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Prognostic value of adding blood and lymphatic vessel invasion to the 8th classification of TNM in lung cancer in stages I and II

Gemma-María Muñoz-Molina Sara Fra-Fernández Alberto Cabañero-Sánchez Diego Germán Rojas-Tula Cristina Cavestany-García-Matres Alfonso Muriel-García Usue Caballero-Silva Luis Gorospe-Sarasúa David Saldaña-Garrido Amparo Benito-Berlinches Nicolás Moreno-Mata

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AUTHORSHIP FILE

Original article

Title: Prognostic value of adding blood and lymphatic vessel invasion to the 8th classification of TNM in lung cancer in stages I and II.

Authors: Gemma-María Muñoz-Molina[a], Sara Fra-Fernández[a], Alberto Cabañero-Sánchez[a], Diego Germán Rojas-Tula[e], Cristina Cavestany-García-Matres[a], Alfonso Muriel-García[b], Usue Caballero-Silva[a], Luis Gorospe-Sarasúa[c], David Saldaña-Garrido[a], Amparo Benito-Berlinches[d], Nicolás Moreno-Mata[a].

Institution:

Ramon y Cajal Hospital, [a]Thoracic Surgery Department, [b]Statistics Department, [c]Radiology Departament, [d]Pathology Department.

[e]Nuestra Señora del Prado Hospital, Department of Pneumology.

Corresponding author. Gemma-María Muñoz-Molina, Thoracic Surgery Department, Ramón y Cajal Hospital, Ctra.Colmenar Viejo Km 9.1, 28034, Madrid, Spain. T. Number: +34 913368048 gmunozmolina@yahoo.es

ABSTRACT

Objectives: Expanding TNM staging system for lung cancer with the addition of new prognostic factors could enhance patient stratification and survival prediction. The goal of this study is to assess if TNM prognosis capacity could be improved by incorporating other pathological characteristics of surgical specimen.

Methods: We retrospectively reviewed lung cancer resections, stages I-II, performed

between January 1st 2010 and May 1st 2019. We collected clinical variables and pathological characteristics, including vascular, lymphovascular and perineural invasion, STAS, necrosis and stromal features. Mortality and recurrence-free survival were assessed with univariable and multivariable Cox analysis. We explored how these factors would modify the TNM Harrel's index.

Results: 629 tumors were analyzed. Median overall survival was 53.9 months. Median recurrence-free survival was 47.6 months. Specific survival at 3, 5 and 10 years was 90, 83 and 74%. Recurrence-free survival at 3, 5 and 10 years was 76, 70 and 65%. The multivariable analysis showed that overall survival was significantly related to TNM classification (p<0.0002), vascular infiltration (HR 1.93, CI 1.42-2.64, P<0.0001), lymphovascular invasion (HR 1.88, CI 1.30-2.71, p<0.0015) and necrosis (HR 1.74, CI 1.24-2.45, p<0.0025). Harrell's index for TNM was 0.6139. Adding vascular, lymphovascular invasion and necrosis, it increased up to 0.6531.

The multivariable analysis showed that specific survival was significantly related to TNM classification (p<0.001), vascular infiltration (HR 2.23, CI 1.44-3.46, P<0.001) and lymphovascular invasion (HR 1.85, CI 1.09-3.13, p<0.021). Harrell's index for TNM was 0.6645. Adding vascular and lymphovascular invasion, it increased up to 0.7103. Recurrence-free survival was related to TNM, vascular infiltration (HR 1.48, CI 1.05-2.09, p<0.023) and lymphovascular invasion (HR 2.40, CI 1.64-3.50, p<0.001). Harrell's index for TNM was 0.6264. Adding vascular and lymphovascular invasion, it increased up to 0.6794.

Conclusions: Including vascular and angiolymphatic invasion in the staging system classification could better stratify patients at risk of recurrence and tumor-related death.

Keywords: Blood vessel invasion; lymphovascular invasion; non-small cell lung cancer.

MAIN TEXT

Introduction

Cancer is one of the leading causes of mortality in the world. Lung cancer was the second cancer in incidence in 2020 and the most frequent cause of tumor-death despite therapeutic advances (18% of world deaths[1]). Patients are stratified according to their risk of recurrence and death by the TNM staging system, which is constantly under revision by the IASLC (International Association for the Study of Lung Cancer). Since January 2017 its 8th edition is in use. Adding molecular features to the anatomical TNM classification complements the pathologic description of the tumor and guides adjuvant therapies.

Previous editions of the TNM system mentioned that other pathological characteristics (such as lymphangitis, grade of differentiation, etc.) could have prognostic roles but none of them were included in the last edition. This possible prognostic role, apart from the anatomical descriptors, was underlined by several authors in the past.

For example, Bodendorf[2] observed that lung cancer patients in early stages with lymphovascular and blood vessel invasion progressed and developed metastases more frequently than those without them. Tsuchiya[3-4], affirmed that patients in stage IA with vascular invasion should be upstaged so their expected survival would be more accurate and they were treated, additionally, with adjuvant therapy.

Several studies have confirmed that the presence of lymphovascular invasion was clearly related to cancer recurrence[5-7] and to cancer-related death[8], specially in early stages.

The negative impact of perineural invasion, though previously studied, couldn't be confirmed, due to its scarce presence in the tumors in the published series[9-10].

Finally, other characteristics such as STAS (Spread through Air Spaces), tumoral necrosis and stromal features have been explored with uneven results.

For this reason, we have revised our database in order to determine the impact of the presence of these pathological characteristics in the patient's survival. We have tested if the prognostic capacity of the TNM system could be improved by adding them. Using

the regression Cox model we have evaluated the prognostic capacity of the TNM system in our series and compared it with our proposed model, using the Harrell's index, AIC, BIC, AUC and the Brier score.

Methods:

The main objective of this study was to evaluate the prognostic value of the presence of several pathological characteristics usually described in the pathological reports but lacking of recognized impact in the patient's survival. The secondary objective was to create a risk model including the variables with significant value.

We retrospectively reviewed the medical reports of all the patients who underwent surgical resection for non-small-cell lung cancer between January 1st 2010 and May 1st 2019 in the Thoracic Surgery Department of Ramón y Cajal Hospital.

We included all the patients treated for non-small-cell lung cancer, stages I-II, with curative intent and complete resection during this period of time. The surgical procedures included anatomic and non-anatomic resections (only in tumor smaller than 2 cm.) performed through open or VATS approaches. All procedures were completed with lymph node sampling. Patients with personal background of head and neck squamous tumors were excluded from the study to avoid the possible confusion between primary and secondary tumor. Finally, patients who died in direct relationship with the surgery, even if the event happened later than the 30th postoperative day, were excluded from the survival analysis (Fig. 1, Flow chart in Supplementary material).

TNM classification:

We revised all pathological reports to collect data regarding histology, pathological TNM and the variables of study (Blood vessel and lymphatic vessel invasion, perineural invasion, spontaneous necrosis, STAS and stromal characteristics). The same pathologist has evaluated all the surgical specimens during the time span of the study,

excluding the reader bias. We excluded cases whose pathological data were incomplete. The pathological data collector was blind to the patient's outcomes.

All the patients operated before 2017 were reclassified according to the 8th edition using the data present in the pathological report and the radiological images (for atelectatic lobe or lung).

Outcomes. Follow-up visits were scheduled every 3 months the first 2 years, every 6 months the third and fourth years and every 12 months afterwards. Local recurrence was defined as the appearance of soft tissue, nodular or mass, of the same histology as the primary tumor in the same lung, chest wall or mediastinum, while distant recurrence was defined when it appears in the other hemithorax, or any other distant site.

Statistical Analysis: For comparison, T-test was used for continuous variables with normal distribution and Mann-Whitney U-test for continuous variables without normal distribution (median, range, quartiles,…). Categorical variables are presented as frequencies and percentages and Chi-square is used for comparison. When the expected frequency of an event is inferior to 5 in more than 25% of cells, we selected Fisher's test.

Overall survival (OS) spans from the day of surgery to the last date of follow up and Recurrence-free survival (RFS) from the day of surgery to the day of demonstrated local or distant recurrence. Cancer-related survival or cancer-specific survival (CRS) extends from the day of surgery to the date of death, when this occurs as a direct result of cancer. Kaplan-Meier method was used to analyse OS, RFS and CRS for each variable.

Multivariable Cox regression analysis was used to test if the presence of the pathological variables of interest simultaneously with the TNM classification influenced the cancer-related and recurrence-free survival.

Significance level is set to 0.05, two-sided. All statistical analysis were performed using STATA 16.1.

The statistically significant variables were included in a model with the TNM classification. We calculated the Harrel's index, the Akaike information criteria (AIC) and the Bayesian Information criteria (BIC) of both, the TNM staging system and the new model that incorporates the TNM with statistically significant pathological characteristics, to evaluate if the new model really improves the prognostic capacity of the TNM staging system. Because adding more variables to a model usually increases the Harrel's Index, even if they are not relevant statistically, we calculated BIC and AIC (which penalize the addition of many variables, making the Harrell's index more useful). To provide a measure of the added prognostic value of the proposed model, we have also calculated the AUC for 36 months of follow-up and the Brier score for 36 and 48 months.

Results

A total of 629 tumors were resected. Eight patients died during the first 30 days of the postoperative period. The distribution of clinical variables are exposed in the table 1. After reaching a median follow-up of 44.32 months, 212 patients (33.70%) died. At the final follow-up, 368 of the patients (88.24%) remained completely free of disease, 37 of them (8.87%) had a relapse of the resected lung tumor, and 12 (2.87%) have developed a different tumor.

The overall survival at 3, 5 and 10 years was 80, 70 and 44% respectively (IA1 92%, 74%, 57%, IA2 87%, 82%, 54%, IA3 77%, 66% 41%, IB 84%, 73%, 42%, IIA 81%, 67%, 37%, IIB 62%, 54%, 38%), with a median survival of 53 months. The cancer-related survival at 3, 5 and 10 years was 90, 83 and 74 % respectively (IA1 95%, 81%, 69%, IA2 97%, 94%, 84%, IA3 90%; 81%, 75%, IB 91%, 82%, 75%, IIA 91%, 86%, 67%, IIB 76%, 71%, 64%). The causes of death are displayed in table 1.

Recurrence-free survival at 3, 5 and 10 years was 76, 70 and 65% respectively (IA1 82%, 79%, 73%, IA2 87%, 83%; 75%, IA3 82%, 76%, 65%, IB 71%, 65%, 62%, IIA 78%, 73%, 66%, IIB59%, 52%, 52%) with a median survival of 48 months.

Table 2 shows the distribution of the pathological characteristics of interest in relation with histology, stage, grade of differentiation, tumor size, pleural invasion and nodal invasion (Expanded information in the supplementary material).

Blood vessel invasion, STAS and spontaneous necrosis seem to be distributed differently in the histological types considered. The presence of blood vessel invasion, perineural invasion and also necrosis increased gradually with the increasing of tumoral stage. The presence of necrosis and inflammatory stroma appeared to be related with the grade of differentiation. All the pathological characteristics except inflammatory stroma were present more frequently when the tumor size increased. Finally, blood vessel invasion, lymphovascular invasion and perineural invasion were related with the presence of nodal invasion (table 2 and supplementary material).

The univariable analysis of patients' characteristics for CRS and RFS is shown in table 3.

In the univariable analysis the factors that influenced the OS were sex ($p<0.0000$), smoking status ($p<0.0006$), type of resection ($p<0.0222$), anatomic resection ($p<0.047$), grade of differentiation ($p<0.0111$), TNM stage ($p<0.0002$), Histology (0.011), distance to the resection border ($p<0.0029$) and achieving R0 ($p<0.0252$). Cancer-related survival was influenced by sex ($p<0.0004$), age ($p<0.0026$), TNM stage ($p<0.0001$), distance to the resection border ($p<0.0001$) and achieving R0 ($p<0.0008$). Recurrence-free survival was mostly influenced by sex ($p<0.0054$), smoking status ($p<0.0051$), anatomic resection ($p<0.012$), TNM stage ($p<0.0000$) and the distance to the resection border ($p<0.0006$). When alternative pathological characteristics were analysed, OS, CRS and RFS were influenced by blood vessel invasion (CRS HR 2.23 CI 1.44-3.46 $p<0.0001$, RFS HR 1.48 CI 1.05-2.09 $p<0.0005$) and lymphovascular invasion (CRS HR 1.85 CI 1.09-3.13, $p<0.0015$, RFS HR 2.40 CI 1.64-3.5 $p<0.0001$) (table 3 and supplementary material).

In the multivariable analysis we included the TNM staging and every pathological characteristics. The results are displayed in table 4 (See also supplementary material).

We created a prognostic model for the OS, CRS and RFS with the variables that maintained significance (table 5).

The predictive capacity of the TNM system for the OS in our series, measured by the Harrell's Index, was 0.6139. It increased up to 0.6531 in the proposed model (TNM with blood vessel invasion, lymphovascular invasion and tumoral necrosis). The predictive capacity of the TNM system for the CRS in our series, measured by the Harrell's Index, was 0.6645. It increased up to 0.7103 in the proposed model (with TNM, blood vessel invasion and lymphovascular invasion). Parallel, AIC and BIC decreased, confirming that the changes observed in Harrell's index really reflected a better prognostic capacity. Regarding the RFS, the Harrell's index for the TNM staging system in our series was 0.6264, which increased up to 0.6794 in the proposed model (with TNM, blood vessel invasion and lymphovascular invasion), while the AIC and BIC decreased.

As we decided to include non-anatomical resection in our series, we performed a Cox regression analysis with the proposed model and the surgical procedure to evaluate if the latter influenced more than the pathological variables. We were able to see that, although non-anatomic resection influenced survival, when analyzed together with the variables of interest for the study (blood and lymphatic invasion), these remained statistically significant as risk factors, with minimal changes in their respective hazard ratios (supplementary material).

We have made an additional analysis focusing on the Stage I. In the univariable analysis the factors that influenced the OS were age ($p<0.001$), sex ($p<0.0001$), smoking status ($p<0.003$), immunosuppression ($p<0.001$), type of resection ($p<0.048$), anatomic resection ($p<0.043$), TNM stage ($p<0.014$), Histology (0.011), distance to the resection border ($p<0.003$) and achieving R0 ($p<0.0002$). Cancer-related survival was influenced by sex ($p<0.003$), immunosuppression ($p<0.011$), TNM stage ($p<0.0148$), distance to the resection border ($p<0.001$) and achieving R0 ($p<0.0001$). Recurrence-

free survival was mostly influenced by sex (p<0.036), smoking status (p<0.011), type of resection (p<0.0255), anatomic resection (p<0.013), TNM stage (p<0.0181), the distance to the resection border (p<0.001) and achieving R0 (p<0.001) (table 22, 28, supplementary material). When alternative pathological characteristics were analysed, OS, CRS and RFS were influenced by blood vessel invasion (OS HR 1.84 CI 1.22-2.77 p<0.003, CRS HR 2.81 CI 1.60-4.93 p<0.0001, RFS HR 1.93 CI 1.26-2.94 p<0.002), lymphovascular invasion (OS HR 1.93 CI 1.22-3.06 p<0.005, CRS HR 2.68 CI 1.41-5.09 p<0.002, RFS HR 3.17 CI 2.00-5.00 p<0.0001) and also necrosis (OS HR 1.96 CI 1.25-3.09 p<0.003, CRS HR 2.11 CI 1.064-4.19 p< 0.032, RFS HR 1.95 CI 1.13-3.38 p< 0.016) (table 23-24, 29 in the supplementary material).

In the multivariable analysis we included the TNM staging and every pathological characteristics. The results are displayed in the supplementary material, tables 25-26, 30.

We created a prognostic model for the OS, CRS and RFS with the variables that maintained significance (Vascular invasion and lymphovascular invasion, tables 27, 31 supplementary material).

The predictive capacity of the TNM system for the OS in stage I, measured by the Harrell's Index, was 0.5610. It increased up to 0.6184 in the proposed model (TNM with blood vessel invasion, lymphovascular invasion and tumoral necrosis). The predictive capacity of the TNM system for the CRS in stage I, measured by the Harrell's Index, was 0.57. It increased up to 0.6943 in the proposed model (with TNM, blood vessel invasion and lymphovascular invasion). Parallel, AIC and BIC decreased, confirming that the changes observed in Harrell's index really reflected a better prognostic capacity.

Regarding the RFS, the Harrell's index for the TNM staging system in our series was 0.5880, which increased up to 0.6736 in the proposed model (with TNM,

blood vessel invasion, lymphovascular invasion and necrosis), while the AIC and BIC decreased.

Discussion

The 8th edition of the TNM staging system stratifies lung cancer patients, correlating their stage with the expected overall survival. It is under continuous revision in order to improve its prognostic capacity.

In this series, we have explored whether other pathological characteristics could complement its predictive information.

The presence of tumoral cells in the vascular lumen could mean that they have traveled through the blood or the lymph to a distant organ and stay as dormant cells, from where they could later grow to become distant metastases. Several authors have explored if both types of vascular invasion were independent prognostic factors with discrepant results. Kessler[11], in a retrospective series of surgical patients confirmed that blood vessel invasion was an independent prognostic factor for overall survival together with the T and the N. Noma[8], using the 8th TNM edition, concluded that the prognosis of the patients in stage IA with blood vessel invasion is similar to that of the stage IB, suggesting that they should be upstaged, a similar conclusion of that of Tsuchiya[3] using the previous edition of TNM.

As commented in the introduction, Bodendorf[2] confirmed the impact of vascular invasion over the recurrence. Recently, in a multicenter study, Dziedzic[12] found that vascular and lymphovascular invasion were associated independently to local and distant metastases.

In our database, lymphovascular invasion influenced both OS and RFS. Recently, Tao[13] affirmed that in tumors less than 2 centimeters, the survival of patients with lymphovascular invasion was equivalent to that of the patients with pleural invasion, and suggested passing these patients to stage T2. Yun[14] also demonstrated the

negative impact of lymphovascular invasion in OS and RFS in the stage IA, which was even stronger in the sublobar resections, recommending to avoid them, something previously stated by Chen[7]. Remarkable is Ruffini's[15] conclusion, who affirmed that the effect of vascular invasion in the OS and RFS was so strong that it cancelled the influence of tumor size.

Al-Alao[6] and Park[16] found a relationship between vascular invasion and OS in stages I and II, whilst lymphovascular invasion was related to RFS.

Spontaneous necrosis, related to hypoxia and higher aggressiveness of the tumor[17], emerged as a significant prognostic factor only for OS in our analysis.

The association between the presence of necrosis and OS and RFS has been previously described and used to stratify the patients for treatment by differents groups[18-20].

Several authors[21-23] have stated that STAS may be present in every stage and in every histologic subtype, confirming likewise the negative repercusions on the OS and RFS. We were not able to demonstrate the prognostic significance of STAS, perineural invasion and stroma. A possible explanation is that the high influence of vascular invasion conceals their importance.

Regarding the inflammatory stroma, we could not demonstrate our hypothesis. Kessler[11] obtained the same results. He had also introduced other variables, like vascular invasion, which could darken the real influence of the stroma in the survival.

Harrell's index measures the prognostic capacity of a model. It was used to evaluate the inclusion of changes in the 8th edition of the TNM system. Slight increases in Harrell's index served to introduce the modifications. External validations[24-25] published after the publication of the 8th edition of the TNM, described the improvements as discrete and slight. In our series, the increase of Harrell's Index was outstanding when adding both types of vascular invasion to the TNM, showing an augmentation of the prognostic capacity of the proposed risk model. As commented, this increase accompanied by the decrease in AIC and BIC support the real improvement of the

prognostic capacity of the model. Further prospective studies should confirm these findings in order to see if including them in the pathological classification could be of interest. In addition, a thorough analysis of the survival and recurrence rates in case of vascular or lymphovascular invasion presence is needed to evaluate if it is appropriate to upstage the patient.

There are several limitations in this study. First of all, its retrospective character makes it prone to several errors. In addition, the need to restage those patients operated before 2017, when the new edition started to be used, makes it possible that we could have made mistakes in the process, specially in evaluating the pleural infiltration. Consequently, patients that should have been included in stage IB could have been mistakenly staged in stage IA. This would have negatively impacted the OS and RFS rates. Regarding the modality of treatments, a possible bias could be found because some of the patients received adjuvant therapy due to the stage with the goal of increasing the survival. Nevertheless, adjuvant therapy is meant to increase survival, so it would have contributed to contradicting the main hypothesis of this work. Additionally, the pathologists may have not described some of these variables along this period. For example, STAS, was accepted as a way of dissemination in 2015. For this reason, the previous pathologic reports could lack of its description even if it was present. Further, without a systematic search for vascular invasion, it could be ignored. This is why homogenization of the techniques to detect vascular invasion remains necessary, making the comparison between studies possible[6, 26].

