Original Article

Presurgical invasive mediastinal staging in lung cancer, unexpected N2 and long-term survival: a registry-based study with data from the Spanish group for video-assisted thoracic surgery

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Background: Mediastinal lymph node staging is a key element in the diagnosis of lung cancer. The combination of computed tomography (CT) and positron emission tomography (PET) has improved staging but some circumstances are known to influence their negative predictive value. The objective of this study was to assess the impact on survival of avoiding invasive mediastinal staging in surgical lung cancer patients with negative mediastinum in CT and PET and intermediate risk of unexpected pN2.

Methods: Data were collected from the prospective cohort of the Spanish Group for Video-Assisted Thoracic Surgery (GEVATS), from December 2016 to March 2018. For this study, patients were selected if they had negative mediastinum in CT and PET findings but tumours >3 cm or located centrally, or with cN1 disease. Patients who did and did not undergo invasive staging [invasive group (IG) and non-invasive group (NIG)] were compared, analysing unexpected pN2 and survival with Kaplan-Meier curves and Cox regression.

Results: A total of 2,826 patients underwent surgery for primary lung cancer. We selected 1,247 patients who had tumours >3 cm, central tumours or cN1. Invasive staging was performed in 275 (22.1%) cases. The unexpected pN2 rate was 9.6% in the NIG and 13.8% in the IG, but half of them were discovered prior to surgery in the IG. Five-year overall survival (OS) was poorer in the IG (52.4% *vs.* 64%; P<0.001). In the Cox regression model, male sex, older age, diabetes, synchronous tumour, lower diffusing capacity for carbon monoxide, larger tumour size, higher pathological N-stage, and IG status were significant independent risk factors.

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Conclusions: Invasive staging recommended by guidelines could be reduced with an appropriate selection in mediastinal CT- and PET-negative patients with risk factors for unexpected pN2, because rates of pN2 and survival did not worsen without invasive staging.

Keywords: Lung cancer; lung resection; mediastinal staging; invasive staging; survival

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Introduction

Mediastinal lymph node staging is a key element in the diagnosis of lung cancer (1). The combination of computed tomography (CT) and positron emission tomography (PET) has improved staging (2,3). Some circumstances are known to influence their negative predictive value: tumour over 3 cm, centrally located or cN1 involvement (4-8). The 2014 clinical guidelines of the European Society of Thoracic Surgeons (ESTS) for the management of mediastinal staging recommend invasive staging in these circumstances (9). Other updated clinical guidelines still recommend this (10). Nonetheless, despite the multiple diagnostic procedures, it is not feasible to completely avoid unexpected mediastinal lymph node involvement (11,12). Further, there is a paucity of evidence on the long-term effect of not performing the recommended pre-surgical mediastinal staging (13).

We conducted a real-world study to assess the impact of avoiding the invasive procedures recommended by the guidelines on rates of unexpected pN2 and long-term survival in surgical lung cancer with data obtained from the prospective cohort of the Spanish Group for Video-Assisted Thoracic Surgery (GEVATS) of the Spanish Society of Thoracic Surgery (SECT) (14). This manuscript is written following the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1900/rc).

Highlight box

Key findings

- In patients with negative mediastinum in computed tomography (CT) and positron emission tomography (PET) and risk factors for pN2 (tumour >3 cm or central tumour or cN1), not performing invasive staging was not associated with a higher rate of pN2 or poorer survival.

What is known and what is new?

- According to the main clinical guidelines on pre-surgical mediastinal staging, invasive testing is recommended despite negative CT and PET scans for the mediastinum in case of tumour >3 cm, central tumour or cN1, because the risk of unexpected N2 is higher.
- Despite the numerous articles on risk factors for unexpected pN2, there is a paucity of evidence concerning the consequences in terms of survival when clinical guidelines are not followed. We found no worse survival in patients without invasive staging despite the recommendation.

What is the implication, and what should change now?

- Clinical guidelines for mediastinal staging in lung cancer could be revised to reduce the number of invasive tests that are performed prior to surgery.

