	23	25.3	-	91	100.0
Age group							
< 60 years	22	32.4	10	43.5	0.334	32	35.2
≥ 60 years	46	67.6	13	56.5		59	64.8
Sex							
Male	30	44.1	10	43.5	0.957	40	44.0
Female	38	55.9	13	56.5		51	56.0
Race							
White	41	60.3	16	69.6	0.427	57	62.6
Non-white	27	39.7	7	30.4		34	37.4
Smoking status							
Never smoked	11	16.2	3	13.0	0.500	14	15.4
Current or former smoker	57	83.8	20	87.0		77	84.6
Smoking load							
< 40 pack-years	18	31.6	5	25.0	0.898	23	29.9
40-59 pack-years	17	29.8	7	35.0		24	31.2
≥ 60 pack-years	22	38.6	8	40.0		30	39.0
Performance Status (PS)							
0	27	39.7	6	26.1	0.240	33	36.3
1	41	60.3	17	73.9		58	63.7
Maximum SUV							
< 10	38	64.4	8	40.0	0.056	46	58.2
≥ 10	21	35.6	12	60.0		33	41.8
Tumor size							
pT1	21	30.9	4	17.4	0.157	25	27.5
pT2	37	54.4	11	47.8		48	52.7
pT3	8	11.8	6	26.1		14	15.4
pT4	2	2.9	2	8.7		4	4.4
pN							
pN0	61	89.7	12	52.2	< 0.001	73	80.2
pN1	2	2.9	8	34.8		10	11.0
pN2	5	7.4	3	13.0		8	8.8
Pathological stage							
IA	21	30.9	2	8.7	0.003	23	25.3
IB	24	35.3	3	13.0		27	29.7
IIA	8	11.8	7	30.4		15	16.5
IIB	8	11.8	3	13.0		11	12.1
IIIA	7	10.3	8	34.8		15	16.5
Histological subtype							
Adenocarcinoma	46	67.6	15	65.2	0.191	61	67.0
Squamous cell carcinoma	20	29.4	5	21.7		25	27.5
Other	2	2.9	3	13.0		5	5.5

Abbreviations: N, number of patients; SUV, standardized uptake value; pN, pathological staging nodal descriptor.

is possible to improve the way NSCLC is currently staged and treated. There is a need for better stratification of these cases so that more aggressive treatments can be offered to subgroups with a higher chance of recurrence. The identification of poor prognostic factors will allow for different strategies, not limited to treatment but also follow-up. An example would be to monitor these high-risk patients with shorter

intervals between consultations, with more frequent or additional imaging tests, perhaps even including magnetic resonance of the brain for patients at risk of distant metastasis. Greater knowledge of prognostic factors is essential to discuss improvements in patient care, to become increasingly customized and efficient.

The definitive answer to how microvascular invasion should be used in clinical practice requires a large,

**Table 2.** Probability of overall survival at 60 months in patients with non-small cell lung cancer treated surgically at INCA from 2010 to 2016.

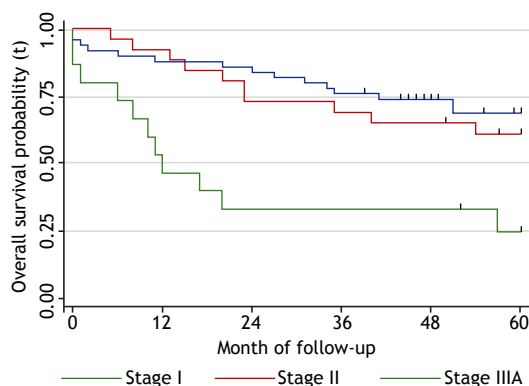
Characteristics	5-y OS	CI <sub>95%</sub>	log-rank p-value
Global	59.4	(48.3-68.9)	n.a.
Age group			
< 60 years	67.8	(48.1-81.3)	0.211
≥ 60 years	54.9	(41.1-66.8)	
Sex			
Male	59.4	(42.4-72.9)	0.683
Female	59.5	(44.3-71.8)	
Race			
White	62.6	(48.5-73.8)	0.618
Non-white	53.9	(35.2-69.4)	
Smoking status			
Never smoked	64.3	(34.3-83.3)	0.997
Current or former smoker	58.7	(46.6-68.9)	
Smoking load			
< 40 pack-years	69.3	(46.1-84.0)	0.456
40-59 pack-years	47.1	(25.5-66.1)	
≥ 60 pack-years	59.1	(39.2-74.4)	
Performance Status (PS)			
0	69.3	(50.3-82.2)	0.188
1	53.8	(39.7-65.9)	
Maximum SUV			
< 10	62.9	(46.3-75.6)	0.588
≥ 10	60.6	(42.0-74.9)	
Tumor size			
pT1	59.4	(37.6-75.8)	0.093
pT2	67.4	(51.6-79.0)	
pT3	42.9	(17.7-66.0)	
pN			
pN0	67.5	(55.1-77.1)	0.001
pN1	15.0	(1.0-45.7)	
pN2	37.5	(8.7-67.4)	
Pathological stage			
I	68.9	(53.5-80.0)	0.001
II	61.0	(39.6-76.9)	
IIIA	25.0	(6.9-48.8)	
Histological subtype			
Adenocarcinoma	61.3	(47.5-72.4)	0.878
Squamous cell carcinoma	58.6	(36.6-75.3)	
Microvascular invasion			
Absent	70.8	(58.0-80.4)	< 0.001
Present	26.1	(10.6-44.7)	