On the other hand, a long period of time was revised. For this reason many patients' information has been lost.

Finally, it could be pointed out that this model is only useful for surgical cases. Nevertheless, vascular invasion can also be identified in some large-core biopsies and, even when these pathological characteristics were only identifiable in surgical cases, their prognostic value should not be underestimated, since pleural involvement can

only be accurately evaluated in surgical specimens and was introduced in the TNM classification.

Conclusion

Including other pathological characteristics such as vascular invasion in the TNM classification could help us better stratify the patients according to their risk of death or recurrence. This could also lead us to include certain patients in a different stage than that in which, with the 8th TNM edition, are classified, and even modify the follow-up or the strategy of treatment. An international prospective study is needed to test other potentially prognostic pathological variables after a necessary homogenization of the detection techniques.

FINAL DECLARATION SECTION:

All authors have contributed equally to the concept, revision, writting and editing of this work.

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The authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.

All the procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by the appropriate institutional committee. This observational retrospective cohort study was approved by the Ethics Committee of Ramón y Cajal Hospital, 25/03/2021, ID number CEIM 082/21. The Institutional Review Board also waived the need for written informed consent from each patient..

The entire manuscript and supplementary material have not been, neither completely nor partialy, produced with the help of any artificial intelligence software or tool.

Meeting presentation: This work was partially presented at the 30th European conference on General Thoracic Surgery, The Hague, The Nederlands,19-21 June 2022 as an oral presentation in the Pulmonary neoplastic I session and in the annual conference of the Sociedad Española de Cirugía Torácica (SECT) in Bilbao, 11-13 May 2022.

Data Availability Statement. *The data underlying this article will be shared on reasonable request to the corresponding author.*

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Variables	N=629
Age, years	68
Sex - Female - Male	 170 (27.03%) 459 (72.97%)
Smoking history - Never - Ever	 73 (11.61%) 556 (88.39%)
High blood pressure	306 (48.65%)
Diabetes	121 (19.24%)
Previous malignancy	264 (41.9%)
Cardiovascular	125 (19.87%)
Immunosuppression	23 (3.66%)
Type of resection - Lobectomy - Bilobectomy/pneumonectomy - Anatomic sublobar resection - Non anatomic	 498 (79.17%) 39 (6.20%) 47 (7.47%) 45 (7.15%)
Adjuvant treatment	108 (17.27%)
Histology - Adenocarcinoma - Squamous - Carcinoid - Other (excluding Small cell lung cancer)	 382 (60.73%) 161 (25.60%) 46 (7.31%) 40 (6.36%)
TNM (8th edition) - IA1 - IA2 - IA3 - IB - IIA - IIB	 72 (11.45%) 161 (25.60%) 90 (14.31%) 145 (23.05%) 30 (4.77) 131 (20.83%)
Death	212 (33.70%)
Cause of death - Tumoral - Complications during treatment - Non-related causes	 93 (43.87%) 20 (9.43%) 99 (46.7%)

Table 1: Patient characteristics.

Variable	BVI	LVI	PNI	STAS	Nec	IS
Histology p value	<0.001	0.454	0.057	0.042	<0.001	0.059
Adenocarcinoma	76 (19.9)	47 (12.3)	5 (1.31)	71 (18.6)	24 (6.28)	48 (12.57)
Squamous	51 (31.7)	22 (13.7)	7 (4.35)	20 (12.42)	31 (19.25)	27 (16.8)
Carcinoid	2 (4.35)	3 (6.52)	0	2 (4.35)	5 (10.87)	1 (2.17)
Other (other subtypes except small cell lung cancer)	15 (37.5)	7 (17.50)	0	7 (17.50)	14 (35)	7 (17.50)
TNM (8th edition) p value	0.016	0.074	0.005	0.925	<0.001	0.604
IA1	9 (12.5)	4 (5.56)	0	10 (13.89)	1 (1.39)	6 (8.33)
IA2	28 (17.40)	14 (8.7)	1 (0.62)	28 (17.39)	11 (6.83)	27 (16.77)
IA3	21 (23.33)	12 (13.3)	0	15 (16.7)	7 (7.78)	10 (11.11)
IB	39 (26.9)	23 (15.86)	2 (1.38)	24 (16.55)	20 (13.79)	19 (13.1)
IIA	6 (20)	3 (10)	2 (6.67)	3 (10)	7 (23.33)	4 (13.33)
IIB	41 (31.3)	23 (17.56)	7 (5.34)	20 (15.27)	28 (21.37)	17 (12.98)
Grade Differentiation	0.157	0.089	0.198	0.756	<0.001	0.000
Size of tumor	0.0249	0.0409	0.0435	0.0004	<0.001	0.89
Pleural invasion	<0.001	0.006	<0.001	0.074	0.020	0.810
N1 p value	<0.001	0.017	0.034	0.279	0.615	0.712

Table 2. Tumor characteristics (N: 629). BVI: Blood vessel invasion; LVI: Lymphovascular invasion; PNI: Perineural invasion; STAS: spread through air spaces; Nec: necrosis; IS: inflammatory stroma. Percentages between parentheses.

Variables	HR OS	CI	p	HR CRS	CI	p	HR RFS	IC	p
Age	1.04	1.024529-1.057438	0.0001	1.035954	1.011693-1.060796	0.0026	1.008768	.9921212-1.025693	0.3001
Sex	2.795269	1.888769-.136835	0.0001	2.542906	1.439986-4.490579	0.0004	1.65761	1.14154-2.406988	0.0054
High blood pressure	1.252676	9561623-1.64114	0.1015	.8139722	.5398334-1.227324	0.324	.9865063	.728219-1.336404	0.9301
Diabetes	1.832367	1.346582-2.4934	0.003	1.451441	.8839988-2.383126	0.1555	1.384293	.9563105-2.003811	0.0949
Cardiovascular	1.393479	1.000953-1.939934	0.0570	986796	.5668308-1.717914	0.9625	.9118657	.6071047-1.369614	0.6534
Immunosupression	2.335895	1.271145-4.292512	0.0154	1.962025	.7191608-5.352823	0.2328	1.673733	.7845657-3.570614	0.2169
Smoker	2.444957	1.365247-4.378559	0.0006	1.86615	.8635721-4.032688	0.0827	2.180592	1.182884-4.019819	0.0051
Type resection -Lobectomy -Bilobectomy-pneumonectomy -Sublobar -Non-anatomic	 Referencia 1.051266 1.92881 1.689667	 .5964- 1.852 1.194- 3.113 1.059- 2.694	0.0222 0.863 0.007 0.028	 Reference 1.472699 1.611372 1.736108	 .7079-3.063 .7386-3.515 .8661-3.479	0.2876 0.3 0.231 0.120	 Reference 1.234823 1.357602 1.950917	 0.682245-2.23306 0.749597-2.458767 1.189715-3.19915	0.0812 0.485 0.313 0.008
Anatomic resection	.62588	.3943137-.9934369	0.047	.6147482	.3089439-1.223249	0.166	.5322019	.3262096-.8682728	0.012
Histology			0.0011						0.6440
Grade of differentiation	1.607778	1.134968-2.277554	0.011	1.295519	.7331557-2.289241	0.3871	1.312532	.8514547-2.023292	0.2331
TNM (8th edition)			0.0002			0.0001			0.0000
Distance to the border of tumor	.9752499	.9594296-.9913312	0.0029	.9567726	.934122-.9799724	0.000	.9688249	.9516588-.9863007	0.0006
R0	3693626	173601-.7858754	0.0252	.1657463	.0723018-.3799604	0.0008	.2333132	.1091558-.4986913	0.0021
Number of nodal stations biopsied	.9683025	.8717441-1.075556	0.5485	.9620959	.8213203 -1.127001	0.6328	.8962669	.7983219-1.006229	0.0653
BVI	1.937535	1.421093-2.641657	0.0001	2.537609	1.647344-3.908997	0.0001	1.85744	1.331697-2.590741	.0005
LVI	1.883256	1.307513-2.71252	0.0015	2.273553	1.357635-3.80739	0.0042	2.86702	.985754-4.139384	0.000

PNI	1.642324	.7285777-3.702048	0.2671	2.390061	.8773838-6.510711	0.1330	2.271679	.005379-5.132915	.0803
STAS	.654145	.3846531-1.112446	0.0968	.6732458	. 309175-1.46603	0.2930	.85455	.5343157-1.366712	.5036
Necrosis	1.74493	1.240818-2.45385	0.0025	1.685657	1.00624-2.823819	0.047	1.575044	1.04222-2.380268	.0406
IS	1.157237	.7808519-1.715046	0.4746	.8185288	.4245934-1.577956	0.5394	.9960347	6360239-1.559824	.9961

Table 3. Univariable analysis for overall and cancer-related survival (CRS) and recurrence-free survival (RFS). BVI: Blood vessel invasion; LVI: Lymphovascular invasion; PNI: Perineural invasion; STAS: Spread through air spaces; IS: inflammatory stroma. Percentages between parentheses.

Var.	HR OS	CI	p	HR CRS	CI	p	HR RFS	IC	p
BVI	1.824	1.328-2.505	0.000	2.32	1.492- 3.610	0.000	1.5514	1.098-2.190	0.013
LVI	1.705	1.171-2.480	0.005	1.99	1.172-3.381	0.011	2.5673	1.749-3.766	0.000
PNI	1.059	.4611-2.430	0.893	1.33	0.476- 3.738	0.583	1.452	.6321-3.335	0.0803
STAS	.5676	.3299-.9765	0.041	0.54	0.243-1.200	0.131	.6777	.4161-1.103	0.118
Nec	1.456	1.023- 2.072	0.037	1.32	0.776- 2.262	0.302	1.253	.8161-1.924	0.302
IS	1.150	0.772-1.712	0.491	0.84	0.434-1.636	0.614	1.022	0.648-1.609	0.926

Table 4. Multivariable analysis. Var: Variable; BVI: Blood vessel invasion; LVI: Lymphovascular invasion; PNI: Perineural invasion; STAS: Spread through air spaces; Nec: necrosis; IS: inflammatory stroma. Percentages between parentheses.

	Harrell's I. OS survival	AIC	BIC	AUC	Brier score 36 months	Brier score 48 months
Current Model						
TNM	0.6139	2355.674	2377.831	0.55	0.18 (0.17-0.19)	0.19 (0.158-0.22)
Proposed Model						
TNM + BVI + LVI + necrosis	0.6531	2338.563	2374.013	0.681	0.17 (0.15-0.18)	0.18 (0.1-0.20)
	Harrell's I. CRS survival	AIC	BIC	AUC	Brier score 36 months	Brier score 48 months
Current Model						
TNM	0.6645	1085.101	1107.101	0.623	0.07 (0.055-0.088)	0.082 (0.06-0.09)
Proposed Model						
TNM + BVI + LVI	0.7103	1071.054	1102.073	0.713	0.07 (0.052-0.085)	0.07 (0.06-0.09)
Variables	Harrell's I. Recurrence-free survival	AIC	BIC	AUC	Brier score 36 months	Brier score 48 months
Current Model						
TNM	0.6264	2013.016	2035.173	0.56	0.17 (0.15-0.18)	0.18 (0.169-0.20)
Proposed Model						
TNM + BVI + LVI	0.6794	1990.61	2021.63	0.694	0.16 (0.14-0.18)	0.17 (0.15-0.19)

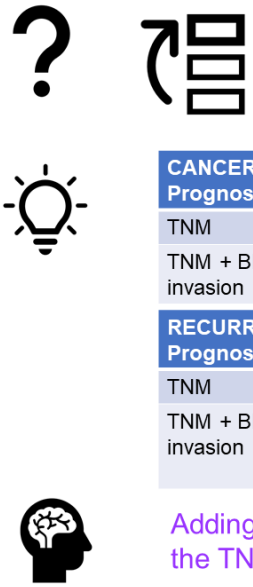
Table 5. Harrell's index, AIC, BIC AUC and Brier score. Comparison between the models. BVI: Blood vessel invasion; LVI: Lymphovascular invasion.

Visual abstract:

Key question: Are there other pathological characteristics that could improve the TNM prognostic model in non-small-cell lung cancer?

Key findings: Including blood vessel and lymphovascular invasion may improve TNM prognostic capacity in the early stages of lung-cancer.

Take home message: The TNM classification may be complemented with other pathological variables to increase its prognostic and predictive capacity.



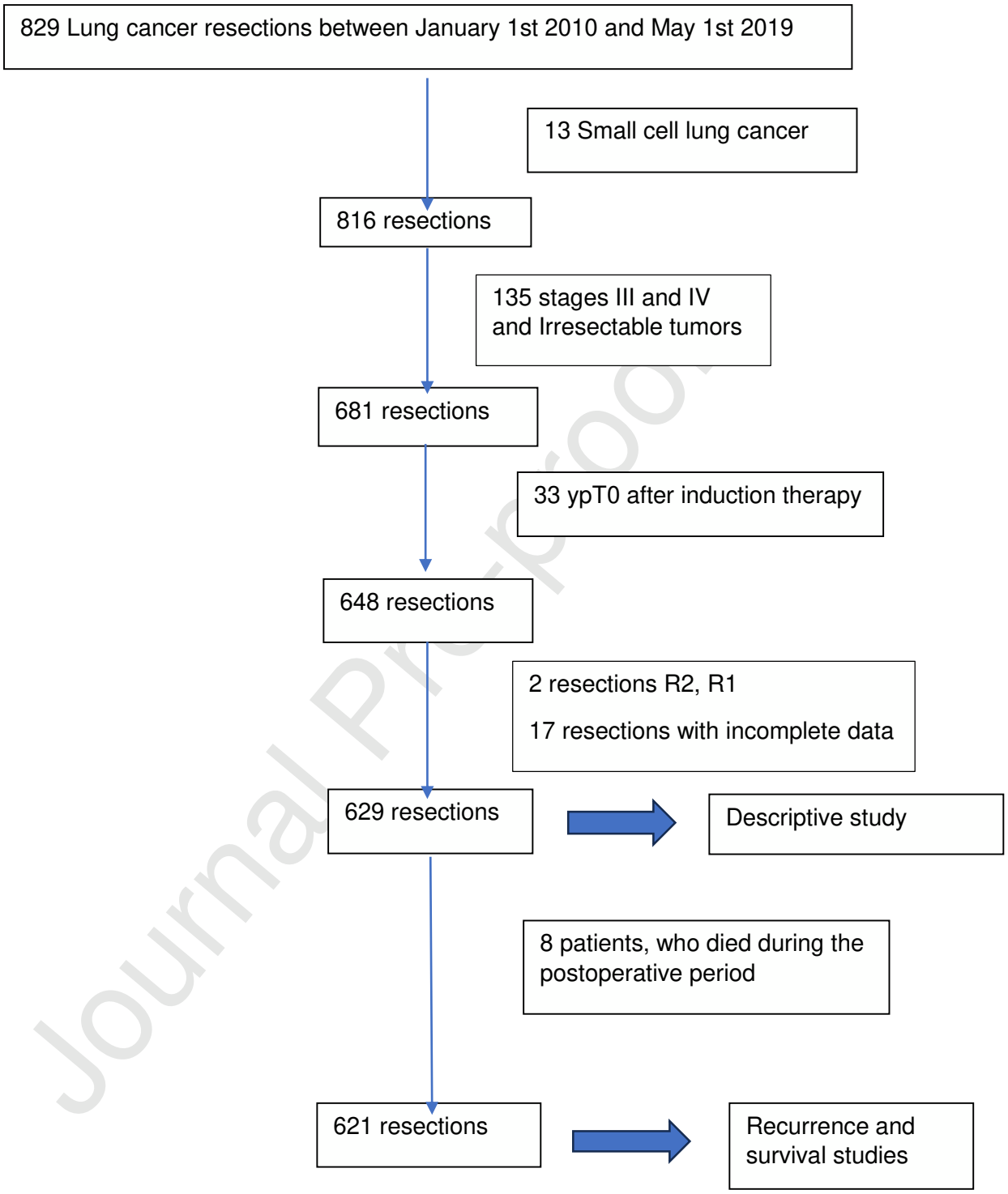


Fig.1. Flowchart.

Pathological Characteristics / Histology n (%)	Adenocarcinoma	Squamous	Carcinoid	Others	p
Blood vessel invasion	76 (19.9)	51 (31.68)	2 (4.35)	15 (37.5)	0.000
Lymphovascular invasion	47 (12.30)	22 (13.66)	3 (6.52)	7 (17.50)	0.454
Perineural invasion	5 (1.31)	7 (4.35)	0 (0)	0 (0)	0.057
STAS	71 (18.59)	20 (12.42)	2 (4.35)	7 (17.50)	0.042
Necrosis	24 (6.28)	31 (19.25)	5 (10.87)	14 (35)	0.000
Inflammatory stroma	48 (12.57)	27 (16.77)	1 (2.17)	7 (17.50)	0.059

Table 1. Distribution of the pathological variables in the histological subtypes.

Pathological Characteristics / Grade of differentiation n (%)	Good / Moderate	Poor / Indiferentiate	p
Blood vessel invasion	122 (22.02)	22 (29.33)	0.157
Lymphovascular invasion	65 (11.73)	14 (18.67)	0.089
Perineural invasion	12 (2.17)	0 (0)	0.198
STAS	89 (16.06)	11 (14.67)	0.756
Necrosis	51 (9.21)	23 (30.67)	0.000
Inflammatory stroma	63 (11.37)	20 (26.67)	0.000

Table 2. Distribution of the pathological variables in the different grades of differentation.

Pathological Characteristics / pleural invasion n (%)n (%)	pl0	pl1	pl2	pl3	p
Blood vessel invasion	92 (19.74)	27 (26.73)	23 (52.27)	2 (11.11)	0.000
Lymphovascular invasion	48 (10.30)	17 (16.83)	12 (27.27)	2 (11.11)	0.006
Perineural invasion	6 (1.29)	2 (1.98)	1 (2.27)	3 (16.67)	0.000
STAS	75 (16.09)	12 (11.88)	12 (27.27)	1 (5.56)	0.074
Necrosis	45 (9.66)	16 (15.84)	8 (18.18)	5 (27.78)	0.020
Inflammatory stroma	62 (13.30)	15 (14.85)	4 (9.09)	2 (11.11)	0.810

Table 3. Distribution of the pathological variables in the different types of pleural invasion.

Pathological Characteristics / Lymph node infiltration n (%)	N0	N1	p
Blood vessel invasion	121(20.97)	23 (44.23)	0.000
Lymphovascular invasion	67 (11.61)	12 (23.08)	0.017
Perineural invasion	9 (1.56)	3 (5.77)	0.034
STAS	89 (15.42)	11 (21.15)	0.279
Necrosis	69 (11.96)	5 (9.62)	0.615
Inflammatory stroma	77 (13.34)	6 (11.54)	0.712

Table 4. Distribution of the pathological variables according to the lymph node invasion.

Pathological Characteristics / tumoral size in mm	p
Blood vessel invasion	0.0249
Lymphovascular invasion	0.0409
Perineural invasion	0.0435
STAS	0.0004
Necrosis	0.0000
Inflammatory stroma	0.89

Table 5. Distribution of the pathological variables according to the tumoral size.