Methods

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research project was approved by all the ethics committees of the participant centres and patients recruited gave written informed consent to the use of the clinical data for scientific purposes. The name and registration number of each Institutional Review Board are available upon request.

Study design and patients

We conducted an observational study using data from a prospective registry. The GEVATS project of the SECT was launched in May 2015 to study the implementation of the video-assisted thoracic surgery (VATS) approach in Spain. A multicentre prospective cohort study was designed to include all anatomical lung resections performed in the 33 Spanish centres; which lasted for over a 15-month period (20 December 2016–20 March 2018). Further details of the database characteristics, auditing methods, and variables included are available elsewhere (14).

The follow-up was completed in 30 centres up to July 2022 (mean length of 51.4 months). We selected patients

with a diagnosis of lung cancer and negative mediastinal CT and PET findings. Lymph nodes more than 1 cm in diameter were considered positive in CT, while PET findings were classified as positive by researchers based on the reference values used at their centre. We selected patients who had a tumour over 3 cm, centrally located or cN1. Tumour size was measured on CT images as the longest diameter. The tumour was considered peripheral if the centre of the tumour was in the outer third of the lung field considering the radial distance from the lung hilum to the periphery. If any N1-node was positive on CT or PET, the disease was classified as cN1.

Mediastinal staging

Patients were divided into two groups as a function of whether they had undergone any invasive procedure for mediastinal staging: endobronchial ultrasound (EBUS), mediastinoscopy or other. We compared the results of these invasive and non-invasive groups (IG and NIG respectively).

Outcomes

The rate of unexpected pN2 was compared between these two groups. For the NIG group the number of unexpected pN2 was based on the findings of the post-surgical pathological analysis. In the IG group, pN2 was considered unexpected if they had pathological N2 in the invasive test prior to surgery or in the post-surgical analysis. Additionally, we compared overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS) between IG and NIG groups. We analysed OS in the subgroup of pN2 patients.

Variables

We included variables that might influence the rate of unexpected pN2 and/or survival.

The following variables were included:

(I) Patient-related variables: age, sex, body mass index, smoking habits, comorbidities, lung function parameters and previous lung cancer.

(II) Surgery-related variables: approach, type of resection, and total number of lymph nodes removed in the lymphadenectomy.

(III) Tumour-related variables: radiological tumour density, size in the CT, maximum standardized uptake value (SUVmax) on PET, histological type, synchronous tumour, pT and pN.

Statistical analysis

Quantitative variables were presented as mean and standard deviation and qualitative variables as absolute and relative frequencies expressed as percentages. Qualitative variables were compared with Chi-squared or Fisher's exact tests as appropriate. Similarly, quantitative variables were compared with Student's *t*- or Mann-Whiney *U* tests, or analysis of variance or Kruskal-Wallis tests, as appropriate.

For survival analysis, OS, CSS, and DFS were assessed using Kaplan-Meier curves and Log-rank tests. Univariable analysis was performed to identify variables related to OS. Any variables with a P value <0.20 were included in a Cox multivariable regression model. We used the pairwise deletion technique as a method of handling the missing data.

The statistical analysis was carried out using STATA version 16.1 (StataCorp, Texas, USA).

Results

Patients

We identified 2,826 patients who underwent lung cancer surgery, and of these, 2,132 had negative mediastinum in CT and PET. We selected those with tumour sizes >3 cm (769/36.1%), central tumours (789/37%), and/or cN1 (310/14.5%). The final sample was composed of 1,247 patients (*Figure 1*).

Mediastinal staging

Out of the 1,247 patients included in the analysis, 275 (22.1%) underwent invasive mediastinal staging. The criterion most commonly met for performing invasive procedures was the presence of cN1 and the method most commonly used was EBUS, especially in cases of cN1 (*Table 1*).

Patient characteristics

Table 2 shows the comparison of clinical characteristics between the two groups (IG and NIG). Significant differences in patient, tumour and surgical characteristics were detected.

