ORIGINAL ARTICLE

Main title: Factors affecting pre-operative staging accuracy in non-small cell lung cancer and its relationship with survival

Running head: Nodal staging accuracy in non-small cell lung cancer

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Abstract

Objectives

Precise staging of non-small cell lung cancer (NSCLC) determines initial treatment and provides more accurate prognostic information for patients. The aim of this cohort study was to determine factors affecting pre- and post-operative mediastinal nodal staging agreement and its effect on 2-year survival.

Materials and Methods

A retrospective multi-centre cohort study was performed, using prospectively collected and pre-defined data from weekly lung cancer multidisciplinary team meetings in 11 hospitals. Consecutive patients who underwent surgical resection of NSCLC between 2015 and 2017 were eligible. Factors associated with concordant and discordant pre- and post-operative nodal staging, and subsequent lung cancer-specific 2-year mortality were identified by univariate and multivariate regression.

Results

973 patients fulfilled the eligibility criteria. Concordant pre- and post-operative nodal staging was observed in 783/973 (80%). 123/973 (13%) were under-staged pre-operatively. 67/973 (7%) were over-staged.

In 173 patients with clinical N1 or N2 disease (in whom invasive mediastinal staging was indicated), staging EBUS was performed in 55/173 (32%). In these patients, younger age and use of staging EBUS were independent predictors of concordant pre- and post-operative staging.

In all patients pre-operative under-staging was independently associated with increased lung cancer-specific 2-year mortality.

Conclusion

Invasive mediastinal staging with EBUS was independently associated with more accurate pre-operative staging. Pre-operative nodal under-staging was associated with increased lung cancer specific mortality. Nodal staging accuracy in potentially curable NSCLC is of fundamental importance to ensure patients receive the correct first-line treatment and to improve survival.

1. Introduction

Modern clinical staging for non-small cell lung cancer (NSCLC) aims to accurately characterize extent of disease, allowing optimal treatment decisions to be made, maximizing potential benefits and minimizing burdens. Staging algorithms for potentially radically treatable NSCLC vary between international guidelines, but universally mandate Positron Emission Tomography–Computed Tomography (PET-CT) scanning and, if intrathoracic lymph node involvement is suspected, invasive assessment by endobronchial ultrasound (EBUS), endoscopic ultrasound (EUS), or mediastinoscopy [1–3]. In patients without extra-thoracic metastases, treatment decisions should therefore be determined by careful mediastinal nodal assessment, assuming the primary tumour can be resected. This allows planning for multi-modality treatment in patients with proven, but resectable N1/2 disease, and avoids futile resection in patients with contralateral N3 involvement. In the N2/3 setting or if the primary lesion is unresectable, mediastinal staging also allows accurate mapping of the volume of disease to be encompassed by radical radiotherapy.

Comparing pre-operative, clinical staging with post-operative, surgical staging based on lymph node resection allows the accuracy of the pre-treatment nodal staging work-up to be objectively assessed. More importantly, such comparisons also allow the impact of discordant pre-operative staging to be quantified and factors associated with this identified and addressed. Previous studies that have used this approach have been limited by small sample sizes or the use of now outdated staging tests, frequently not including integrated PET-CT and EBUS [4–8]. A more recent study reported agreement between pre- and post-surgical nodal staging of 79% and another study found that staging inaccuracy was not independently associated with all-cause mortality [9,10].

The aim of this retrospective cohort study was to determine the level of concordance between pre- and post-operative staging in a cohort of surgically resected NSCLC patients assessed using modern staging investigations. We also sought to identify any impact of discordant staging on lung cancer-specific 2-year mortality and factors associated with this.

2. Patients and Methods

2.1 Patients

Consecutive patients diagnosed in the West of Scotland (a region including 11 centres with a mix of both university teaching and district general hospitals) were included. Cases were eligible if they were diagnosed with NSCLC between January 1, 2015, and December 31, 2017 and underwent surgical resection as first treatment. Cases were excluded if they had incomplete pre- or post-operative staging and/or no PET-CT performed. These data are prospectively collected locally by clinical audit staff in each NHS Board from diagnosis to definitive treatment in accordance with the nationally agreed Quality Performance Indicator dataset and definitions, and storage of this data for future analysis is approved nationally. These routine data were then matched with cause of death data from death certification held by NHS National Services Scotland. The Caldicott Guardian oversees the storage and use of

these patient identifiable data for audit and research purposes. Permissions for specific analyses were sought *a priori* and were approved by the local Caldicott Guardian. Patients' electronic clinical records were reviewed to identify lung cancer recurrence in all patients at two years post-surgery. In patients deemed to have died of other causes, electronic clinical records were reviewed to confirm this. Patients who died either during their admission for lung cancer resection or within 30 days of their discharge were excluded from the survival analyses. Details regarding invasive mediastinal staging and any missing data were extracted from electronic patient records. Performance status was defined according to the Eastern Cooperative Oncology Group scale [11]. Patients were classified into 3 histopathological groups: squamous cell carcinoma, adenocarcinoma and other. Waiting time until surgery was defined as the number of days between the first radiological diagnosis by CT and resection. The follow-up period for survival was 2 years from the date of surgery.