Variables	HR O. Survival	CI	p	HR Cancer-specific survival	CI	p
Age	1.040853	1.024529 - 1.057438	0.000	1.035954	1.011693 - 1.060796	0.0026
Sex	2.795269	1.888769 - 4.136835	0.000	2.542906	1.439986 - 4.490579	0.0004
High blood pressure	1.252676	.9561623 - 1.64114	0.1015	.8139722	.5398334 - 1.227324	0.324
Diabetes	1.832367	1.346582 2.4934	0.0003	1.451441	.8839988 - 2.383126	0.1555
Cardiovascular	1.393479	1.000953 - 1.939934	0.0570	.986796	.5668308 - 1.717914	0.9625
Inmunosupression	2.335895	1.271145 - 4.292512	0.0154	1.962025	.7191608 - 5.352823	0.2328
Smoking habit	2.444957	1.365247 - 4.378559	0.0006	1.86615	.8635721 - 4.032688	0.0827
Type of resection - Lobectomy - Bilobectomy -	Reference		0.0222	Reference		0.2876

pneumonectomy	1.051266	.5964 1.852	0.863	1.472699	.7079 3.063	0.3
- Sublobar						
- Non anatomic	1.92881	1.194 3.113	0.007	1.611372	.7386 3.515	0.231
	1.689667	1.059 2.694	0.028	1.736108	.8661 3.479	0.120
Anatomic Resection	.62588	.3943137 .9934369	0.047	.6147482	.3089439 1.223249	0.166
Histology			0.0011			0.1681
- Adenocarcinoma	Reference			Reference		
- Squamous	1.305376	.9564 1.781	0.093	1.392604	.8825 2.197	0.155
- Carcinoid	.5500281	.2787 1.085	0.085	.6856727	.2735 1.718	0.421
- Others	2.163062	1.356 3.448	0.001	1.835979	.8709 3.870	0.110
Grade of differentation	1.607778	1.134968 2.277554	0.0111	1.295519	.7331557 2.289241	0.3871
TNM			0.0002			0.0001
- IA1	Reference			Reference		
- IA2	.9446696	.5227 - 1.707	0.850	.3514802	.1386 .8907	0.028
- IA3	1.632735	.8981 - 2.968	0.108	1.071437	.4695 2.444	0.870
- IB	1.295196	.7351 - 2.281	0.371	1.087971	.5221 2.267	0.822
- IIA	1.633809	.7853 - 3.398	0.189	1.01997	.3483 2.986	0.971
- IIB	2.407819	1.385 - 4.184	0.002	2.113847	1.038 4.300	0.039
Distance to the border of the tumor	.9752499	.9594296 - .9913312	0.0029	.9567726	.934122 - .9799724	0.000
R0	.3693626	173601 - .7858754	0.0252	.1657463	.0723018 - .3799604	0.0008
Number of nodal stations biopsied	.9683025	.8717441 - 1.075556	0.5485	.9620959	.8213203 - 1.127001	0.6328

Table 6. Univariate analysis for overall and cancer specific survival according to personal background and other characteristics.

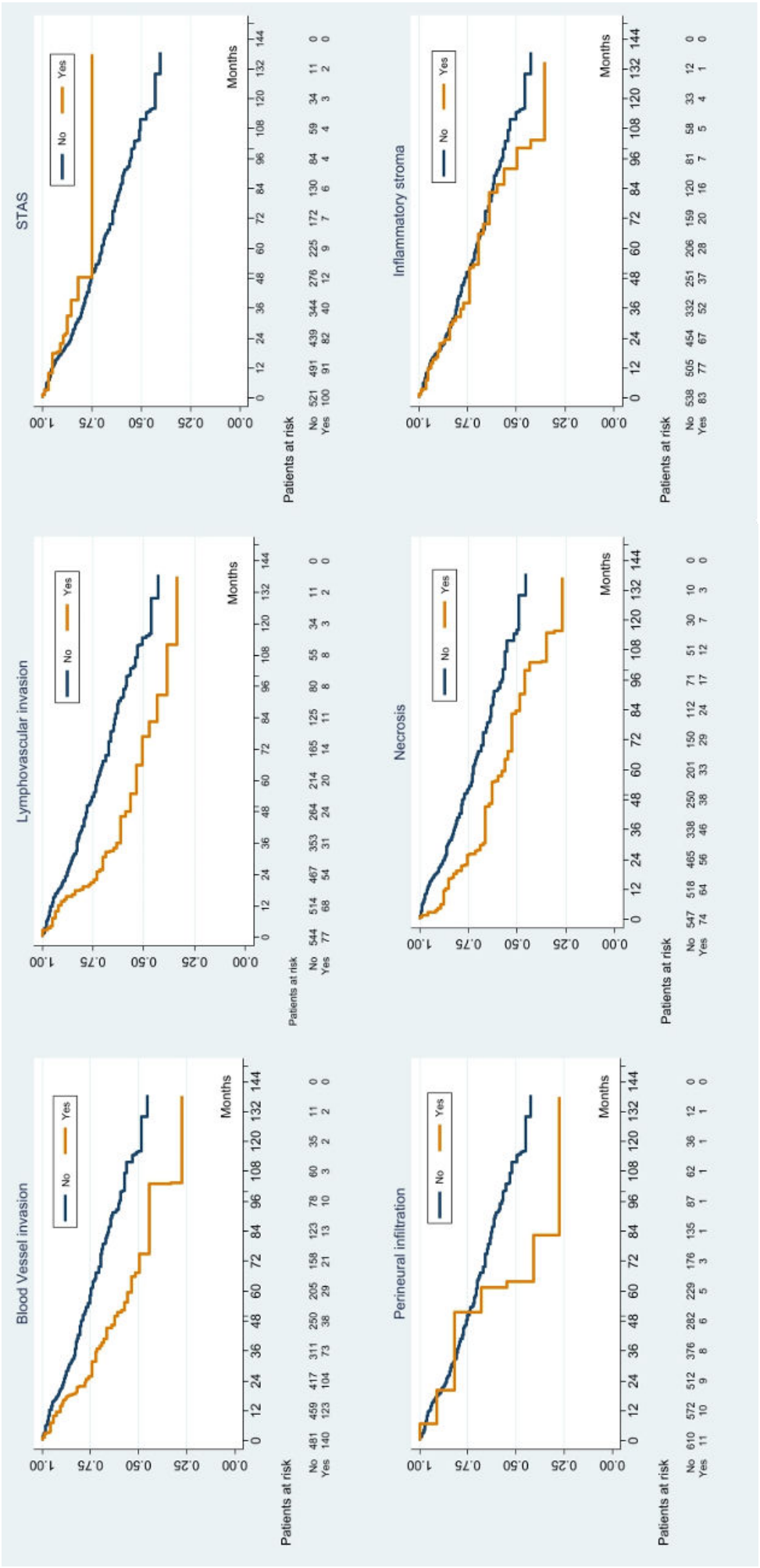


Figure 2. Kaplan Meier curves for overall survival according to the presence or absense of the pathological characteristics of interest.

Variables	HR	CI	p
Blood vessel invasion	1.937535	1.421093 2.641657	0.0001
Lymphovascular invasion	1.883256	1.307513 2.71252	0.0015
Perineural infiltration	1.642324	.7285777 3.702048	0.2671
STAS	.654145	.3846531 1.112446	0.0968
Necrosis	1.74493	1.240818 2.45385	0.0025
Inflammatory stroma	1.157237	.7808519 1.715046	0.4746

Table 7. Univariate analysis of overall survival for the pathological variables.

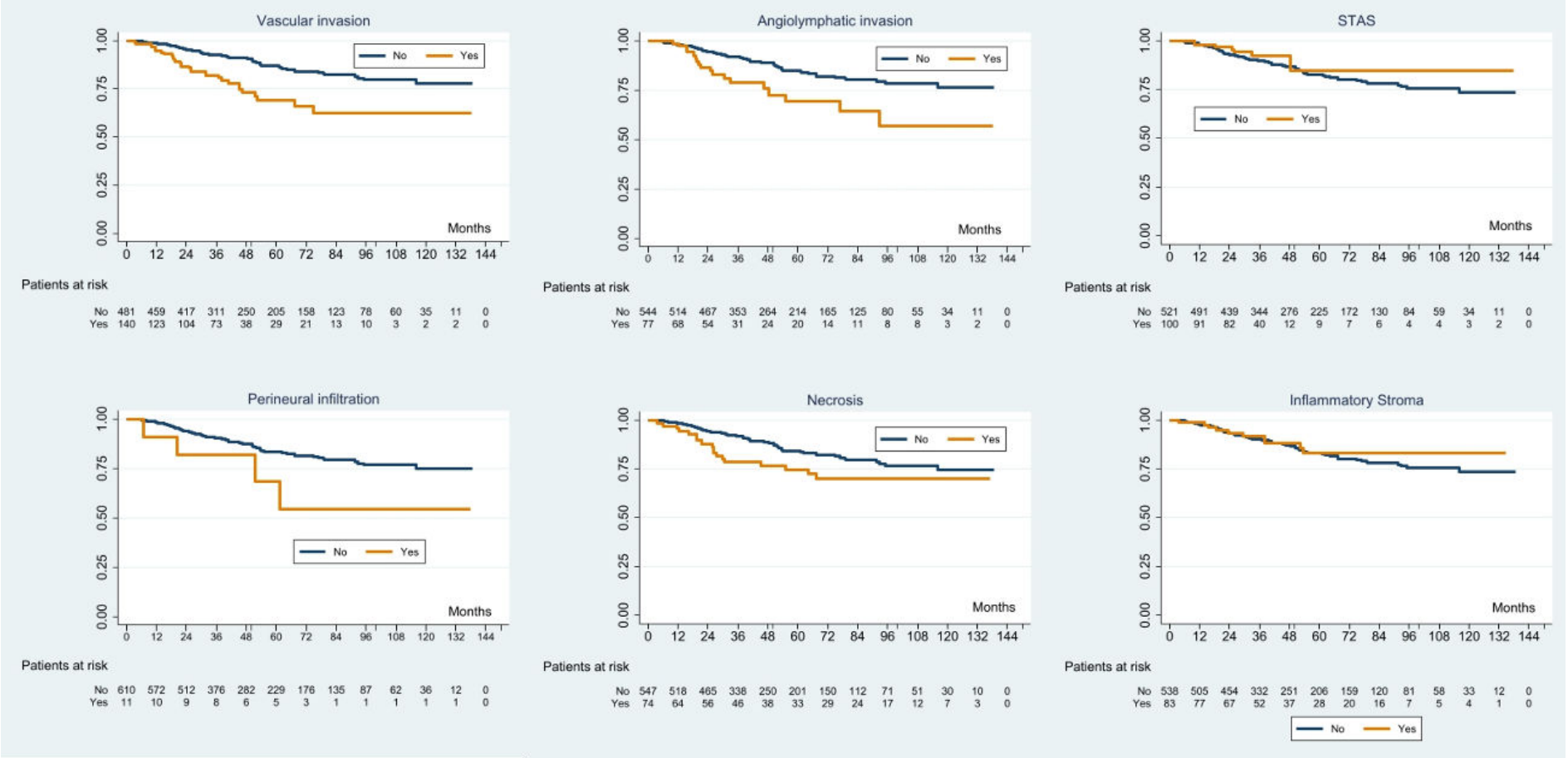


Figure 3. Kaplan Meier curves for cancer specific survival according to the presence or absense of the pathological characteristics of interest.

Variables	HR	CI	p	SubHR	CI	p
Blood vessel invasion	2.537609	1.647344 - 3.908997	0.0001	2.334072	1.519883 - 3.584414	0.0001
Lymphovascular invasion	2.273553	1.357635 - 3.80739	0.0042	2.002985	1.197494 - 3.350286	0.0081
Perineural infiltration	2.390061	.8773838 - 6.510711	0.1330	2.567906	.9460506 - 6.970178	0.0642
STAS	.6732458	.309175 - 1.46603	0.2930	.6540099	.3006696 - 1.422588	0.2842
Necrosis	1.685657	1.00624 - 2.823819	0.047	1.587124	.9290974 - 2.711194	0.0909
Inflammatory stroma	.8185288	.4245934 - 1.577956	0.5394	.7897072	.407648 - 1.529843	0.4841

Table 8. Univariate analysis of cancer-specific survival for the pathological variables.

Variables	HR	CI	p	Harrell index
Blood vessel invasion	1.831368	1.340397 2.502176	0.000	0.6361
Lymphovascular invasion	1.722365	1.190137 2.492606	0.0040	0.6339
Perineural infiltration	1.264824	.5525071 2.895492	0.578	0.6154
STAS	.6844375	.4019501 1.165455	0.163	0.6184
Necrosis	1.484098	1.043808 2.110105	0.028	0.6271
Inflammatory stroma	1.21456	.8168497 1.805909	0.337	0.6167

Table 9. Bivariate analysis of overall survival for the pathological variables and the 8th edition of TNM classification.

Variables	HR	CI	p	Harrell index	SubHR	CI	p
Blood vessel invasion	2.3499	1.520208 - 3.632418	0.000	0.6924	2.117982	1.360708 - 3.296703	0.000 1
Lymphovascular invasion	2.054219	1.218944 - 3.461861	0.007	0.6733	1.809562	1.068623 - 3.064236	0.027
Perineural infiltration	1.676641	.6036394 - 4.656962	0.321	0.6655	1.877162	.6783239 - 5.194773	0.225
STAS	.7148727	.3276657 - 1.559647	0.399	0.6725	.6645109	.3045297 - 1.450022	0.305
Necrosis	1.383972	.8132919 - 2.355094	0.231	0.6741	1.317706	.7416663 - 2.341146	0.347
Inflammatory stroma	.8990942	.464746 - 1.739381	0.752	0.6633	.8519475	.4325281 - 1.678075	0.643

Table 10. Bivariate analysis of cancer-specific survival for the pathological variables and the 8th edition of TNM classification.

Variables	HR	Standard Error	p	CI

IA1	Reference			
IA2	0.8533612	0.2591628	0.602	0.4705719 - 1.547533
IA3	1.433028	0.4397305	0.241	0.785344 - 2.614865
IB	1.052893	0.3087158	0.860	0.5926605 - 1.87022
IIA	1.373751	0.5217682	0.403	0.6525655-2.892046
IIB	1.808988	0.5252001	0.041	1.024019 – 3.195681
Blood vessel invasion	1.824162	0.2952473	0.000	1.328291 – 2.505149
Lymphovascular invasion	1.704883	0.3263168	0.005	1.171584 – 2.480937
Perineural infiltration	1.058787	0.4489666	0.893	0.4611755 – 2.43081
STAS	0.567651	0.1571325	0.041	0.3299581 – 0.9765715
Necrosis	1.456442	0.2337186	0.491	0.7722465 – 1.712823
Inflammatory stroma	1.150096	0.2337186	0.491	0.7722465 – 1.712823
After step by step removal				
IA1	Reference			
IA2	0.8778672	0.2655558	0.667	0.4852208 – 1.588248
IA3	1.43579	0.4410749	0.667	0.4852208 – 1.588248
IB	1.0784.09	0.3151689	0.796	0.6081582 – 1.9112274
IIA	1.383453	0.523031	0.391	0.659413 – 2.902494
IIB	1.896996	0.5483164	0.027	1.076542 – 3.342732
Blood vessel invasion	1.769335	0.2834907	0.000	1.292489 – 2.422108
Lymphovascular invasion	1.584442	0.3003628	0.015	1.092733 - 2.297411
Necrosis	1.48065	0.2651232	0.028	1.042408 – 2.103137

Table 11. Multivariate analysis of overall survival.

Variables	HR	Standard Error	p	CI

IA1	Reference			
IA2	0.3202728	0.1527506	0.017	0.1257618 – 0.8156264
IA3	0.9298584	0.3938783	0.864	0.4053748 – 2.132932
IB	0.8615283	0.3288832	0.696	0.4076886 – 1.820583
IIA	0.8572838	0.4773275	0.782	0.2878615 – 2.553087
IIB	1.548572	0.581125	0.244	0.7421732 – 3.231154
Blood vessel invasion	2.321185	0.5232717	0.000	1.492179 – 3.61076
Lymphovascular invasion	1.99098	0.5379868	0.011	1.172363 – 3.381208
Perineural infiltration	1.334225	0.7014215	0.583	0.4761462 – 3.738978
STAS	0.5410499	0.2199554	0.131	0.2438903 – 1.200273
Necrosis	1.325529	0.361555	0.302	0.776282 – 2.262379
Inflammatory stroma	0.8430794	0.2854196	0.614	0.4342093 – 1.636959
After step by step removal				
IA1	Reference			
IA2	0.3243422	0.1541079	0.08	0.1278096 – 0.8230824
IA3	0.9539538	0.4029905	0.911	0.4168154 – 2.183287
IB	08891407	0.3344075	0.756	0.4233756 – 1.867305
IIA	0.9386469	0.5149141	0.908	0.3203009 – 2.75072
IIB	1.741919	0.63912.5	0.130	0.8486277 - 3.575518
Blood vessel invasion	2.235055	0.5012206	0.000	1.440133 – 3.468756
Lymphovascular invasion	1.855014	0.4978778	0.021	1.096197 – 3.139107

Table 12. Multivariate analysis of cancer-specific survival (pathological characteristics).

Variables	HR	Standard Error	p	CI

IA1	Reference			
IA2	0.9215557	0.2789494	0.787	0.5091761 – 1.66792
IA3	1.451149	0.4451118	0.225	0.7954673 – 2.64729
IB	1.072782	0.3130101	0.810	0.6055538 – 1.90051
IIA	1.542134	0.580468	0.250	0.737437 – 3.224922
IIB	1.917734	0.5508861	0.023	1.092127 - 3.367468
Blood vessel invasion	1.703841	0.2770095	0.001	1.238914 – 2.34324
Lymphovascular invasion	1.694297	0.326433	0.006	1.161428 – 2.471649
Histology Adenocarcinoma	Reference			
Squamous	1.091045	0.1780083	0.593	0.7924386 – 1.502171
Carcinoid	0.5751424	0.2011689	0.114	0.2897669 – 1.141569
Other histology	1.755001	0.4292185	0.021	1.086676 – 2.834358

Table 13. Multivariate analysis of overall survival (pathological characteristics including Histology).

Variables	HR	Standard Error	p	CI
IA1	Reference			
IA2	0.3285298	0.1562497	0.019	0.1293424 – 0.8344659
IA3	0.9390816	0.3978191	0.882	0.4093667 – 2.15424
IB	0.8676786	0.3295977	0.709	0.4121166 – 1.826828
IIA	0.9276093	0.5117945	0.892	0.3145773 – 2.735286
IIB	1.707538	0.631887	0.148	0.8267552 – 3.526661
Blood vessel invasion	2.173457	0.4919581	0.001	1.394707 – 3.38703
Lymphovascular invasion	1.836495	0.4951514	0.024	1.082657 – 3.11522
Histology Adenocarcinoma	Reference			
Squamous	1.063639	0.2540922	0.796	0.665965 – 1.698781
Carcinoid	0.787822	0.3736325	0.615	0.3109835 – 1.995809
Other histology	1.260528	0.4870952	0.549	0.5910577 – 2.688284

Table 14. Multivariate analysis of cancer-specific survival (pathological characteristics including Histology).

Variables	HR	Standard Error	p	CI

IA1	Reference			
IA2	0.9489511	0.2881946	0.863	0.5232817 – 1.720886
IA3	1.649021	0.5135932	0.108	0.8956047 – 3.036238
IB	1.190173	0.3508651	0.555	0.6678429 – 3.121025
IIA	1.63617	0.6263491	0.198	0.7726383 – 3.464818
IIB	3.196607	0.6467046	0.008	1.233529 – 3.911607
Blood vessel invasion	1.727705	0.2778619	0.001	1.260589 – 2.367914
Lymphovascular invasion	1.527907	0.2906586	0.026	1.052374 – 2.218318
Type of Resection Lobectomy	Reference			
Bilobectomy / Pneumonectomy	0.8936903	0.2635612	0.703	0.5013677 – 1.593007
Sublobar	1.753009	0.4320018	0.023	1.081481 – 2.841512
Non anatomic	1.93454	0.4706807	0.007	1.200818 – 3.11658
Distance to the border of the tumor	0.9718873	0.0084065	0.001	0.9555497 – 0.9885043

Table 15. Multivariate analysis of overall survival (including pathological characteristics and surgical procedures).

Variables	HR	Standard Error	p	CI

IA1	Reference			
IA2	0.343332	0.1637002	0.025	0.1348536 - 0.8741098
IA3	1.047395	0.4501213	0.914	0.4511327 – 2.43174
IB	0.9445234	0.3620379	0.882	0.4456002 – 2.002074
IIA	1.073575	0.5971061	0.898	0.3609167 – 3.193432
IIB	1.893145	0.7157034	0.091	0.9023749 – 3.971738
Blood vessel invasion	2.235113	0.5029763	0.000	1.437044 – 3.473282
Lymphovascular invasion	1.844807	0.4996586	0.026	1.084942 – 3.136862
Type of Resection Lobectomy	Reference			
Bilobectomy / Pneumonectomy	1.28826	0.4940624	0.509	0.6077365 – 2.731941
Sublobar	1.439605	0.5792162	0.365	0.6542857 - 3.167517
Non anatomic	1.906757	0.6913351	0.075	0.9368592 – 3.880758
Distance to the border of the tumor	0.9561392	0.116888	0.000	0.9335018 – 0.9793256

Table 16. Multivariate analysis of cancer-specific survival (including pathological characteristics and surgical procedures).