Unexpected pN2

The overall rate of unexpected pN2 disease was 13.8% and 9.6% (P=0.04), in IG and NIG (*Table 3*). The factor most commonly associated with unexpected pN2 was cN1

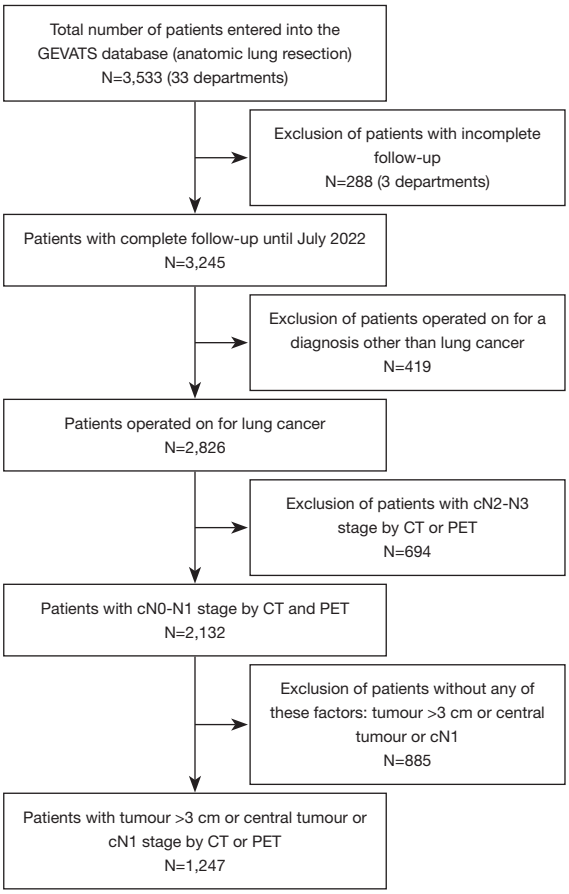

Figure 1 Flow chart of patients included in the study. GEVATS, Spanish Group for Video-Assisted Thoracic Surgery; CT, computed tomography; PET, positron emission tomography.

(*Table 3*). The higher the number of these factors, the higher the risk of pN2 (*Table 3*). In the IG, 19 out of 38 (50%) unexpected N2 were discovered in the invasive staging test prior to surgery. Of these 19 patients, 10 received neoadjuvant treatment (6 chemotherapy and 4 chemo-radiotherapy).

Survival

Five-year OS was lower in the IG [52.4% (95% CI: 45.6–58.7%) *vs.* 64% (95% CI: 60.6–67.3%) in the NIG, P<0.001; *Figure 2*]. Similar results were observed for lung CSS and DFS.

In the multivariable model for OS, male sex, older age, diabetes mellitus, lower percentage of predicted diffusion capacity of the lung for carbon monoxide (DLCO), larger tumour size on CT, synchronous tumour, higher pathological N-stage, and IG status were significant independent predictors of death (*Table 4*).

In the subgroup of patients with unexpected pN2, there were no significant differences in 5-year OS between the IG and NIG (40.1% *vs.* 46%, P=0.56; *Figure 3*).

Discussion

In this real-world study, with a highly representative sample of major lung resections carried out in Spain for lung cancer (14), we have obtained evidence concerning the real management of mediastinal clinical staging and its long-

Table 1 Mediastinal invasive staging

Variables	Invasive staging	P value	EBUS	Mediastinoscopy
All patients (n=1,247)	275 (22.1)			
Tumour size		0.04*		
≤3 cm	90 (19.0)		58 (12.3)	40 (8.5)
>3 cm	183 (23.8)		111 (14.4)	74 (9.6)
Tumour localization		0.04*		
Peripheral	87 (19.0)		51 (11.1)	27 (5.9)
Central	188 (23.8)		119 (15.1)	88 (11.2)
cN		<0.001*		
cN0	148 (15.8)		78 (8.3)	73 (7.8)
cN1	127 (41.0)		92 (29.7)	42 (13.5)

Results are expressed as count and percentage of invasive staging, EBUS and mediastinoscopy of the total number of patients with valid value in the variable in the category of each line. P values of the comparison of the frequency of mediastinal invasive staging in each factor. *, P values <0.05. EBUS, endobronchial ultrasound.