The pre-operative stage was defined as the stage determined prior to surgery after all pre-operative staging investigations were complete, including PET-CT and any invasive mediastinal staging procedures eg EBUS, EUS or mediastinoscopy, usually established at multi-disciplinary team meetings. In general, only patients with N0, N1 or single station N2 disease would be deemed suitable for surgery. Post-operative stage was based on the pathological examination of the resected tumour and lymph nodes. Patients were staged using the TNM Classification of Malignant Tumours, 7th Edition [12]. Concordant (or accurate) staging was defined as identical pre- and post-operative nodal stage. Regarding discordant or inaccurate staging, *pre-operative under-staging* was defined as a lower pre-operative than post-operative nodal stage and *pre-operative over-staging* is defined as a higher pre-operative than post-operative nodal stage.

2.2 Statistical analyses

Data are reported as simple proportions (%), mean (SD) if normal distributed or median (IQR) if not. A univariate analysis for factors associated with discordant clinical N staging in all patients was performed using Chi-squared and Mann-Whitney U tests as appropriate; those variables with a $p<0.05$ were subsequently entered in a binary logistic regression analysis focussed on the same outcome measure. This method was repeated for a pre-planned sub-group analysis of patients with pre-operative N1 and N2, in whom invasive mediastinal staging was indicated according to international guidelines [1–3].

A competing relative risk analysis (Fine and Gray) was performed to examine cancer-specific 2-year mortality in all patients, as a proportion of patients in our cohort had died of non-cancer related causes [13]. This allowed us to determine factors independently associated with mortality including nodal staging concordance and post-operative staging, presented with hazard ratios with 95% confidence intervals.

IBM® SPSS® Statistics 25.0 (Armonk, USA) and R 4.1.1 (Vienna, Austria) were used for the statistical analyses. $p<0.05$ was considered to indicate significance.

3. Results

The study flowchart is presented in Figure 1. 1084 patients with clinical stage IA to IIIB NSCLC were potentially eligible, having undergone surgical resection as an initial treatment between 2015 and 2017. 973/1084 (90%) fulfilled all eligibility criteria. Exclusions are documented in Figure 1. 18 patients were excluded from the survival analyses as they died in the immediate post-operative period. Baseline characteristics of the study population are summarized in Table 1. The mean (SD) age was 69 (8.7) and there was a slight female predominance (Table 1).

3.1 Accuracy of pre-operative nodal (N) stage compared to post-operative (N) stage

Pre- and post-operative N stage were concordant in 783/973 of patients (80%, Table 2). Pre-operative stage N0 was associated with most accurate pre-operative staging with 89% concordance, in comparison to stages N1 and N2 (37% and 58% respectively). After adjusting for variables significant on univariate analysis, both pre-operative N1 and N2 (OR 11.5, 95% CI=7.3-18.0, p<0.001 and OR 5.0, 95% CI=2.7-9.3, p<0.001, respectively) and resection by pneumonectomy (OR 3.4, 95% CI=1.5-7.5, p=0.002) were associated with higher risk of discordant pre-operative nodal staging (Table 3). Age, sex, performance status, site of the tumour, histology, waiting time until surgery and the year of the diagnosis were not associated with concordance of pre- and post-operative staging on univariate analysis. There was a higher rate of post-operative stage III disease in patients undergoing pneumonectomy than in those treated by lobectomy or sublobar resection (40% vs 14% vs 2%; χ^2 51.2, p<0.001). More patients had 3 or more N2 nodes resected at pneumonectomy, compared to lobar or sublobar resections (98% vs 85% vs 38% respectively; χ^2 273.3, p<0.001).

3.2 Patients with pre-operative nodal under-staging

123/973 patients (13%) were under-staged pre-operatively, of which 54/123 and 69/123 (56%) had clinically undetected N1 and N2 respectively (Table 2). 58/123 (47%) patients had intrathoracic lymph nodes with axial diameter more than 1 cm on CT and/or FDG-avid intrathoracic lymph nodes on PET-CT, meeting the criteria for invasive mediastinal staging according to the guidelines current at time of diagnosis (American College of Chest Physicians, 2013 and European Society of Thoracic Surgery, 2014) [2,3]. In these patients, only 16/58 (27%) underwent staging EBUS.

3.3 Invasive mediastinal staging in patients with pre-operative N1/N2

173/973 (18%) patients had pre-operative N1 or N2 suitable for invasive mediastinal staging. Among those patients, staging EBUS was done in 55/173 (32%) patients and mediastinoscopy was done in 5/173 (3%) patients. In these 173 patients, after adjusting for covariates, younger age (OR 1.05, 95% CI=1.01-1.09, p=0.02) and staging EBUS (OR 2.0, 95% CI=1.01-4.05, p<0.05)

were independent predictors of staging accuracy (Table 4). In this analysis, sex, performance status, location of the primary tumour, surgical procedure, histology, waiting time until surgery and the diagnosis year were not significant on univariate analysis.