Variables	HR	IC	p

Age	1.008768	.9921212 1.025693	0.3001
Sex	1.65761	1.14154 2.406988	0.0054
High Blood pressure	.9865063	.728219 1.336404	0.9301
Diabetes	1.384293	.9563105 2.003811	0.0949
Cardiovascular	.9118657	.6071047 1.369614	0.6534
Inmunosuppression	1.673733	.7845657 3.570614	0.2169
Smoking habit	2.180592	1.182884 4.019819	0.0051
Type of resection			0.0812
- Lobectomy	Reference		
- Bilobectomy - pneumonectomy	1.234823	.6828245 2.23306	0.485
- Sublobar	1.357602	.7495971 2.458767	0.313
- Non anatomic	1.950917	1.189715 3.19915	0.008
Anatomic resection	.5322019	.3262096 .8682728	0.012
Histology			0.6440
- Adenocarcinoma	Referencia		
- Squamous	.9559816	.6655878 1.373073	0.807
- Carcinoid	.8147766	.4374619 1.517529	0.519
- Others	1.3751	.7560672 2.500968	0.297
Grade of differentiation	1.312532	.8514547 2.023292	0.2331
TNM			0.0000
- IA1	Referencia		
- IA2	.8040646	.4198358 1.539935	0.511
- IA3	1.173624	.5927775 2.323624	0646
- IB	1.688894	.9296914 3.068075	0.085
- IIA	1.300586	.5453517 3.101712	0.553
- IIB	2.559586	1.41842 4.618858	0.002
Distance to the border of the tumor	.9688249	.9516588 .9863007	0.0006
R0	.2333132	.1091558 .4986913	0.0021

Number of nodal stations biopsied	.8962669	.7983219 1.006229	0.0653

Table 17. Univariate analysis for recurrence-free survival according to personal background and other characteristics.

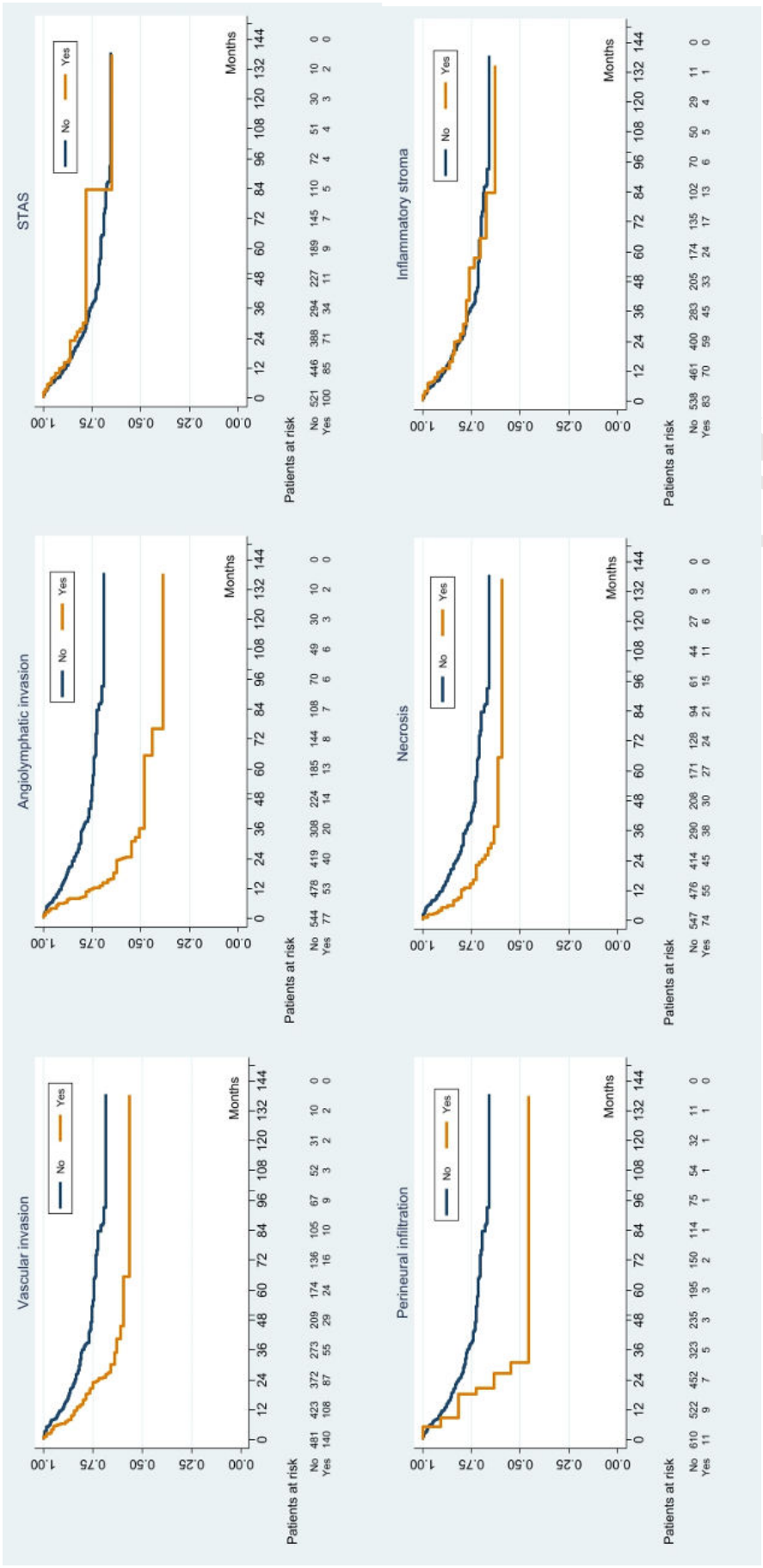


Figure 4. Kaplan Meier curves for recurrence-free survival according to the presence or absense of the pathological characteristics of interest.

Variables	HR	CI	p	SubHR	CI	p
Blood vessel invasion	1.85744	1.331697 2.590741	0.0005	1.777188	1.273104 2.480863	0.001
Lymphovascular invasion	2.86702	1.985754 4.139384	0.000	2.751499	1.895736 3.993564	0.000
Perineural infiltration	2.271679	1.005379 5.132915	0.0803	2.354457	1.062565 5.217063	0.0349
STAS	.85455	.5343157 1.366712	0.5036	.8386244	.5259278 1.337239	0.4597
Necrosis	1.575044	1.04222 2.380268	0.0406	1.472474	.951072 2.279721	0.0827
Inflammatory stroma	.9960347	.6360239 1.559824	0.9961	.9726003	.6249879 1.513552	0.9020

Table 18. Univariate analysis of recurrence-free survival of the pathological variables of interest.

	HR	CI	p	Harrell index	SubHR	CI	p
Blood vessel invasion	1.689588	1.208299 2.362584	0.002	0.6472	1.602791	1.138446 2.256532	0.007
Lymphovascular invasion	2.61249	1.801969 3.787583	0.000	0.6599	2.5104	1.70947 3.686586	0.000
Perineural invasion	1.669798	.728642 3.826607	0.226	0.6283	1.781292	.7731355 4.10407	0.175
STAS	.8859461	.5532982 1.418585	0.614	0.6274	.846092	.5288528 1.353631	0.486
Necrosis	1.272187	.8321689 1.94487	0.266	0.6333	1.195935	.7535878 1.897935	0.448
Inflammatory stroma	1.024115	.6525563 1.607234	0.917	0.6255	.9932473	.6243841 1.580021	0.977

Table 19. Bivariate analysis of recurrence-free survival of the pathological variables and the 8th edition of TNM classification.

Variables	HR	Standard Error	p	CI
IA1	Reference			
IA2	0.7204055	0.2416591	0.333	0.3764231 – 1.39273
IA3	0.9774273	0.3433121	0.948	0.4910299 – 1.945633
IB	1.377308	0.4252947	0.300	0.7519537 – 2.522731
IIA	1.081197	0.4843759	0.865	0.4493316 – 3.545133
IIB	1.928719	0.5990158	0.034	1.049314 – 3.545133
Blood vessel invasion	1.551359	0.2432396	0.013	1.098477 -2.190957
Lymphovascular invasion	2.56728	0.5020942	0.000	1.749852 – 3.766578
Perineural infiltration	1.452073	0.6161669	0.379	0.6321106 – 3.335677
STAS	0.6779613	0.1685776	0.118	0.4161914 – 1.103496
Necrosis	1.253145	0.2741338	0.302	0.8161977 – 1.92401
Inflammatory stroma	1.021896	0.2367689	0.926	0.6489141 – 1.609261
After step by step removal				
IA1	Reference			
IA2	0.7462061	0.247816	0.378	0.3892008 – 1.430685
IA3	1.011877	0.3543774	0.973	0.5093567 – 1.430685
IB	1.428453	0.4386885	0.246	0.7824487 – 2.607812
IIA	1.197753	0.5315643	0.684	0.5018836 – 2.858457
IIB	2.143747	0.6519619	0.012	1.181147 – 3.890838
Blood vessel invasion	1.489699	0.2605063	0.023	1.057419 – 2.098696
Lymphovascular invasion	2.402031	0.464191	0.000	1.64469 – 3.508107

Table 20. Multivariate analysis of recurrence-free survival of the pathological variables and the 8th edition of TNM classification.

Variables	HR	Standard Error	p	CI
IA1	Reference			
IA2	0.7906992	0.2634392	0.481	0.4115423 – 1.519176
IA3	1.115113	0.3951252	0.758	0.5568099 – 2.23215
IB	1.500607	0.4638749	0.189	0.818728 – 2.750392
IIA	1.368193	0.613593	0.485	0.5680797 – 3.295227
IIB	2.350085	0.7300243	0.006	1.278405 – 4.320148
Blood vessel invasion	1.504989	0.2650643	0.020	1.065655 – 2.125446
Lymphovascular invasion	2.376224	0.4661915	0.000	1.61767 – 3.490476
Type of resection Lobectomy	Reference			
Bilobectomy / Pneumonectomy	1.078233	0.33506	0.808	0.5864111 – 1.982544
Sublobar	1.069276	0.3310868	0.829	0.5828098 – 1.961792
Non anatomic	3.102477	0.5398697	0.004	1.241046 - 3.477771
Distance to the tumor border	0.9694364	0.0089479	0.001	0.9520564 – 0.9871336

Table 21. Multivariate analysis of recurrence-free survival (including pathological characteristics and treatment procedures).

STAGE I

Variables	HR O. Survival	CI	p	HR Cancer-specific survival	CI	p
Age	1.034043	1.013877 1.05461	0.001	1.021501	.9918 1.052	0.157
Sex	3.430564	2.060666 5.711148	0.000	3.097977	1.464 6.551	0.003
Inmunosuppression	3.380734	1.713969 6.668361	0.000	3.754765	1.352 10.42	0.011
Smoking habit	3.887059	1.590164 9.501679	0.003	2.806795	.8768 8.984	0.082
Type of resection			0.048			0.0879
- Lobectomy	Reference					
- Bilobectomy – pneumonectomy	1.192389	.552 2.573	0.654	2.299259	.9046 5.843	0.080
- Sublobar	2.027328	1.106 3.713	0.022	2.206566	.8634 5.639	0.098
- Non anatomic	1.834473	1.079 3.117	0.025	2.142373	.9568 4.796	0.064
Anatomic Resection	.5822277	.3448314 .9830574	0.043	.5279431	.2388 1.167	0.114
Histology			0.011			0.1853
- Adenocarcinoma	Reference					
- Squamous	1.430138	.9693 2.109	0.071	1.501391	.8355 .6977	0.174
- Carcinoid	.5369876	.2334 1.235	0.143	.4279288	.1026 1.784	0.244
- Others	2.063748	1.121 3.798	0.020	1.619913	.57342 4.576	0.363
Grade of differentation	1.574699	.99521 2.4916	0.052	.9601846	.4112 2.242	0.9248
TNM			0.1408			0.0148
- IA1	Reference					
- IA2	.9365512	.518228 1.692	0.828	.3476351	.1371 .881	0.026
- IA3	1.599548	.87933 2.909	0.124	1.049368	.4596 2.395	0.909
- IB	1.266298	.71850 2.231	0.414	1.049547	.5033	0.897

					2.188	
Distance to the border of the tumor	.9680313	.94776 .98872	0.003	.9471849	.9178 9774	0.001
R0	.094257	.03793 .23419	0.0002	.0342824	.0131 - .0897	0.0000

Table 22. Univariate analysis of overall and cancer-specific survival according to personal background and other characteristics in Stage I.

Variables	HR	CI	p
Blood vessel invasion	1.8434	1.2266 - 2.77048	0.003
Lymphovascular invasion	1.9387	1.2261 - 3.0657	0.005
Perineural	2.46828	0.609527 – 9.995	0.205
STAS	0.5246467	0.25501 – 1.07938	0.080
Necrosis	1.9676	1.2525 – 3.0909	0.003
Inflammatory stroma	1.3124	0.822538 – 2.0939	0.254

Table 23. Univariate analysis of overall survival for the pathological variables in stage I.

Variables	HR	CI	p
Blood vessel invasion	2.812854	1.603058 4.935662	0.000
Lymphovascular invasion	2.689933	1.419869 5.09606	0.002
Perineural infiltration	2.655114	.3668782 19.21517	0.334
STAS	.4725142	.1462607 1.526519	0.210
Necrosis	2.113428	1.064722 4.195064	0.032
Inflammatory stroma	.9604259	.4349149 2.120915	0.920

Table 24. Univariate analysis of cancer-specific survival for the pathological variables in stage I.

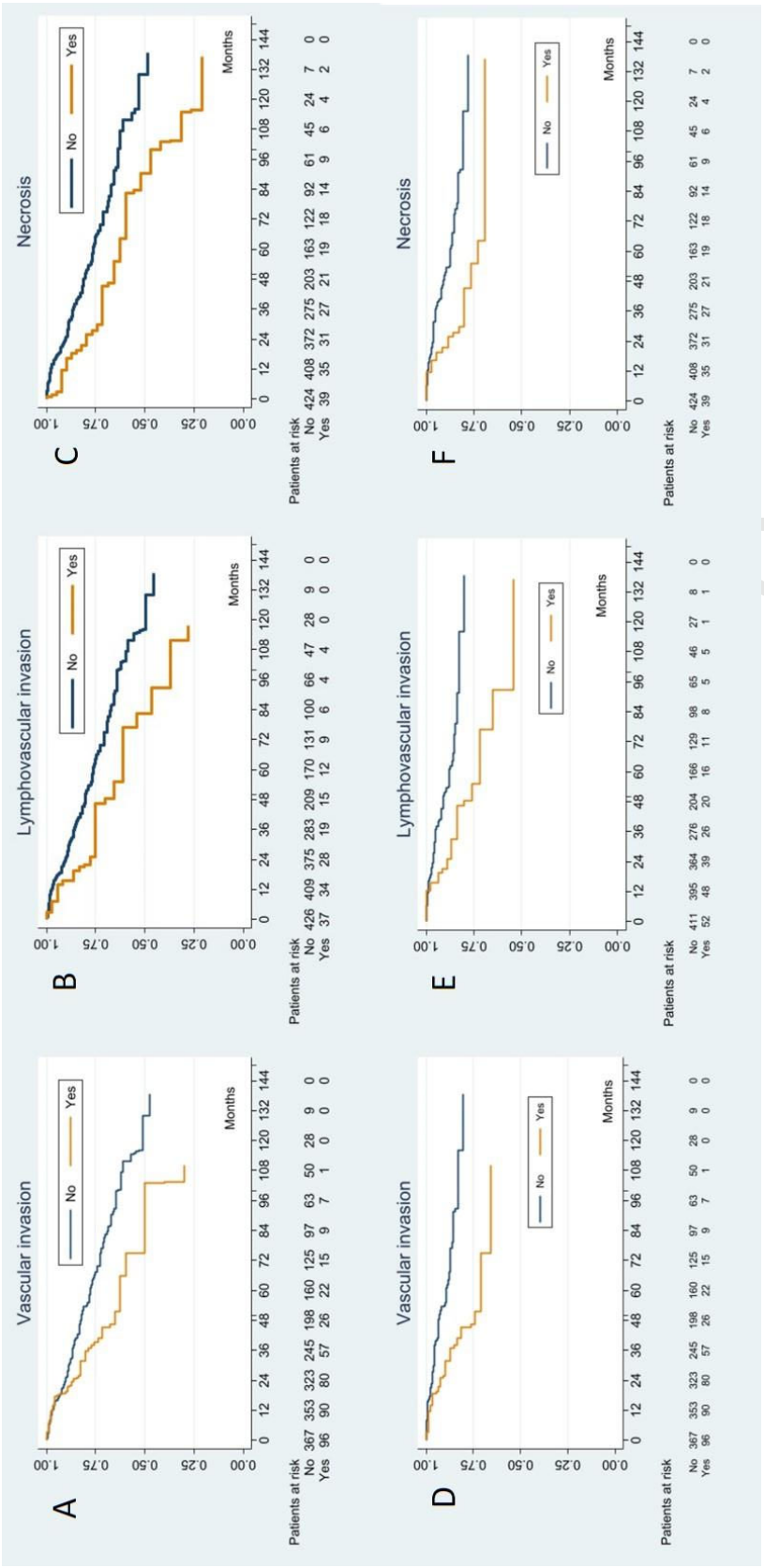


Figure 5. Kaplan Meier curves of overall (A, B, C) and cancer-specific survival (D, E F) according to the presence or absense of the pathological characteristics of interest with statistical significance in stage I.

Variables	HR	Standard Error	p	CI
IA1	Reference			
IA2	0.81085	0.2475688	0.492	0.4457121 – 1.47513
IA3	1.34309	0.4152548	0.340	0.732709 – 2.467946
IB	0.9644675	0.2867278	0.903	0.5385584 – 1.727199
Blood vessel invasion	1.803963	0.3824192	0.005	1.190647 – 2.733207
Lymphovascular invasion	1.871277	0.4571091	0.010	1.159336 – 3.020415
Perineural infiltration	1.059905	0.8000017	0.08	0.2414323 – 4.65323
STAS	0.4049359	0.151766	0.016	0.1942515- 0.8441278
Necrosis	1.847297	0.4397963	0.10	1.15878 – 2.94569
Inflammatory stroma	1.239603	0.3083823	0.388	0.7612459 – 2.018554
After step by step removal				
IA1	Reference			
IA2	0.8538191	0.2588685	0.602	0.471293 – 1.546823
IA3	1.351799	0.4192023	0.331	0.73612 – 2.482422
IB	1.017688	0.300311	0.953	0.570732 – 1.814667
Blood vessel invasion	1.767878	0.3712011	0.007	1.171455 – 2.667958
Lymphovascular invasion	1.643784	0.3916113	0.037	1.03052 – 2.622002
Necrosis	1.787727	0.4205895	0.014	1.12831 – 2.835039

Table 25. Multivariate analysis of overall survival for the pathological variables in stage I.

Variables	HR	Standard Error	p	CI
IA1	Reference			
IA2	0.2952156	0.1416534	0.011	0.1152675 – 0.7560868
IA3	0.8409367	0.3591005	0.685	0.3641493 – 1.941991
IB	0.7374288	0.2870512	0.434	0.3438601 – 1.581461
Blood vessel invasion	2.840153	0.8328637	0.000	1.598564 – 5.046069
Lymphovascular invasion	2.53319	0.857113	0.006	1.305152 – 4.916709
Perineural infiltration	1.005847	1.074345	0.996	0.1239836 – 8.16018
STAS	0.3138768	0.1901386	0.056	0.0957465 – 1.028953
Necrosis	1.956078	0.7042514	0.062	0.9658865 – 3.961378
Inflammatory stroma	0.8748542	0.3718853	0.753	0.3802811 – 2.012652
After step by step removal				
IA1	Reference			
IA2	0.3115126	0.14837	0.014	0.1224779 – 0.7923069
IA3	0.9020606	0.3827428	0.808	0.3927103 – 2.072045
IB	0.8077407	0.3090966	0.577	0.3815437 – 1.710014
Blood vessel invasion	2.649442	0.775034	0.001	1.493327 – 4.700608
Lymphovascular invasion	2.347309	0.7775003	0.010	1.226384 – 4.49277

Table 26. Multivariate analysis of cancer-specific survival for the pathological variables in stage I.

Overall survival	Harrell's I.	AIC	BIC
Current model: TNM	0.5610	626.1489	630.4105
Proposed model: TNM with vascular invasion and lymphovascular invasion	0.6184	616.1345	630.4087
Cancer-specific survival	Harrell's I.	AIC	BIC
Current model: TNM	0.57	625.2836	629.4213
Proposed model: TNM with vascular invasion and lymphovascular invasion	0.6943	608.9837	629.6723

Table 27. Harrell's index, AIC, BICo foverall survival and cancer-specific survival. Comparison between the models in stage I.