Table 2 Clinical characteristics of the 1,247 patients of the study divided in IG and NIG

Variables	IG (n=275)	NIG (n=972)	P value
Sex (male)	203 (73.8)	706 (72.6)	0.69
Age (years)	65.4 (9.7)	66.2 (9.3)	0.25
BMI, kg/m^2	26.3 (4.9)	27.2 (4.7)	0.004*
Smoking			0.29
Never	27 (9.8)	135 (13.9)	
Ex-smoker 1–12 m	123 (44.7)	421 (43.3)	
Ex-smoker >12 m	37 (13.5)	128 (13.2)	
Current smoker	86 (31.3)	272 (28.0)	
Unknown	2 (0.7)	16 (1.6)	
HBP	129 (46.9)	452 (46.5)	0.91
DM	52 (18.9)	204 (21.0)	0.44
IHD	31 (11.3)	86 (8.8)	0.22
Previous LC	6 (2.2)	51 (5.2)	0.03*
FEV_1 (%)	83.4 (19.2)	87.1 (20.6)	0.02*
DLCO (%)	77.2 (18.7)	83.1 (22.8)	<0.001*
TD (CT)			0.06
Solid	242 (89.3)	863 (89.6)	
Mixed	29 (10.7)	84 (8.7)	
Ground-glass	0	16 (1.7)	
TS (CT, mm)	40.3 (21.6)	36.8 (20.7)	0.006*
T SUVmax (PET)	12.2 (8.1)	10.1 (6.9)	<0.001*
Histological type			0.005*
ADC	124 (45.4)	475 (49.0)	
Squamous	114 (41.8)	333 (34.3)	
Other	35 (12.8)	162 (16.7)	
Synchronous tumour	22 (8.0)	69 (7.1)	0.60
pT			<0.001*
T0	8 (2.9)	2 (0.2)	
Tis	2 (0.7)	6 (0.6)	
Tx	1 (0.4)	2 (0.2)	
T1a	8 (2.9)	44 (4.6)	
T1b	21 (7.7)	141 (14.8)	
T1c	23 (8.4)	88 (9.2)	
T2a	79 (28.9)	306 (32.1)	
T2b	32 (11.7)	115 (12.1)	
T3	59 (21.6)	173 (18.2)	
T4	40 (14.7)	76 (8.0)	
pN			0.007*
N0	177 (64.8)	702 (73.7)	
N1	69 (25.3)	156 (16.4)	
N2	27 (9.9)	93 (9.8)	
Nx	0	2 (0.2)	
Surgical approach			<0.001*
Open	188 (68.4)	478 (49.2)	
VATS	87 (31.6)	494 (50.8)	
Type of resection			<0.001*
Lobectomy	226 (82.2)	872 (89.7)	
Segmentectomy	3 (1.1)	29 (3.0)	
Pneumonectomy	46 (16.7)	71 (7.3)	
Lymph nodes (n)†	9.1 (6.9)	9.7 (6.4)	0.03*
Adjuvant treatment	145 (55.8)	388 (41.9)	<0.001*

Quantitative variables are presented as mean (standard deviation) and qualitative variables as count (percentage) of the total of patients with valid value in the variable. *, P values <0.05. †, total number of lymph nodes removed in the lymphadenectomy. IG, invasive group; NIG, non-invasive group; BMI, body mass index; m, month; HBP, high blood pressure; DM, diabetes mellitus; IHD, ischemic heart disease; LC, lung cancer; FEV_1, forced expiratory volume in 1 second; DLCO, diffusion capacity of the lung for carbon monoxide; TD, tumour density; CT, computed tomography; TS, tumour size; T, tumour; SUVmax, maximum standardized uptake value; PET, positron emission tomography; ADC, adenocarcinoma; pT, post-surgical pathological classification of the tumour; pN, post-surgical pathological classification of lymph nodes; VATS, video-assisted thoracic surgery.