Abbreviations: 5-y OS, 5-year overall survival; CI, confidence interval; SUV, standardized uptake value; pN, pathological staging nodal descriptor.

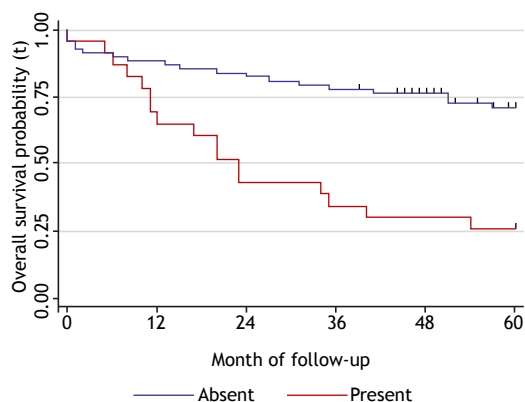
properly-designed clinical trial that systematically analyzes microvascular invasion and other pathological risk factors to assess adjuvant treatment. Additionally, microvascular invasion should be routinely studied in trials evaluating novel adjuvant therapies, such as immunological checkpoint blockade and targeted therapies. Such clinical trials require a multicenter effort, which was beyond the scope of the present study. In order to assess the impact of microvascular invasion

on the current staging group, the data collected herein was inserted into the IASLC database to construct the ninth edition of the TNM. These data will hopefully contribute to proving the role of microvascular invasion in NSCLC staging.

One limitation of this study was the relatively small sample size, which influenced the power to make inferences regarding potentially relative prognostic factors, including older age and symptomatic patients.



**Figure 2.** Overall survival probability curves of patients with non-small cell lung cancer treated surgically at INCA from 2010 to 2016, according to pathological stage.



**Figure 3.** Overall survival probability curves of patients with non-small cell lung cancer treated surgically at INCA from 2010 to 2016, according to the presence of microvascular invasion.

**Table 3.** 60-month risk of death in patients with non-small cell lung cancer treated surgically at INCA from 2010 to 2016.

Characteristics	Hazard Ratio (HR)					
	HR	Crude CI <sub>95%</sub>	p-value	HR	Adjusted CI <sub>95%</sub>	p-value
Age group						
< 60 years	1.0			1.0		
≥ 60 years	1.6	(0.8-3.3)	0.217	1.9	(0.9-3.9)	0.101
Pathological stage						
I	1.0			1.0		
II	1.3	(0.6-2.9)	0.521	0.8	(0.3-1.8)	0.555
IIIA	4.0	(1.8-8.8)	0.001	2.8	(1.2-6.5)	0.017
Microvascular invasion						
Absent	1.0			1.0		
Present	3.7	(1.9-7.1)	< 0.001	3.9	(1.9-8.2)	< 0.001

Abbreviations: CI, confidence interval.

However, the number of resected patients reflects the reality of how lung cancer presents in late stages at tertiary reference centers in the public healthcare system. Since microvascular invasion was systematically assessed in the pathology routine, tumor slides were not reviewed by the research investigators. As a consequence, contemporary prognostic factors such as tumor spread through air spaces<sup>(23)</sup> and histological patterns<sup>(24)</sup> were not reviewed. Also, a significant amount of data on tumor differentiation grade was missing, a fact that impacted the analysis.

Another limitation of the present study was that the seventh edition of the staging system was used in the analysis. This was because it was originally used when the cohort was treated. Also, the current analysis was

based on real-world data, thus lacking the quality control of a clinical trial. However, all patients were treated at the same institution, a reference cancer center in South America with solid expertise in lung cancer care and research. Importantly, long-term follow-up was achieved thanks to strong patient adherence.

Considering that NSCLC is one of the most incidental and aggressive types of cancer, with high mortality rates, even at early stages, the identification of prognostic factors is of utmost relevance and should enable healthcare providers to offer more appropriate treatment to each patient. The presence of microvascular invasion was an independent factor related to a worse prognosis and, therefore, should be routinely assessed in resected specimens.

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