	HR	CI		p
Age	.9972368	.97715	1.017737	0.790
Sex	1.616443	1.032294	2.531146	0.036
Inmunosuppression	2.091358	.8508158	5.140686	0.108
Smoking habit	3.210842	1.308106	7.88125	0.011
Type of resection				0.0255
- Lobectomy	Reference			
- Bilobectomy - pneumonectomy	2.083568	1.00535	4.31815	0.048
- Sublobar	1.521537	.7321714	3.161929	0.261
- Non anatomic	2.20962	1.249059	3.90888	0.006
Anatomic resection	.4893809	.2787895	.8590481	0.013
Histology				0.5852
- Adenocarcinoma	Reference			
- Squamous	.8778342	.5444532	1.415352	0.593
- Carcinoid	.6393668	.2778612	1.471202	0.293
- Others	1.27115	.5848198	2.762939	0.545
Grade of differentiation	.9766974	.5229513	1.824143	0.941
TNM				0.0181
- IA1	Reference			
- IA2	.8045088	.4200452	1.540869	0.512
- IA3	1.170626	.5912413	2.317775	0.651
- IB	1.684725	.9272744	3.060904	0.087
Distance to the border of the tumor	.962746	.941245	.9847382	0.001
R0	.2333132	.1091558	.4986913	0.0021
Number of nodal stations biopsied	.0756783	.0303109	.1889484	0.000

Table 28. Univariate analysis of recurrence-free survival according to personal background and other characteristics in Stage 1.

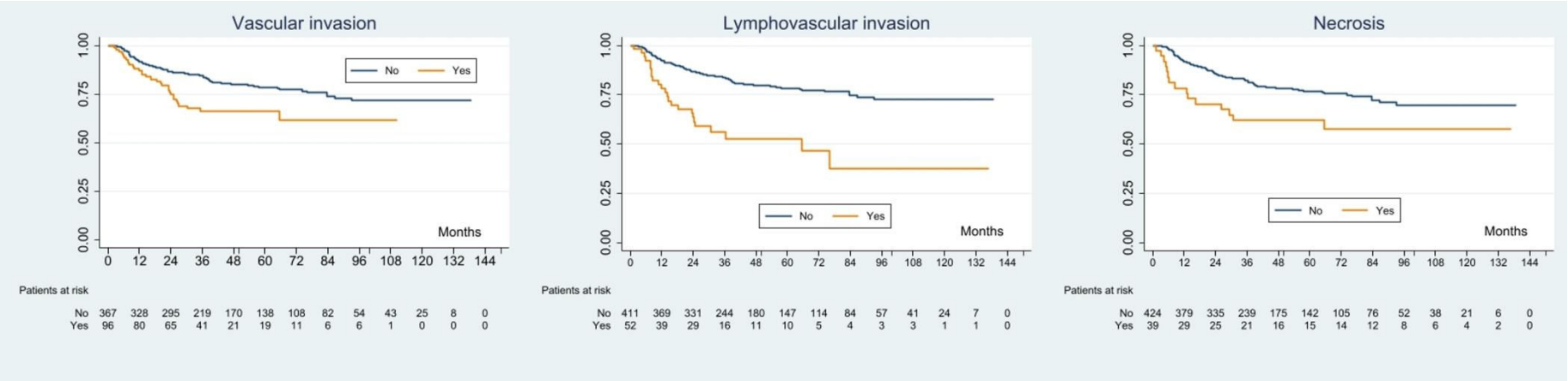


Figure 5. Kaplan Meier curves of Recurrence-free survival according to the presence or absense of the pathological characteristics of interest with statistical significance in stage I.

Variables	HR	CI	p	SubHR	CI	p
Blood vessel invasion	1.933038	1.269505 2.943379	0.002	1.933038	1.269505 2.943379	0.002
Lymphovascular invasion	3.171427	2.008276 5.00825	0.000	3.171427	2.008276 5.00825	0.000
Perineural infiltration	3.325211	.8178188 13.52014	0.093	3.325211	.8178188 13.52014	0.093
STAS	.8215792	.4585113 1.472139	0.509	.8215792	.4585113 1.472139	0.509
Necrosis	1.957797	1.132554 3.384357	0.016	1.957797	1.132554 3.384357	0.016
Inflammatory stroma	1.149498	.6756013 1.955806	0.607	1.149498	.6756013 1.955806	0.607

Table 29. Univariate analysis of recurrence-free survival of the pathological variables of interest in Stage I.

Variables	HR	Standard Error	p	CI
IA1	Reference			
IA2	0.6824741	0.229355	0.256	0.3532059 – 1.318695
IA3	0.9014296	0.3195691	0.770	0.4499552 – 1.805903
IB	1.269045	0.3962352	0.445	0.6881857 – 2.340176
Blood vessel invasion	1.721549	0.3844463	0.015	1.111307 – 2.666888
Lymphovascular invasion	2.965612	0.7343335	0.000	1.825337 – 4.818208
Perineural infiltration	1.180474	0.9050777	0.829	0.2626842 – 5.304918
STAS	0.5672365	0.1756171	0.067	0.309194 – 1.040632
Necrosis	1.843723	0.5361675	0.034	1.048032 – 3.264669
Inflammatory stroma	1.06448	0.3011364	0.825	0.6114161 – 1.853269
After step by step removal				
IA1	Reference			
IA2	0.6999442	0.2337262	0.385	0.3637719 – 1.346783
IA3	0.9191889	0.3255297	0.812	0.459148 – 1.840165
IB	1.292145	0.4021659	0.410	0.7020764 – 2.378145
Blood vessel invasion	1.637089	0.3607602	0.025	1.062908 – 2.521441
Lymphovascular invasion	2.680128	0.642159	0.000	1.675743 – 4.286507
Necrosis	1.838637	0.5202063	0.031	1.056003 – 3.201303

Table 30. Multivariate analysis of recurrence-free survival of the pathological variables and the 8th edition of TNM classification in Stage I.

Recurrence-free survival	Harrell's I.	AIC	BIC
Current model: TNM	0.5880	1235.084	1247.497
Proposed model: TNM with vascular invasion, lymphovascular invasion and necrosis	0.6736	1209.743	1230.431

Table 31. Harrell's index, AIC, BIC of recurrence-free survival. Comparison between the models in stage I.

COMPARISON OF OVERALL SURVIVAL, CANCER-SPECIFIC SURVIVAL AND RECURRENCE-FREE SURVIVAL BETWEEN STAGES REGARDING THE PATHOLOGICAL CHARACTERISTICS OF INTEREST.

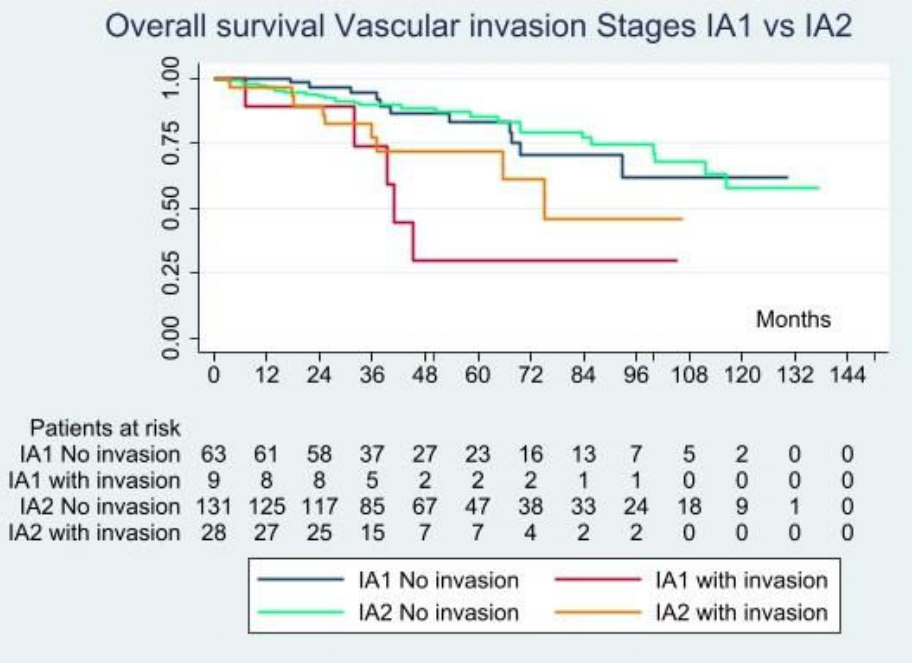


Figure 6: Kaplan meier curves representing overall survival in stages IA1 and IA2 regarding pathological features with statistical significance (vascular invasion).

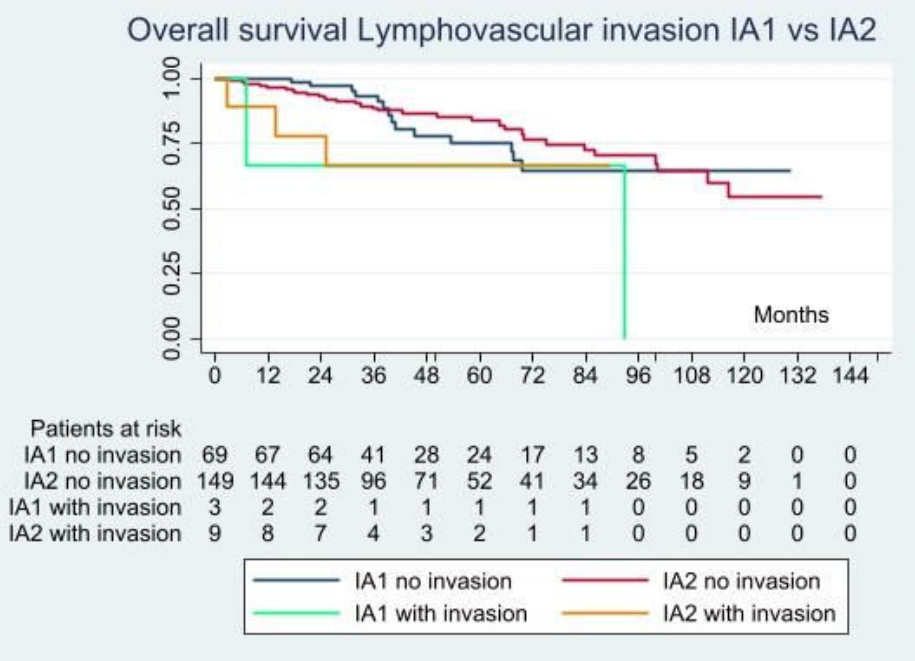


Figure 7: Kaplan meier curves representing overall survival in stages IA1 and IA2 regarding pathological features with statistical significance (lymphovascular invasion).

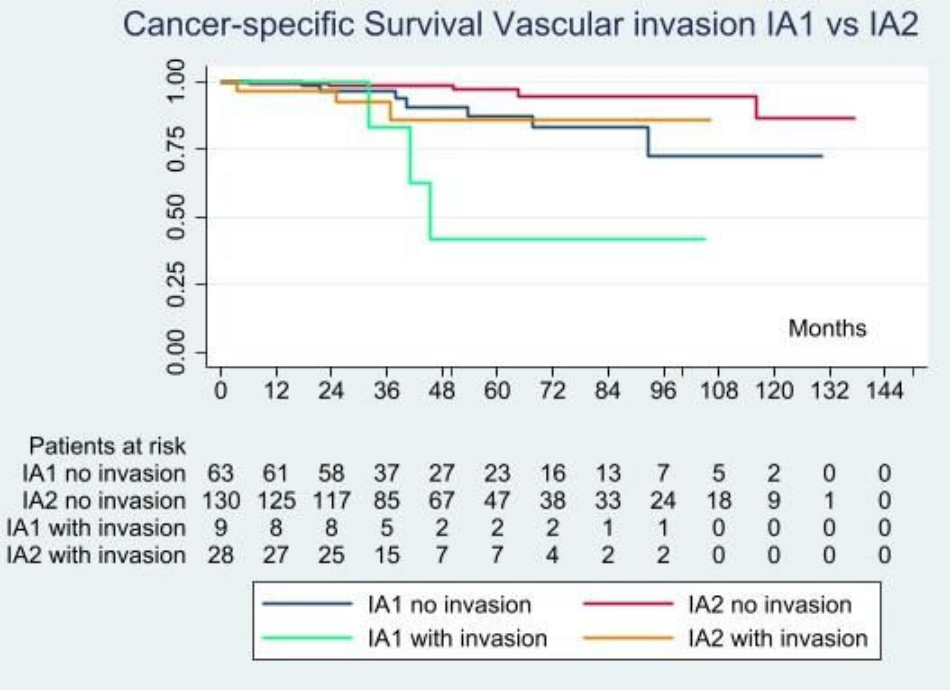


Figure 8: Kaplan meier curves representing cancer-specific survival in stages IA1 and IA2 regarding pathological features with statistical significance (vascular invasion).

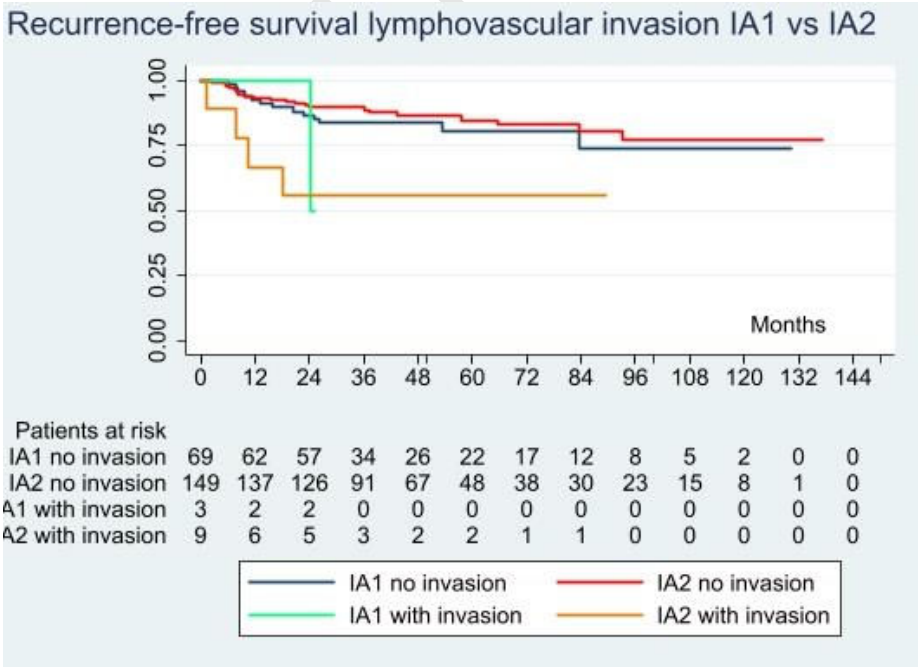


Figure 9: Kaplan meier curves representing recurrence-free survival in stages IA1 and IA2 regarding pathological features with statistical significance (lymphovascular invasion).

2.- IA2 vs IA3

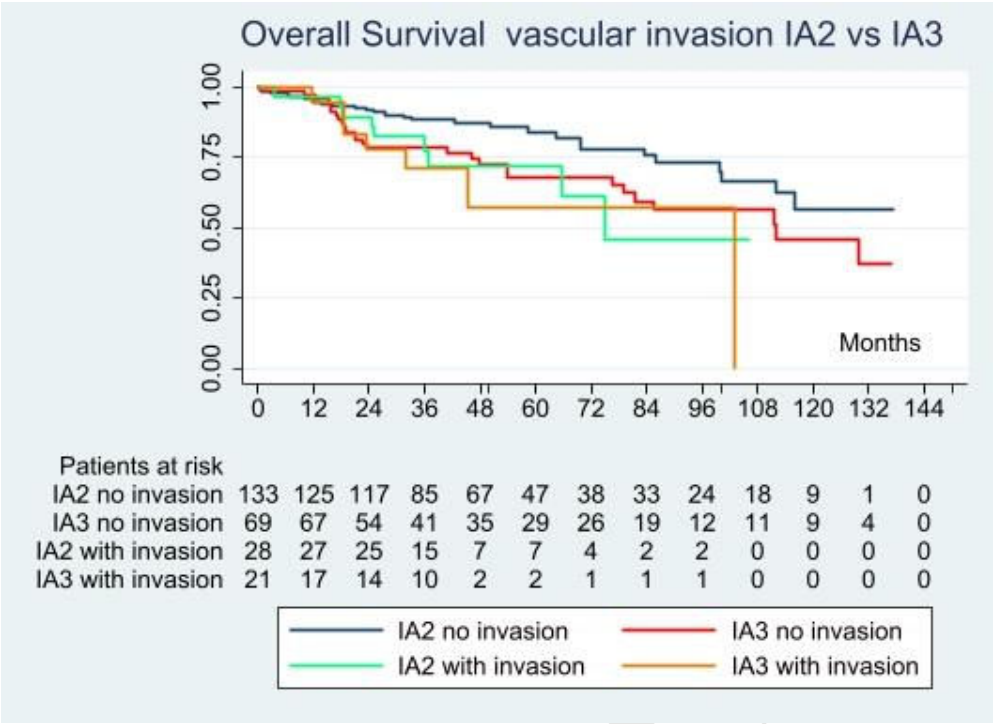


Figure 10: Kaplan meier curves representing overall survival in stages IA2 and IA3 regarding pathological features with statistical significance (vascular invasion).

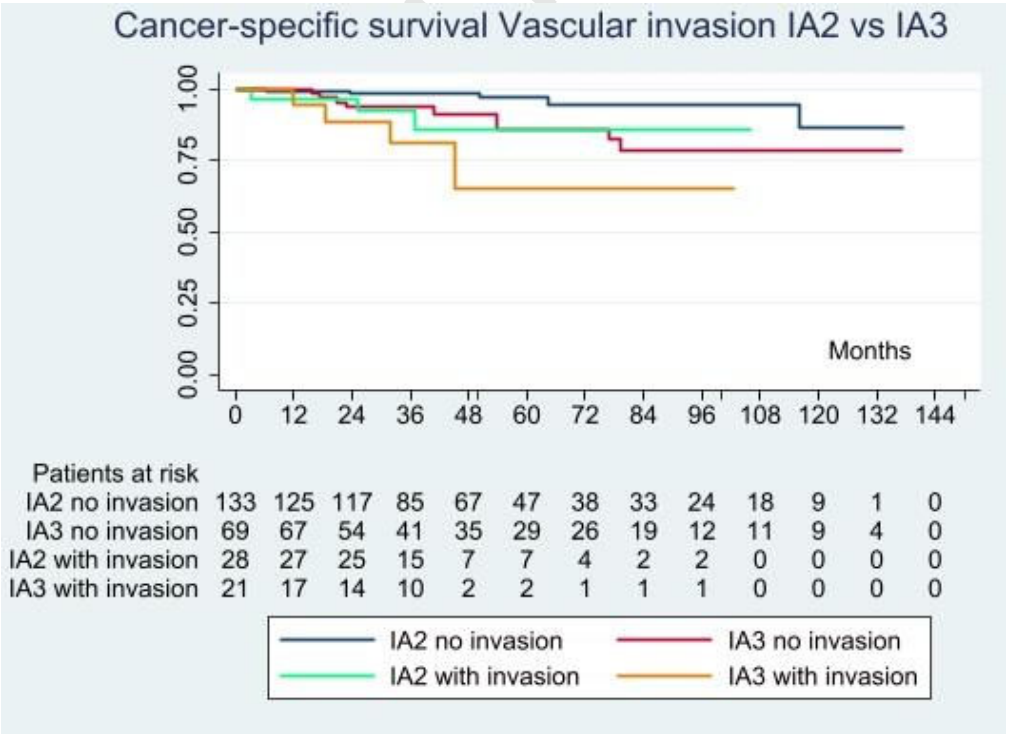


Figure 11: Kaplan meier curves representing cancer-specific survival in stages IA2 and IA3 regarding pathological features with statistical significance (vascular invasion).