term consequences. In a group of patients with a negative mediastinum in CT and PET, but with risk factors for unexpected pN2, and hence, in whom clinical guidelines recommend invasive staging, only 22% of operated patients actually underwent that mediastinal invasive staging. Nonetheless, the patients who had not undergone invasive staging were not more likely to have pN2 disease and nor did they have poorer long-term survival.

The rate of invasive staging was lower in patients with tumours measuring >3 cm or centrally located (around 23%), but significantly higher in those with cN1 disease compared to cN0 (41%). This can be attributed to their greater risk of pN2 (6,15), but is probably also related to the diagnosis of N1 lymph nodes. This is reflected in a

Table 3 Unexpected pN2

Variables	Unexpected pN2	P value
Mediastinal staging		0.04*
IG	38 (13.8)	
NIG	93 (9.6)	
Tumour size		0.36
≤3 cm	45 (9.5)	
>3 cm	86 (11.2)	
Tumour localization		0.57
Peripheral	51 (11.2)	
Central	80 (10.1)	
cN (CT or PET)		<0.001*
cN0	75 (8.0)	
cN1	56 (18.1)	
Number of factors		<0.001*
1	62 (8.6)	
2	47 (11.2)	
3	22 (22.0)	

Results are expressed as count (percentage) of unexpected pN2 of the total number of patients with valid value in the variable in the category of each line. *, P values <0.05. IG, invasive group; NIG, non-invasive group; CT, computed tomography; PET, positron emission tomography.

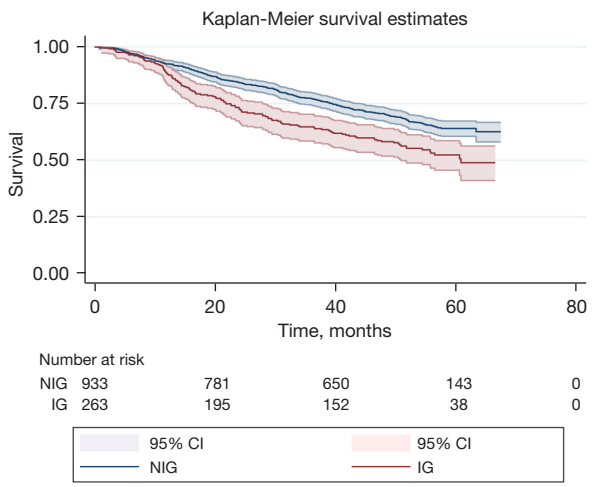

Figure 2 Overall survival according to the mediastinal staging group. NIG, non-invasive group; IG, invasive group; CI, confidence interval.

Table 4 Multivariable Cox regression model for overall survival

Variables	HR (95% CI)	P value
Gender (male)	1.56 (1.18–2.06)	0.002
Age (years)	1.02 (1.01–1.03)	0.004
DM	1.38 (1.08–1.76)	0.009
DLCO (%)	0.99 (0.98–0.99)	<0.001
Tumour size (mm)	1.01 (1.00–1.01)	<0.001
Synchronous tumour	1.73 (1.23–2.42)	0.001
pN		
pN1	1.99 (1.55–2.55)	<0.001
pN2	2.35 (1.71–3.22)	<0.001
IG	1.31 (1.04–1.66)	0.02

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; DLCO, diffusion capacity of the lung for carbon monoxide; IG, invasive group.

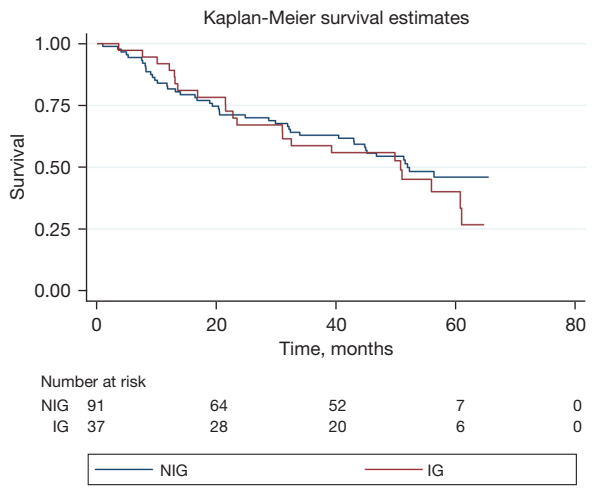

Figure 3 Overall survival according to the mediastinal staging group in the subgroup of patients with pN2. NIG, non-invasive group; IG, invasive group.

wider use of EBUS in patients with cN1. The observed practice is not in line with the ESTS and other guidelines recommendations. According to some authors, this aspect of staging is the one with the greatest variability in lung cancer (16). Specifically, across five hospitals in the USA, Thornblade *et al.* observed that invasive staging rates ranged from 17% to 94%, differences that were not explained by clinical stage. In the Danish Lung Cancer Registry, 66% of stage I patients underwent invasive staging (17), while in more recent data from the Italian VATS registry, in which

2.6% of cases had cN1 disease, 22.1% cT2, and 1.8% cT3, only 3.5% of patients underwent invasive staging (18).

Not adhering to the recommendations on mediastinal staging and performing a less thorough work-up might lead to higher rates of unexpected pN2 disease. In our series, in the group without invasive testing the unexpected N2 was 9.6% while in the group with invasive testing with a 13.8% of unexpected N2, a half of them were discovered prior to surgery. These rates are similar to that in the Danish Registry (7.8%) with stage I and the Italian Registry (8.5%) with cN0 patients and tumour sizes >3 cm (17,19). Rates of unexpected pN2 tend to vary, ranging between 5% and 15% in the series published, and above all depend on patient selection (11-13,17,19-23).

Several risk factors for mediastinal lymph node involvement when CT and PET findings are negative have been studied. The key factors are the presence of a tumour size >3 cm (7,15,20,23,24), a centrally located tumour (4), and cN1 (6,15,25). Regarding the centrality criterion, there is no consensus and results may vary depending on the definition used (21,26). The strongest risk factor for pN2 is cN1 (6,15,25). In our study, we observed a significant difference in the rate of pN2 associated with cN1: 16.8% *vs.* 7.3% in patients with cN0. Nonetheless, there are other factors, such as histological type and SUVmax on PET, that have been shown to influence unexpected pN2 and should be taken into account (8,19,20). In a recent study based on the same GEVATS database, SUVmax on PET was an independent risk factor for unexpected lymph node involvement (27). It is also important to assess the combination of several factors. Including six factors, Farjah *et al.* obtained a negative predictive value of 100% (15). In our previous study using GEVATS data, considering the three factors proposed by the ESTS, the rate of unexpected pN2 increased from 4.5% with no risk factors to 18.8% in the presence of all three (28). Similar results were observed in the present study. In some studies, patients undergoing invasive staging have had higher rates of unexpected pN2 (12,13,17). This may be the result of tumour boards' work to optimise the selection of patients for invasive mediastinal staging, focusing on those with a higher pretest probability of pN2 based on multiple risk factors (12).

Despite the numerous articles on risk factors for unexpected pN2 (7,9,12,15,19,21,23,24), there is a paucity of evidence concerning the consequences in terms of survival when clinical mediastinal staging is less exhaustive or guidelines are not followed (13,16). Thornblade *et al.* showed great variability in mediastinal staging between centres but did not provide data on long-term outcomes (16). In our study, we selected a group of patients for whom invasive mediastinal staging was recommended by the guidelines (9,10). And notably, the 5-year survival rate was higher in patients who did not undergo invasive procedures for staging (64% *vs.* 52.4%). Further, they did not show poorer cancer-specific or DFS. Results in other studies have been similar, with greater survival among patients not invasively staged (13,17). As can be observed in our data, this is achieved through the selection of patients for invasive staging, with a higher risk for mortality. Boada *et al.* also found a worse risk profile in patients with invasive staging (13). Nevertheless, after adjusting for other factors in the multivariable analysis, being in the invasively-staged group was still a risk factor.