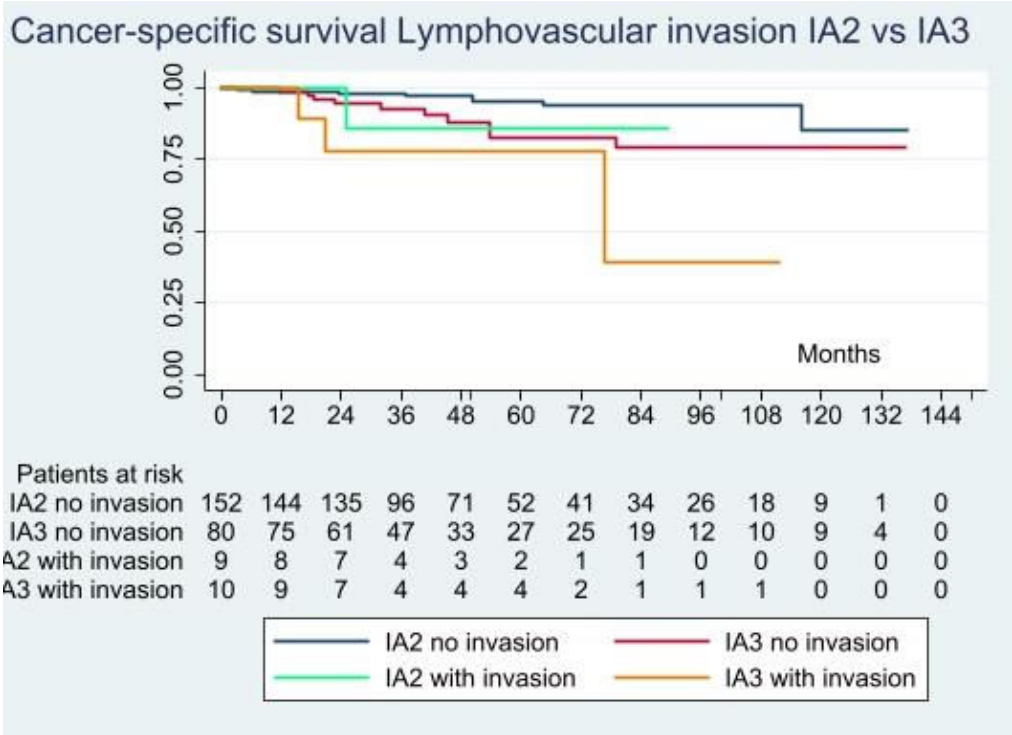


Figure 12: Kaplan meier curves representing cancer-specific survival in stages IA2 and IA3 regarding pathological features with statistical significance (lymphovascular invasion).

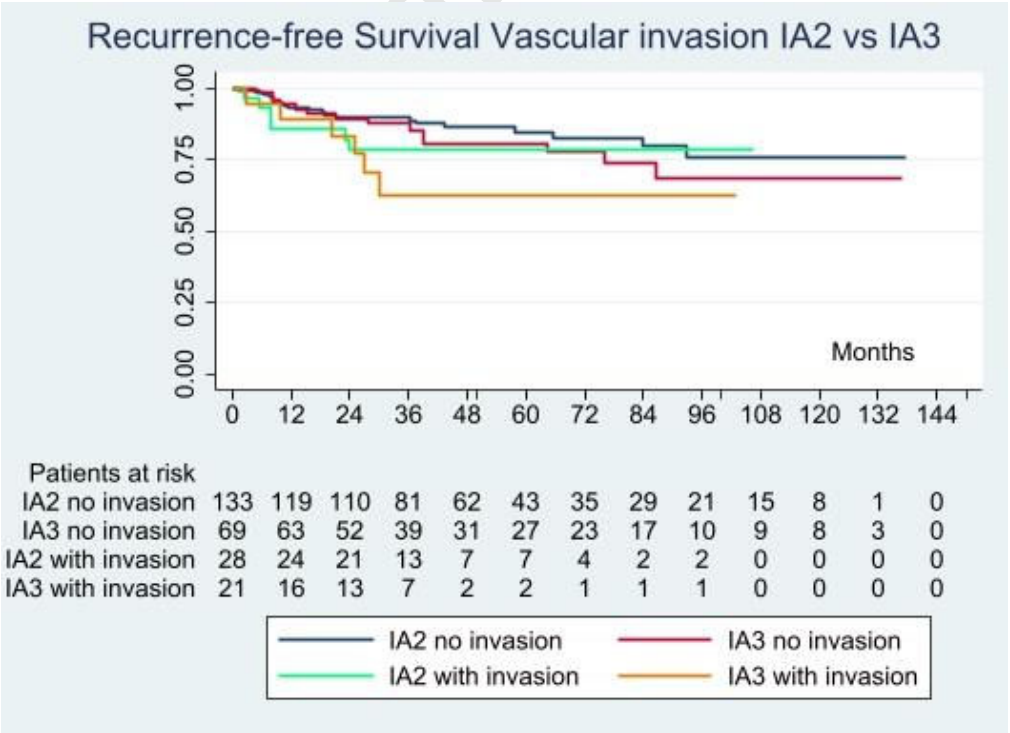


Figure 13: Kaplan meier curves representing recurrence-free survival in stages IA2 and IA3 regarding pathological features with statistical significance (vascular invasion).

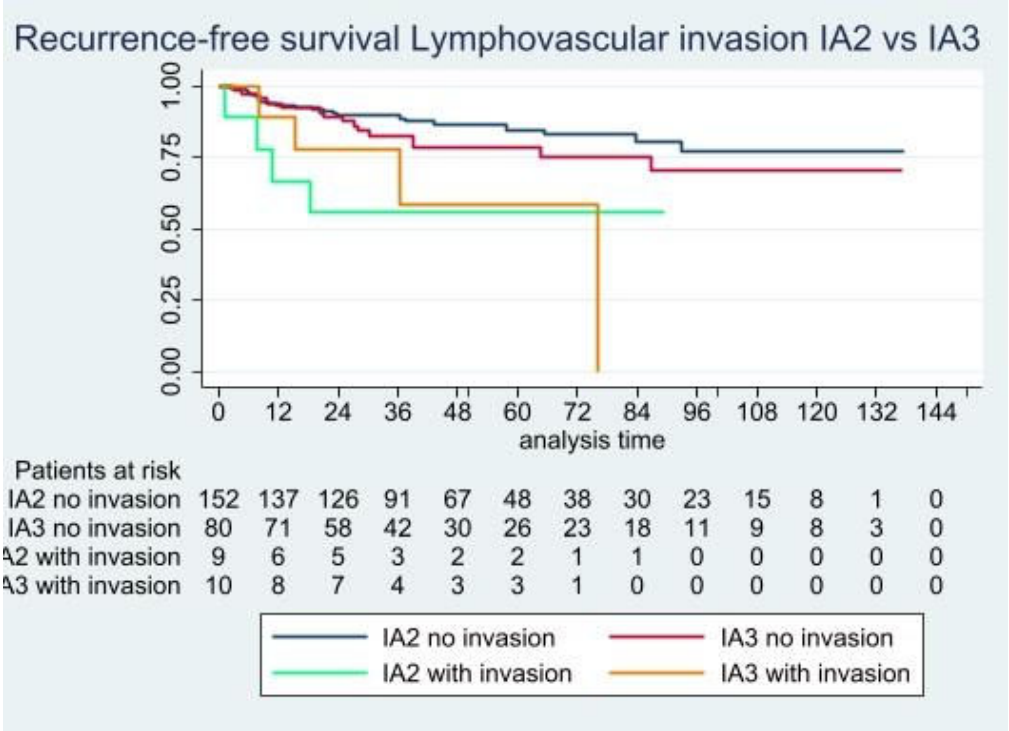


Figure 14: Kaplan meier curves representing recurrence-free survival in stages IA2 and IA3 regarding pathological features with statistical significance (lymphovascular invasion).

3.- IA3 vs IB

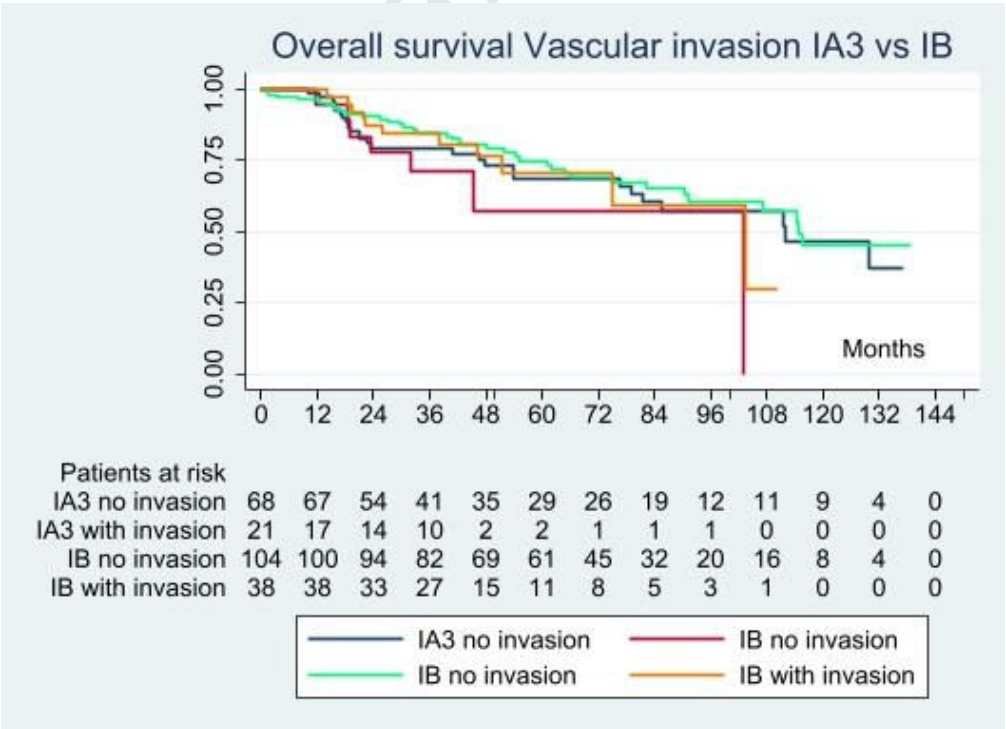


Figure 15: Kaplan meier curves representing overall survival in stages IA3 and IB regarding pathological features with statistical significance (vascular invasion).

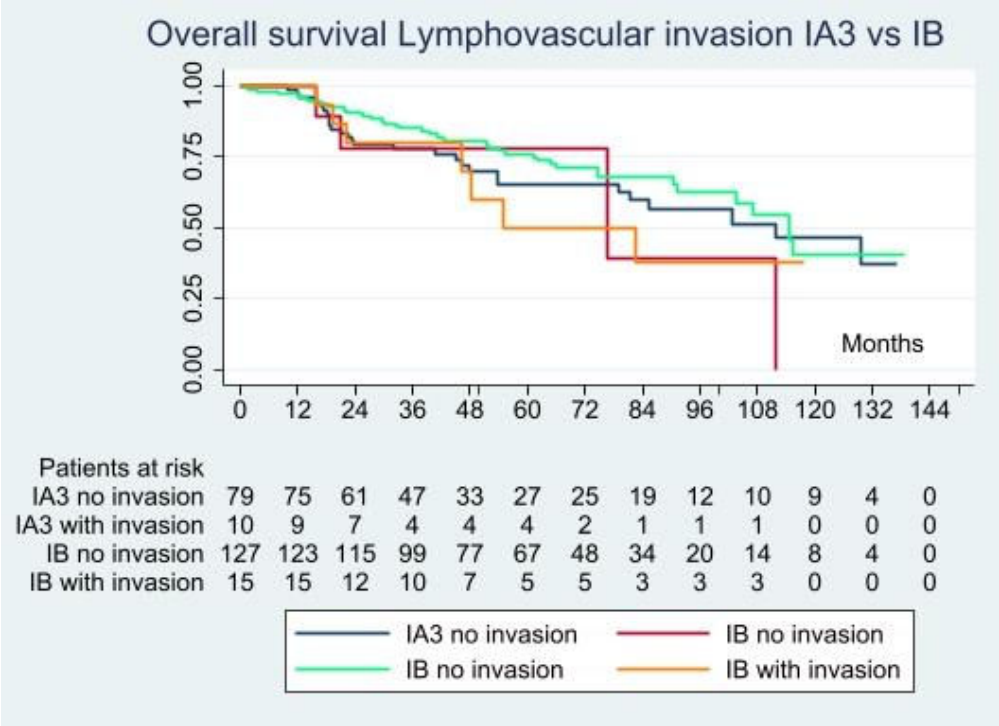


Figure 16: Kaplan meier curves representing overall survival in stages IA3 and IB regarding pathological features with statistical significance (lymphovascular invasion).

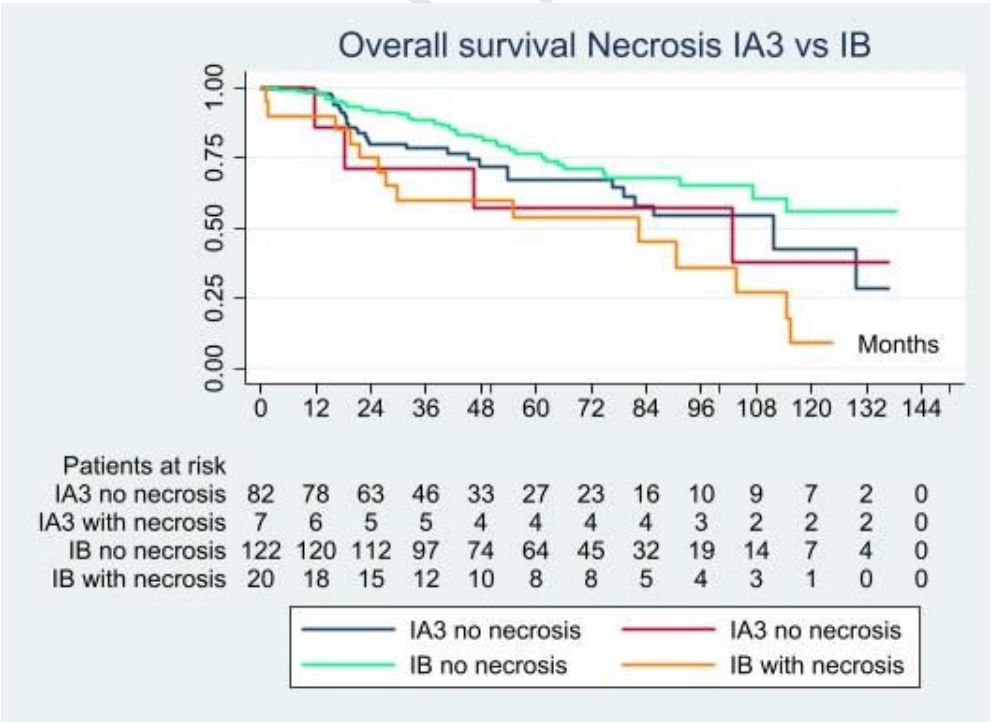


Figure 17: Kaplan meier curves representing overall survival in stages IA3 and IB regarding pathological features with statistical significance (necrosis).

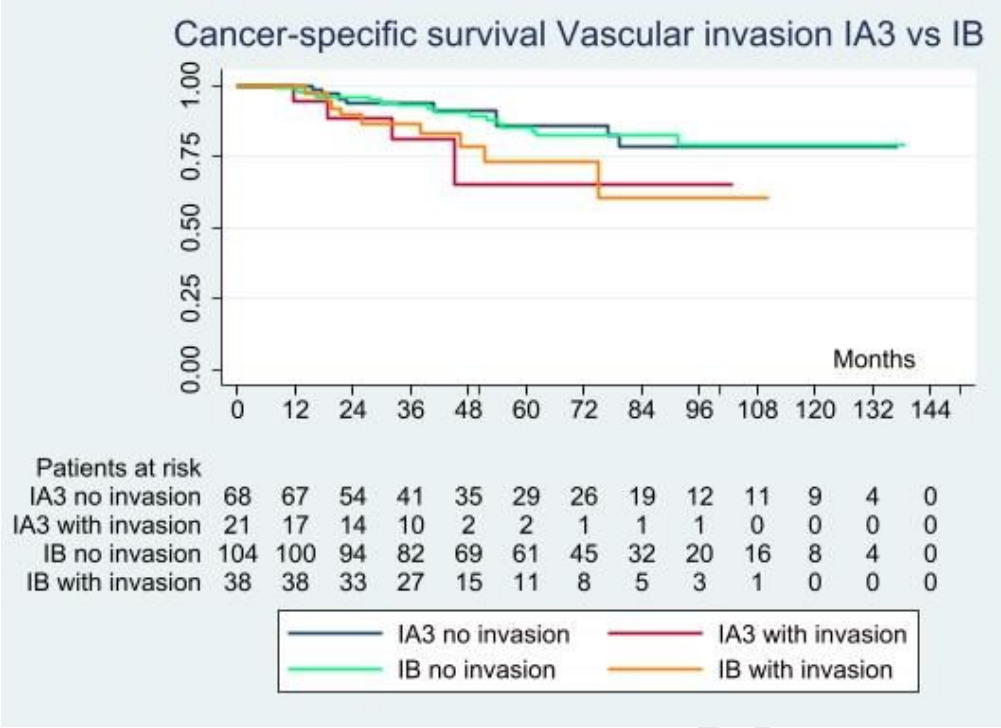


Figure 18: Kaplan meier curves representing cancer-specific survival in stages IA3 and IB regarding pathological features with statistical significance (vascular invasion).

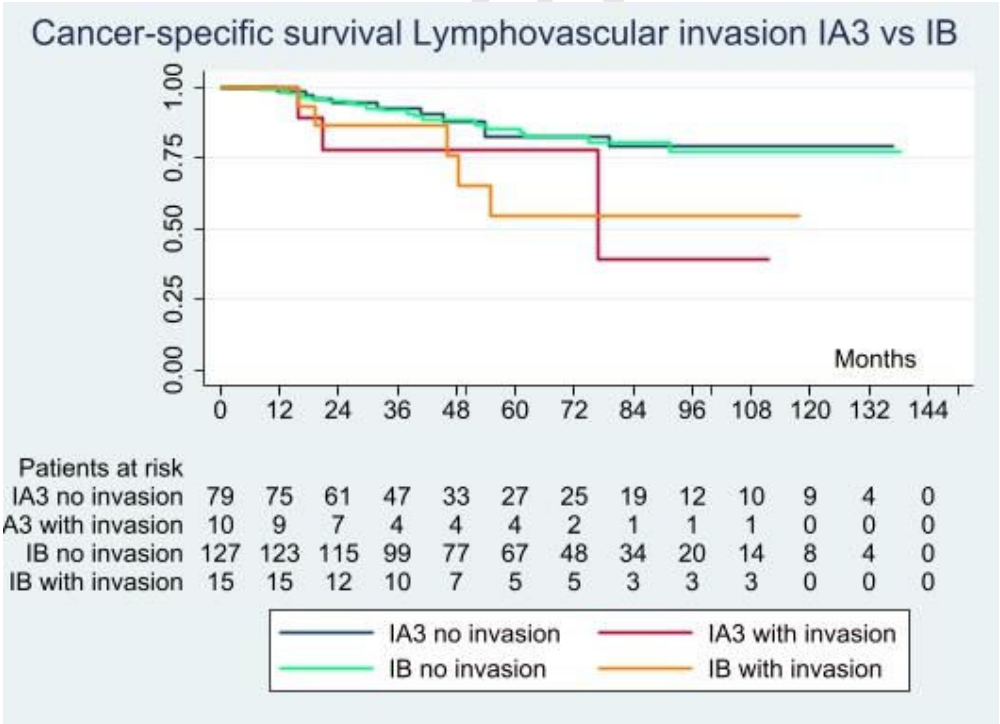


Figure 19: Kaplan meier curves representing cancer-specific survival in stages IA3 and IB regarding pathological features with statistical significance (lymphovascular invasion).

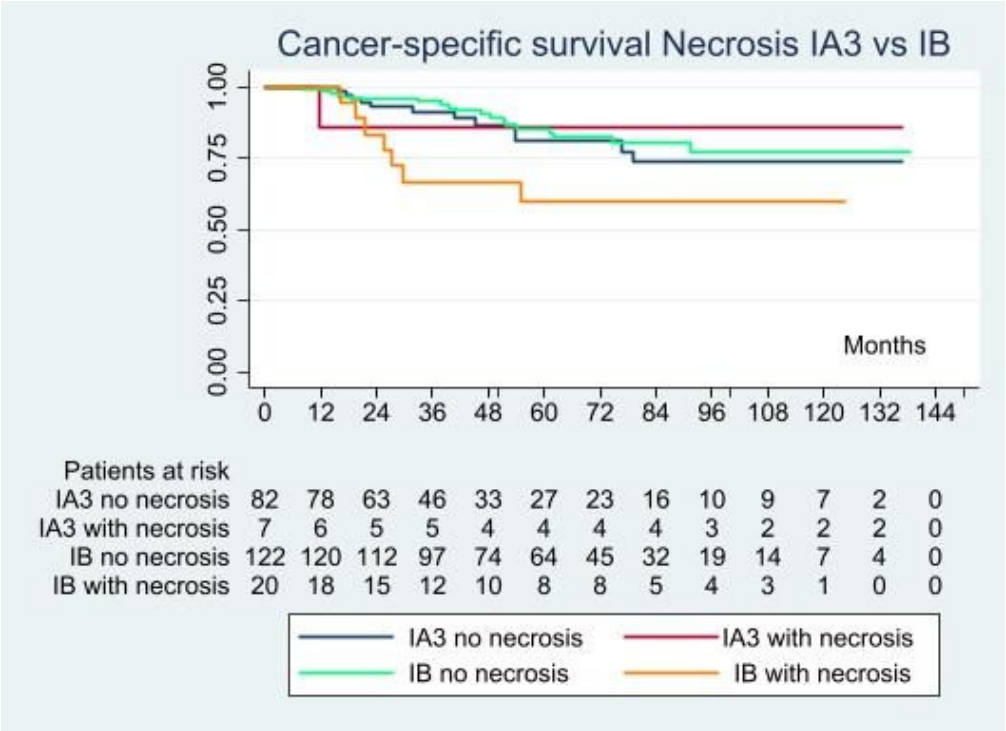


Figure 20: Kaplan meier curves representing cancer-specific survival in stages IA3 and IB regarding pathological features with statistical significance (necrosis).

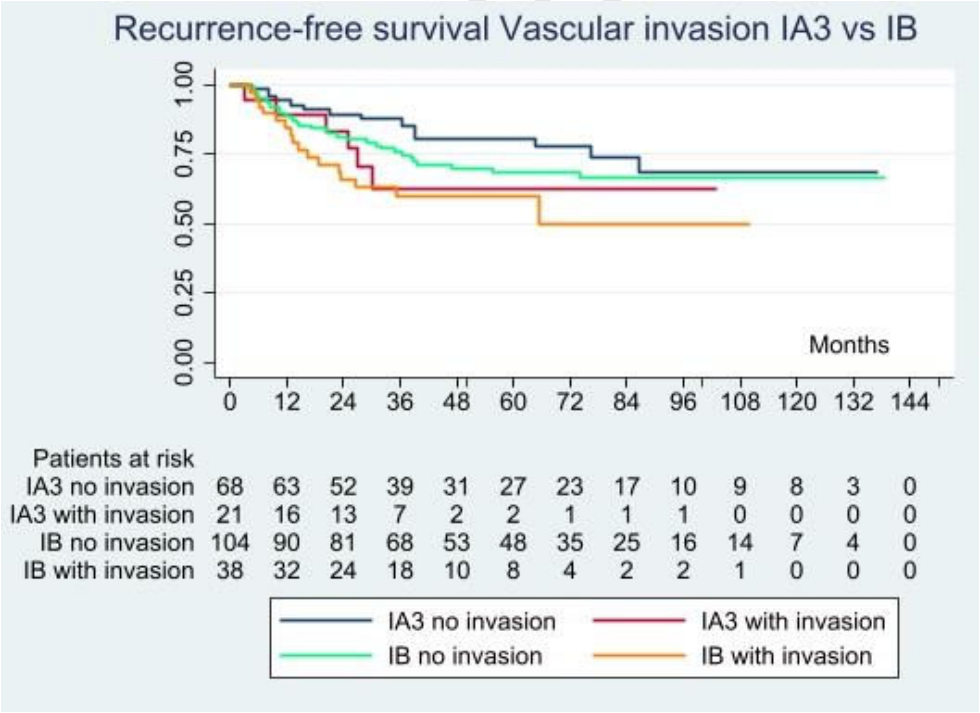


Figure 21: Kaplan meier curves representing recurrence-free survival in stages IA3 and IB regarding pathological features with statistical significance (vascular invasion).

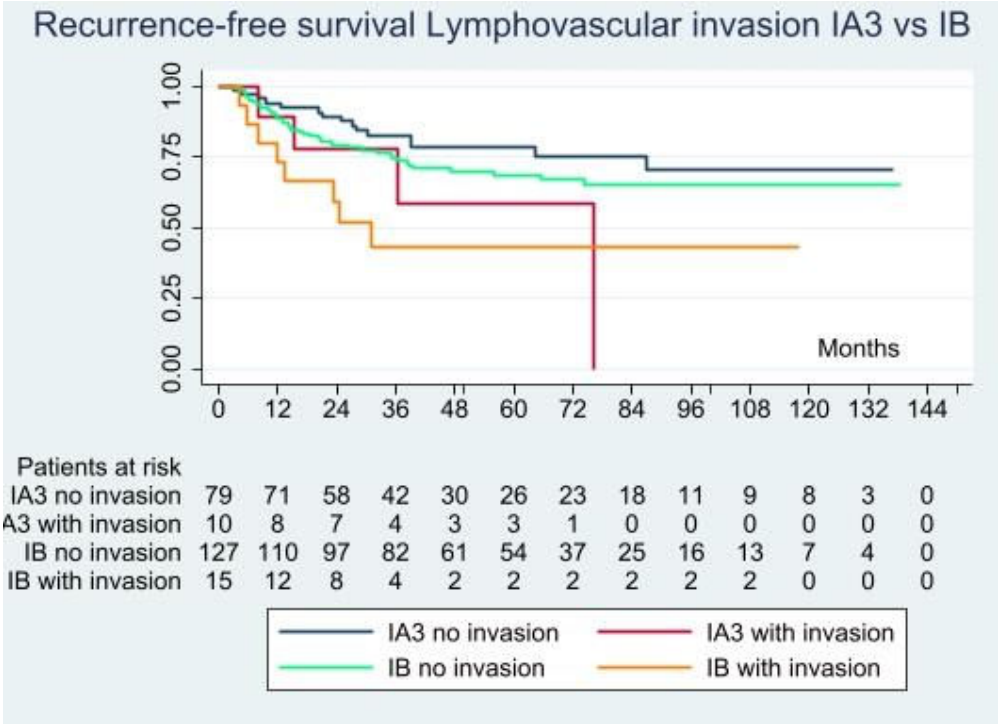


Figure 22: Kaplan meier curves representing recurrence-free survival in stages IA3 and IB regarding pathological features with statistical significance (lymphovascular invasion).

4.- IB vs IIA

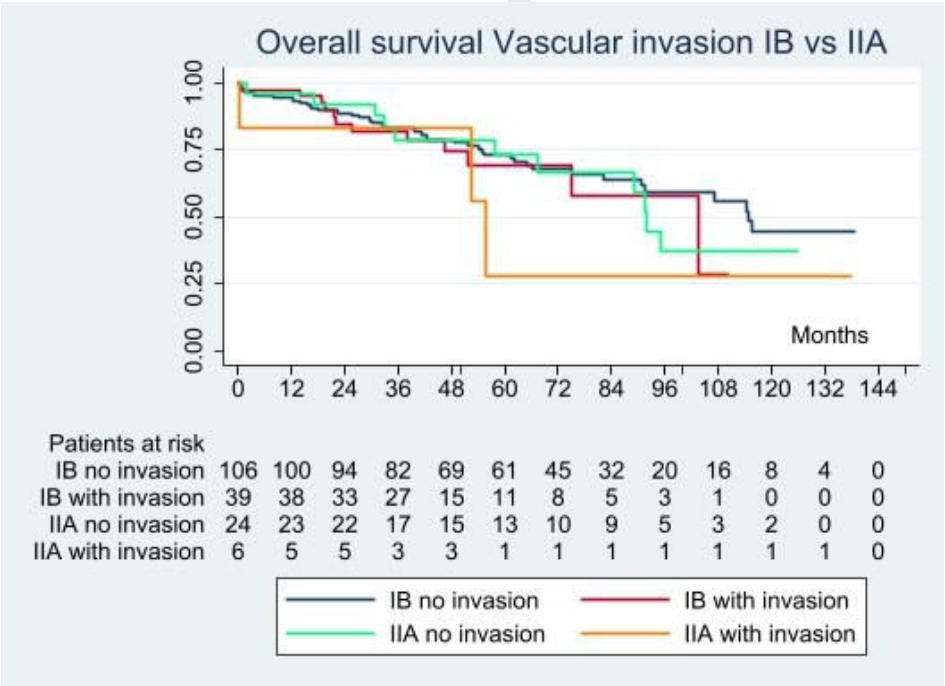


Figure 23: Kaplan meier curves representing overall survival in stages IB and IIA regarding pathological features with statistical significance (vascular invasion).

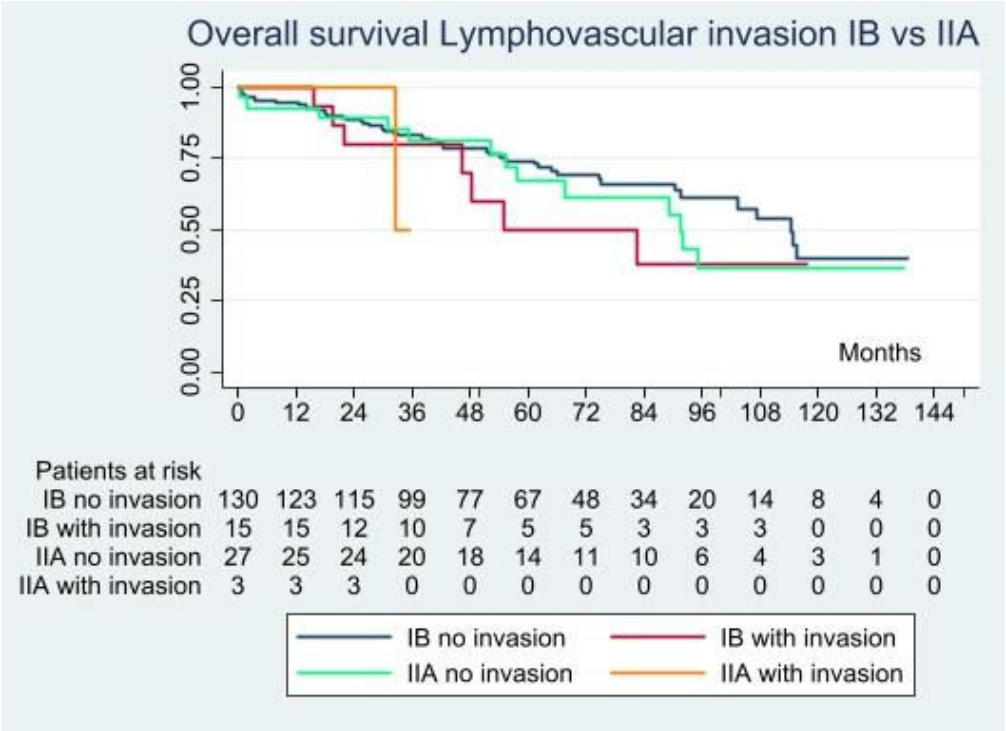


Figure 24: Kaplan meier curves representing overall survival in stages IB and IIA regarding pathological features with statistical significance (lymphovascular invasion).

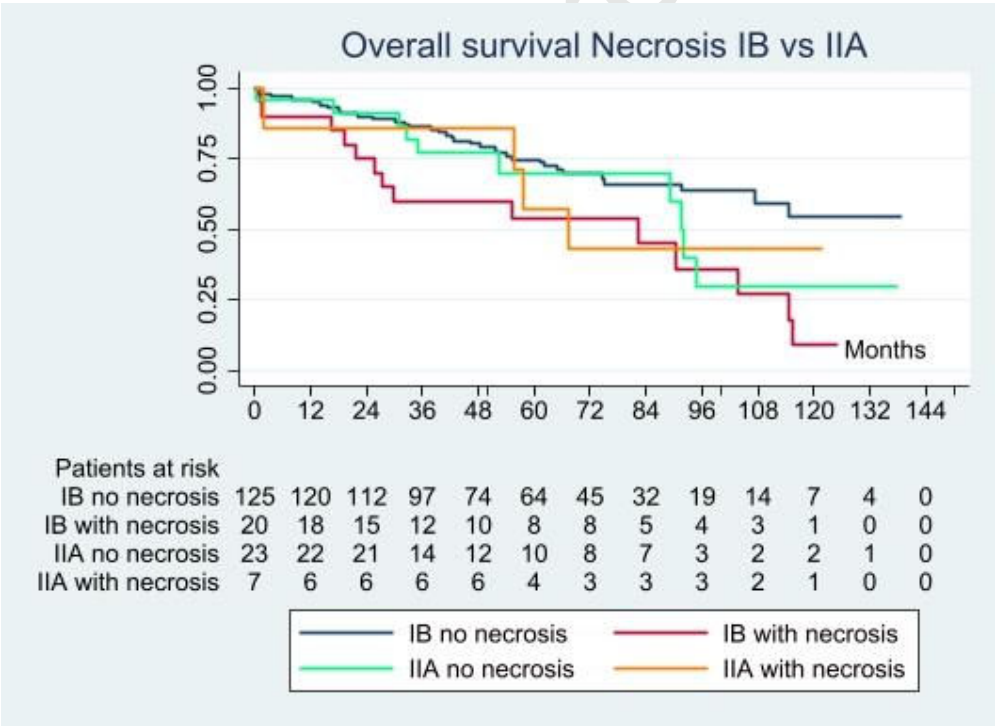


Figure 25: Kaplan meier curves representing overall survival in stages IB and IIA regarding pathological features with statistical significance (necrosis).

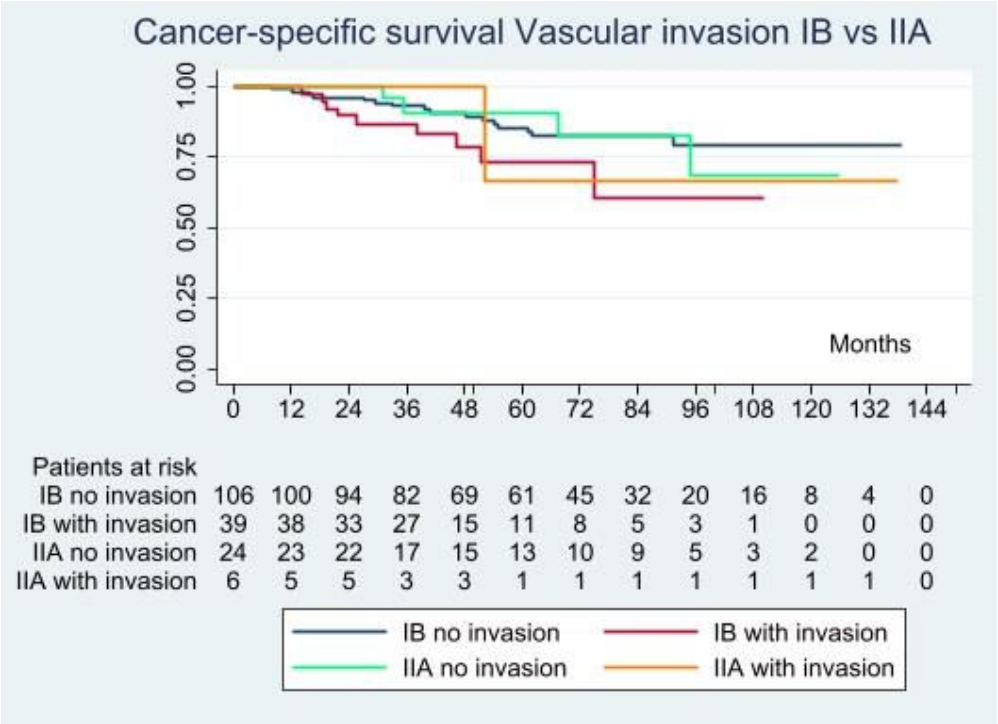


Figure 26: Kaplan meier curves representing cancer-specific survival in stages IB and IIA regarding pathological features with statistical significance (vascular invasion).

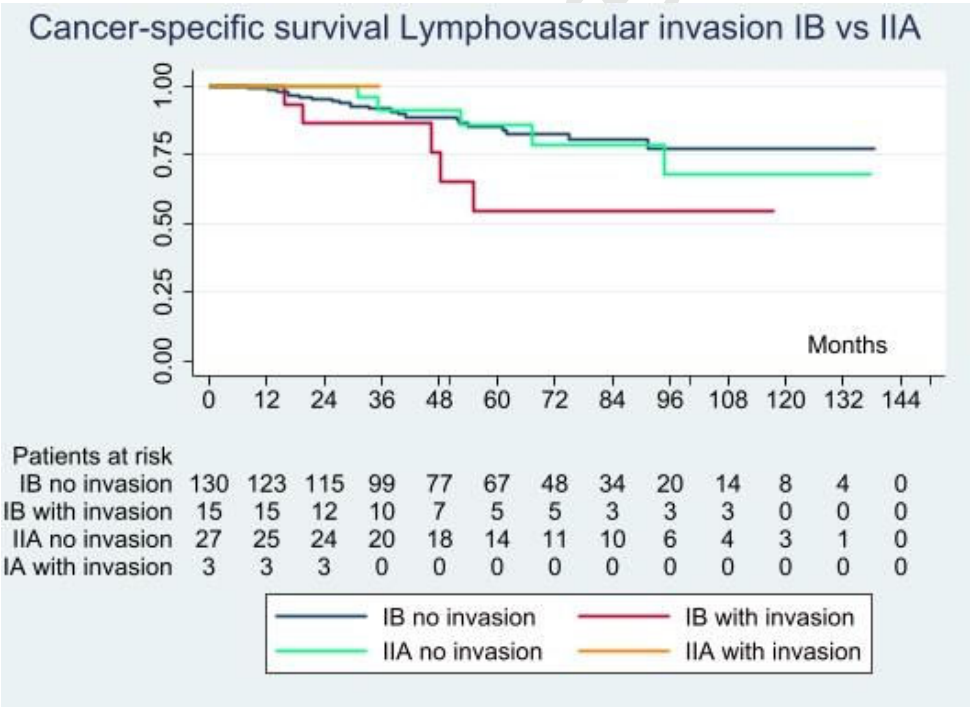


Figure 27: Kaplan meier curves representing cancer-specific survival in stages IB and IIA regarding pathological features with statistical significance (lymphovascular invasion).

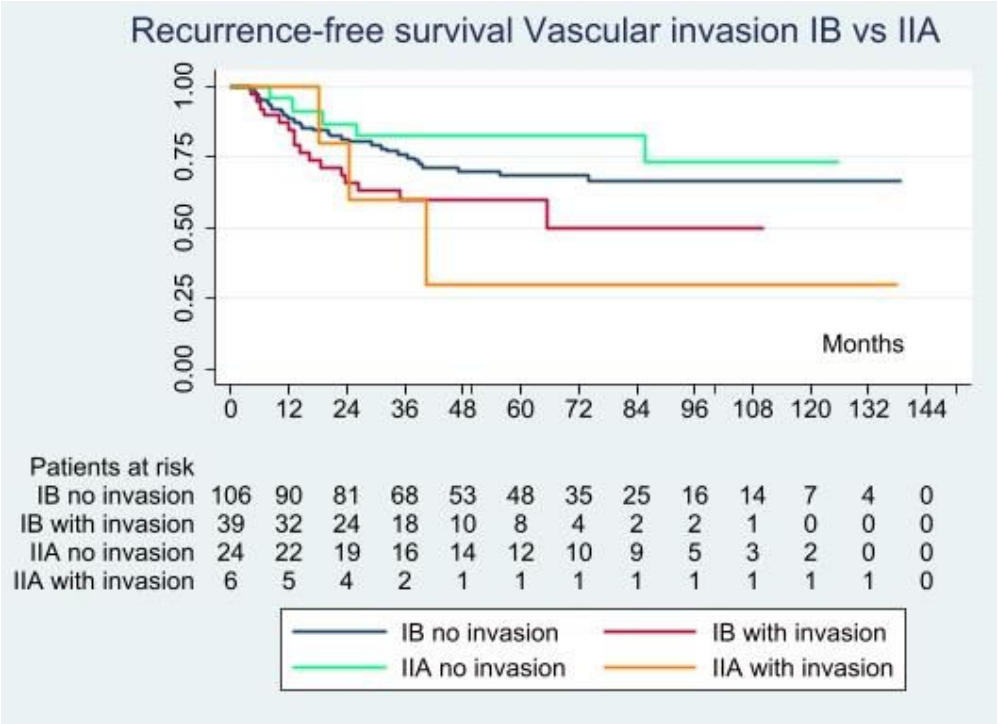


Figure 28: Kaplan meier curves representing recurrence-free survival in stages IB and IIA regarding pathological features with statistical significance (vascular invasion).