Analysing the subgroup of patients with pN2, we also found longer survival in the non-invasively-staged group, although this difference did not reach statistical significance. Boada *et al.* reported non-significant poorer survival in their pN2 non-invasively-staged group. Probably, through invasive staging, a group of pN2 patients with a better prognosis could be selected. In our study, in patients with pN2, we observed 5-year survival rates of 40.1% *vs.* 46% in the IG and NIG, respectively. Similar survival rates have been found in other studies (11,20,29).

It is important to properly select patients for invasive mediastinal staging, but it is just as important to identify those in whom we could avoid unnecessary invasive procedures. In this way, we can optimise the use of resources, reduce the likelihood of complications associated with the diagnosis, and reduce patient time to referral for surgery. In our series, 78% of patients with surgical treatment did not undergo invasive mediastinal staging, despite the recommendations in the clinical guidelines. Likely thanks to rigorous selection, this has not resulted in either higher rates of unexpected pN2 or poorer long-term survival. As pointed out by other authors, increasing the rate of invasive staging does not avoid the occurrence of pN2, and therefore, thorough examination of the lymph nodes during surgery is still essential (12).

On the other hand, given that the main benefit of identifying N2 before surgery is to be able to provide neoadjuvant therapy, it would be interesting to have stronger evidence on its superiority over adjuvant therapy, to justify more invasive mediastinal staging. Based on data in the literature, Decaluwé and Dooms estimated that between 580 and 2,900 invasive procedures would be necessary to save one life after 5 years (30). There is still no consensus on

the best time to give complementary chemotherapy (31). Fiorelli *et al.* compared 27 patients with confirmed cN2 given neoadjuvant chemotherapy with 61 patients with unexpected pN2, and after adjusting with propensity score matching, the latter group had a longer median survival (56 *vs.* 20 months) (20). Overall, in the presence of negative CT and PET mediastinal findings, it may not be justifiable to increase the use of invasive mediastinal staging procedures to achieve a relatively small reduction in the rate of pN2 without a clear benefit from providing therapies before surgery.

Limitations

The prospective database was not designed for the purposes of the study. Therefore, differences in survival observed between the study groups may be influenced by uncontrolled factors. Nonetheless, it does provide data on the main factors usually considered in survival studies for lung cancer.

We analysed survival of all patients with any of the risk factors for unexpected pN2 considered overall but have not examined each factor in isolation. Numerous patients have various risk factors simultaneously and we wanted to maximise the sample sizes in the comparison groups.

The type of lymphadenectomy performed and total number of lymph nodes removed may have an impact on upstaging (27). Given the multicentre nature of this study, there may be considerable variability in protocols for surgical lymph node staging. Fewer lymph nodes were removed in the invasively-staged group (a median of 7 *vs.* 8). Nevertheless, we included the number of lymph nodes in the multivariable analysis. In any case, this study provides real-world evidence on rates of unexpected pN2 and survival obtained with lymphadenectomy as currently performed in Spain.

Conclusions

Regarding the staging of surgical lung cancer, when CT and PET mediastinal results are negative, we believe that it is justifiable to use invasive staging procedures less often than recommended in the guidelines, as is already occurring in routine clinical practice. In a group of patients with risk factors for unexpected mediastinal lymph node involvement, we did not observe a higher rate of unexpected pN2 or poorer survival when the recommended invasive staging had not been performed.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research project was approved by all the ethics committees of the participant centres and patients recruited gave written informed consent to the use of the clinical data for scientific purposes. The name and registration number of each Institutional Review Board are available upon request.

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