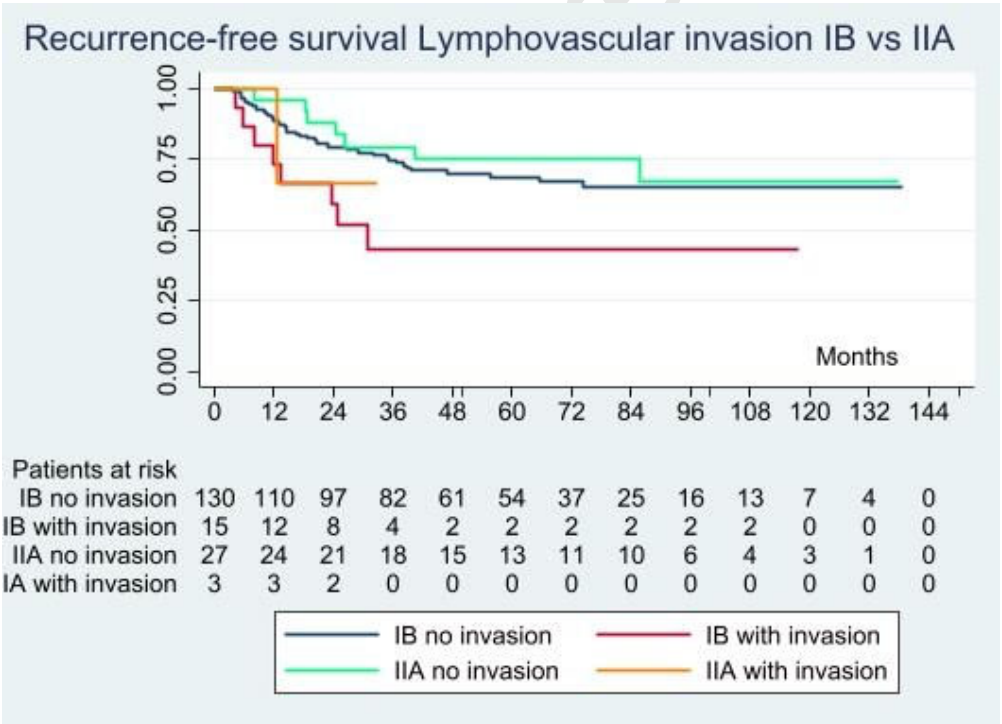


Figure 29: Kaplan meier curves representing recurrence-free survival in stages IB and IIA regarding pathological features with statistical significance (lymphovascular invasion).

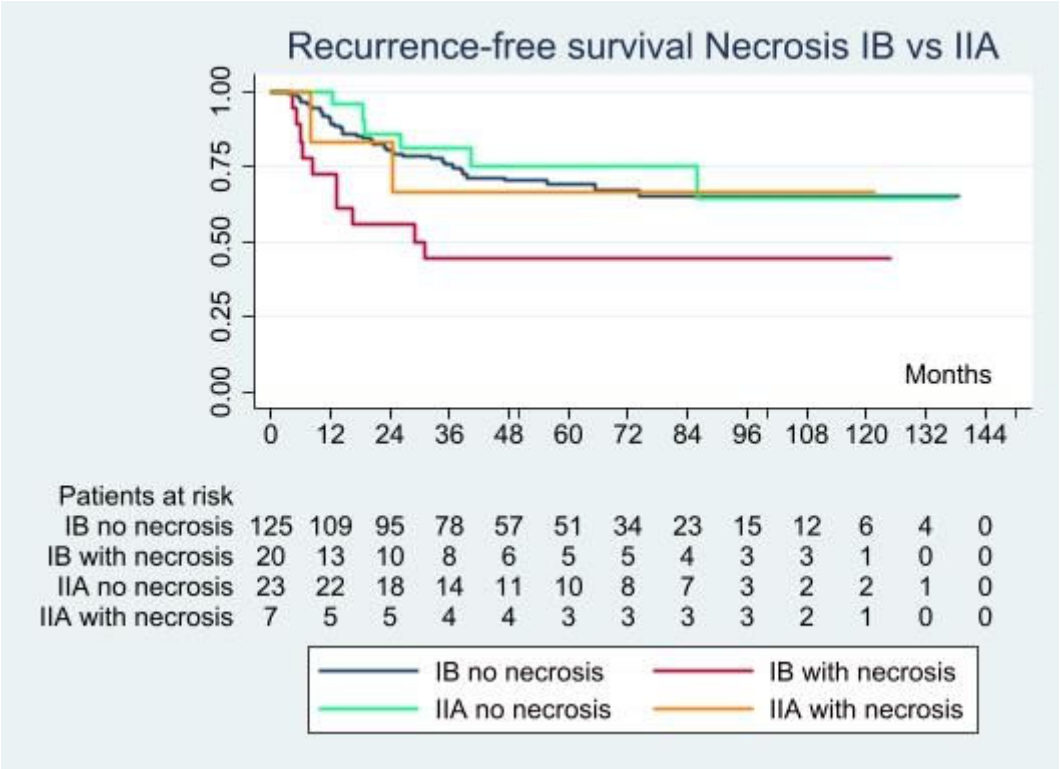


Figure 30: Kaplan meier curves representing recurrence-free survival in stages IB and IIA regarding pathological features with statistical significance (necrosis).

5.- IIA vs IIB

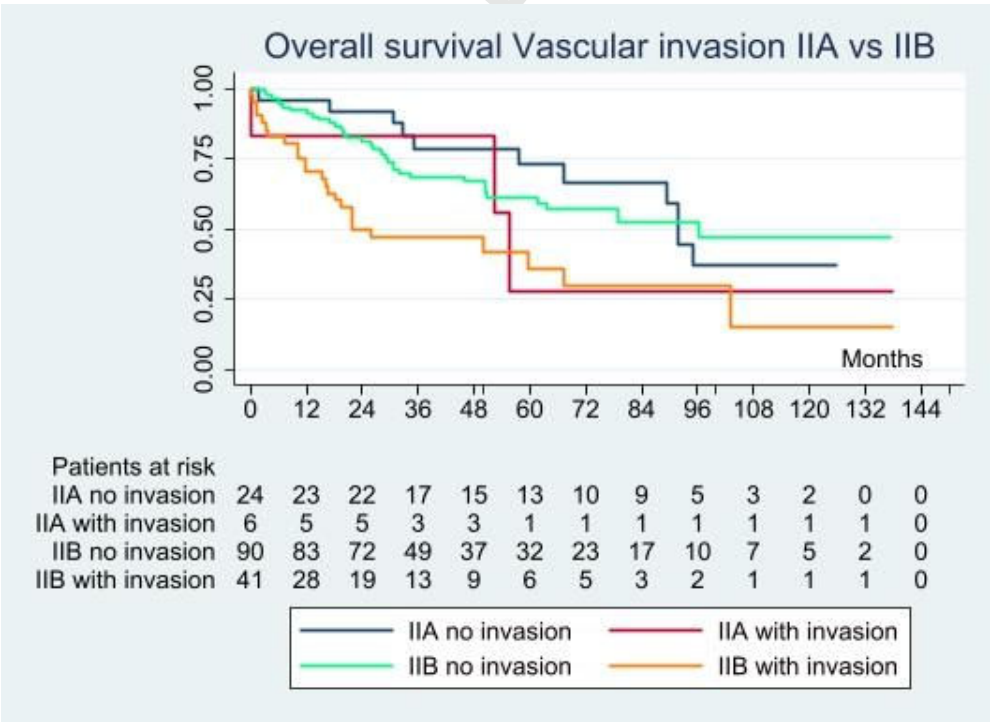


Figure 31: Kaplan meier curves representing overall survival in stages IIA and IIB regarding pathological features with statistical significance (vascular invasion).

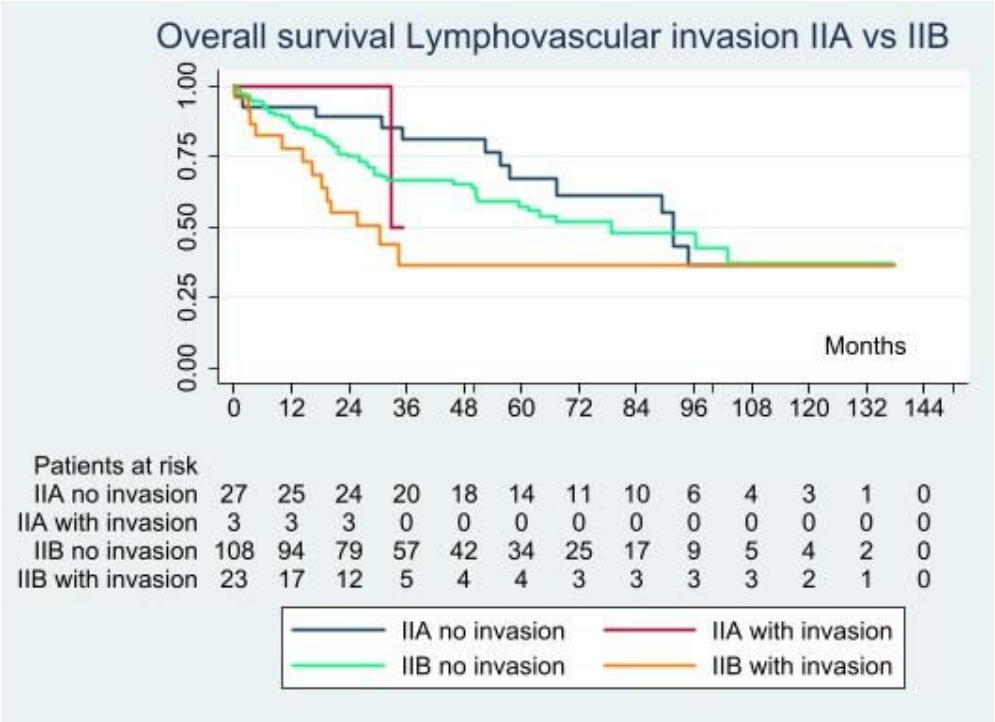


Figure 32: Kaplan meier curves representing overall survival in stages IIA and IIB regarding pathological features with statistical significance (lymphovascular invasion).

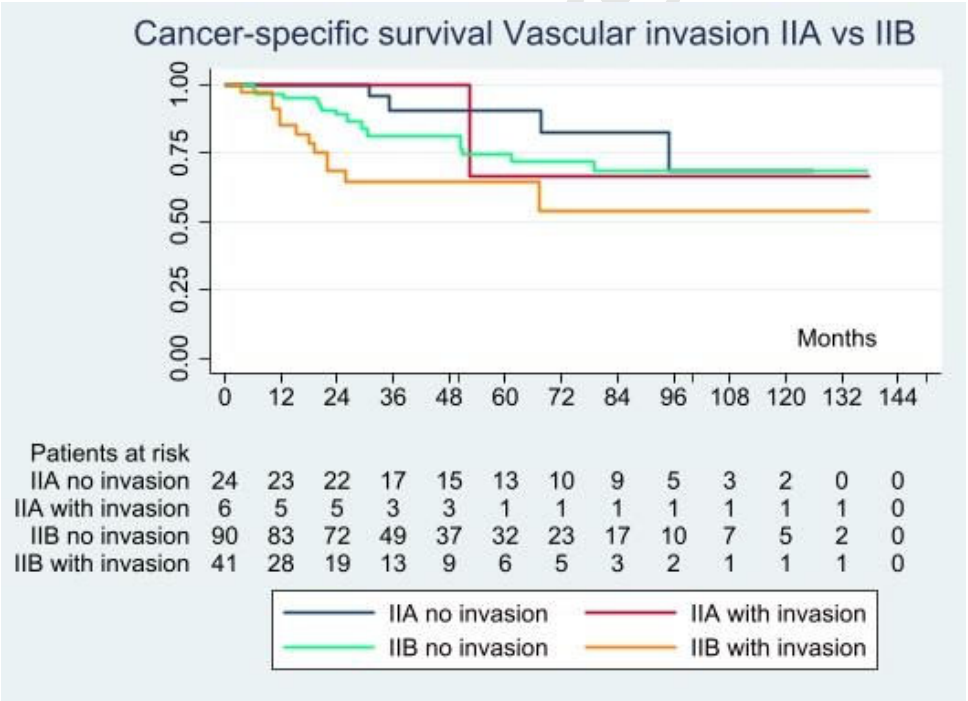


Figure 33: Kaplan meier curves representing cancer-specific survival in stages IIA and IIB regarding pathological features with statistical significance (Vascular invasion).

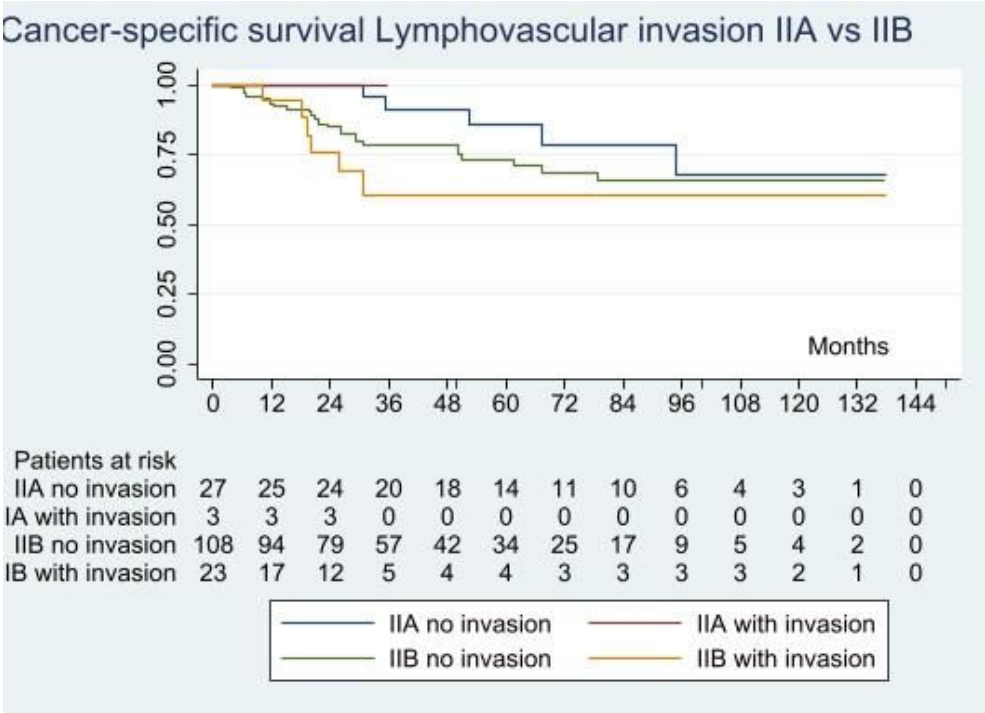


Figure 34: Kaplan meier curves representing cancer-specific survival in stages IIA and IIB regarding pathological features with statistical significance (lymphovascular invasion).

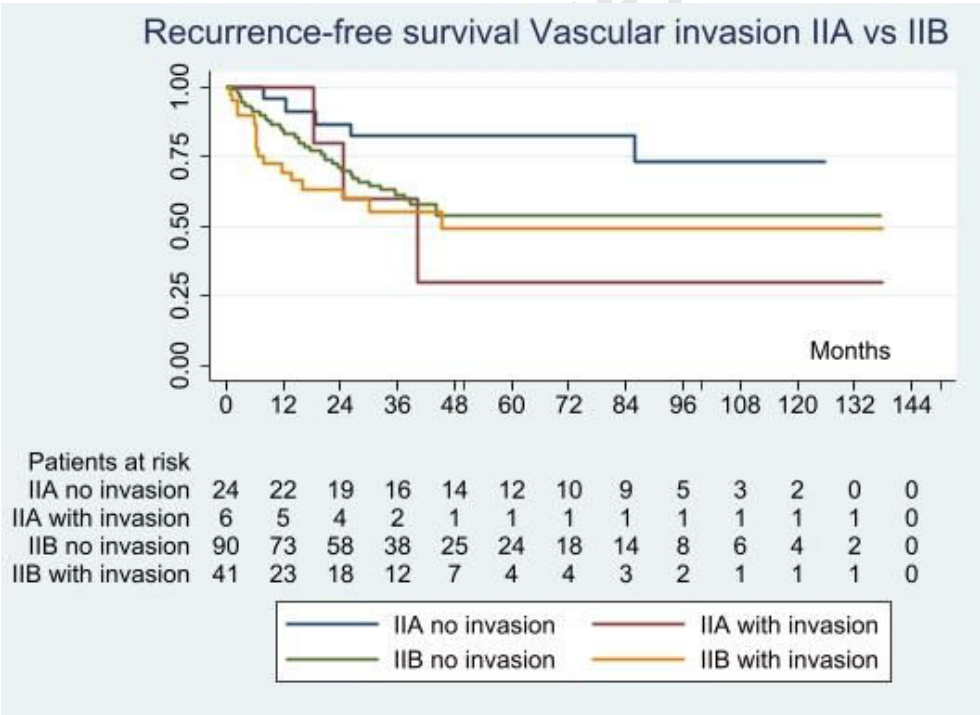


Figure 35: Kaplan meier curves representing recurrence-free survival in stages IIA and IIB regarding pathological features with statistical significance (vascular invasion).

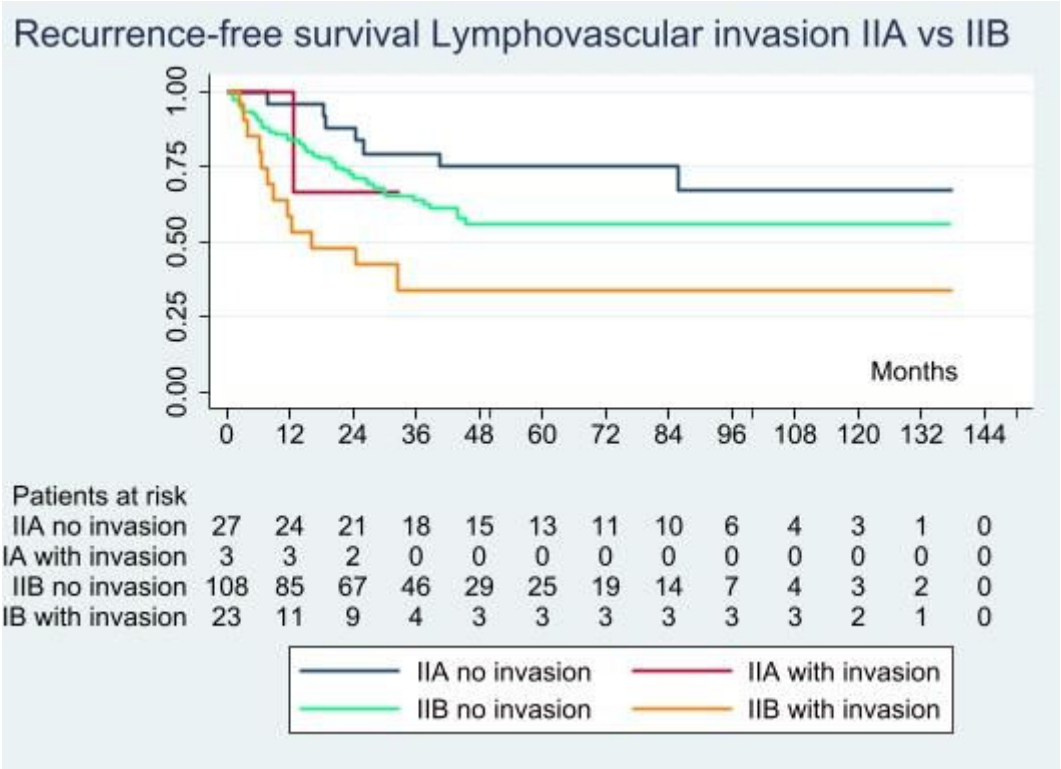


Figure 36: Kaplan meier curves representing recurrence-free survival in stages IIA and IIB regarding pathological features with statistical significance (lymphovascular invasion).

Visual abstract:

Key question: Are there other pathological characteristics that could improve the TNM prognostic model in non-small-cell lung cancer?

Key findings: Including blood vessel and lymphovascular invasion may improve TNM prognostic capacity in the early stages of lung-cancer.

Take home message: The TNM classification may be complemented with other pathological variables to increase its prognostic and predictive capacity.

TNM classification allows to better classify patients with lung cancer according to their risk of recurrence and cancer-related death.
We want to test if other tumor characteristics may improve TNM's prognostic and predictive capacity using Harrell's Index.

CANCER-RELATED SURVIVAL Prognostic model	Prognostic capacity
TNM	0,6645
TNM + Blood vessel invasion+ Lymph vessel invasion	0,7103

RECURRENCE-FREE SURVIVAL Prognostic model	Prognostic capacity
TNM	0,6264
TNM + Blood vessel invasion+ Lymph vessel invasion	0,6794

Adding other pathological characteristics to the Parameter T of the TNM could better stratify lung-cancer patients.