3.4 Effect of pre-operative nodal under- and over-staging on survival

Of the patients with concordant pre- and post-operative stage, 81% were alive and 12% died due to lung cancer (Table 1). In the patients with pre-operative under-staging, 54% were alive and 36% died due to lung cancer. In the regression analysis, as expected, the hazard ratio increased with higher T-stage (T1 staging vs T4 staging HR 7.6, 95%CI 4.1-14.2, p<0.001; Table 5). In patients with post-operative N1 and N2 disease, pre-operative nodal under-staging conferred an increased risk of lung cancer related mortality in comparison to those with accurate pre-operative staging, independent of T stage (N0 concordant as reference; N1 staging concordance HR 1.8, 95%CI 0.8-3.8, p=0.13 vs N1 nodal under-staging HR 2.9, 95%CI 1.6-5.2, p<0.001; N2 staging concordance HR 2.3, 95%CI 1.02-5.0, p=0.04 vs N2 nodal under-staging HR 5.2, 95%CI 3.3-8.3, p<0.001). Not receiving adjuvant chemotherapy was associated with a trend suggesting increased mortality (HR 1.6, 95%CI 0.96-2.6, p=0.07). Age, sex, performance status, type of surgical procedure, number of nodes sampled at surgery, time to surgery and pathological subtype had no association with survival on univariate analysis.

4. Discussion

Mediastinal nodal stage is of fundamental importance in making decisions regarding treatment of non-small cell lung cancer (NSCLC) with no distant metastases. Treatment of patients with small lesions and no size significant or FDG avid lymphadenopathy is straightforward and they account for the majority of patients who have potentially curable lung cancer. However, patients with size significant or FDG avid intrathoracic lymph nodes are more likely to have nodal disease, and thus the accuracy of pre-operative staging is vital to ensure delivery of the most effective treatment first. Confirmation of nodal involvement is essential to ensure patients receive gold standard treatment and that best treatment is not prevented by false positive nodes based on imaging alone. In patients undergoing stereotactic ablative radiotherapy (SABR), exclusion of any nodal disease is required and in patients with inoperable mediastinal nodal disease, accurate assessment allows mapping of hilar and mediastinal disease to administer radical radiotherapy [14,15]. Finally, exclusion of extension to contralateral mediastinal lymph nodes (N3) is essential as it usually implies the disease is inoperable and incurable (except when encompassable in a radical radiotherapy field).

We examined the accuracy of pre-operative nodal staging using modern staging techniques including PET-CT and EBUS in a large 'real-life' cohort of patients undergoing surgical resection for NSCLC in multiple centres including university teaching and district general hospitals. We considered what factors influence discordant pre- and post-operative nodal staging and the impact of this on two-year survival. To our knowledge, this is the first time that discordant

nodal staging, has been shown to be associated with a higher risk of lung cancer specific mortality, *independent* of post-operative nodal stage

4.1 Concordance of nodal staging

In this study, the agreement between pre- and post-operative nodal staging was 80%. 13% of patients had a higher pathological nodal stage, and 7% had unforeseen N2. A meta-analysis published by Navani and colleagues in 2019 showed a lower concordance with only 62% of patients staged accurately and higher proportion of patients with higher nodal stage post-surgery and unforeseen N2 (24% and 12% respectively) [9]. However, PET-CT was used only in only 10% of patients and EBUS was not used at all as the nine studies included in the analysis dated from 1987 to 2005, in contrast to our study where these investigations were used routinely. Other older studies predating PET scan and EBUS, reported the pre-operative nodal staging accuracy to be between 35% and 56% [4,5,16]. More recently, Heineman reported very similar findings to those presented in this manuscript using the Dutch Lung Surgery Audit, with an accuracy of nodal staging of 79%, 15% pre-operative nodal under-staging and 6% unforeseen N2, using modern staging techniques [10].

Pneumonectomy was associated with a higher proportion of discordant staging in comparison to lobectomy and sublobar resection. This is important as generally patients with known pre-operative N2 disease are not considered for pneumonectomy. On closer review of the 18 patients upstaged at surgery, 10 were upstaged from N0 to N1. Of these, all 10 were N1 by direct extension with a N1 node found in the main specimen. 8 were upstaged from N1 to N2 and all 8 had occult N2 disease (not FDG avid). This highlights the importance of performing staging EBUS, particularly in patients undergoing a planned pneumonectomy. In addition, a higher number of lymph nodes were resected at pneumonectomy in comparison to lobectomy and sublobar resection in these patients, increasing the likelihood of discovering occult nodal disease. Similar to our cohort, Edwards et al described that a higher proportion of patients who underwent pneumonectomy had at least three N2 nodal stations sampled, in comparison to lobectomies and sublobar resections [17]. Thus, pre-operative under-staging may be underestimated in patients undergoing lobectomy and sublobar resection due to less thorough lymph node resection. Of note, although patients undergoing pneumonectomy had proportionally higher stage disease, type of surgery was not associated with increased lung cancer specific mortality.

4.2 Use of invasive mediastinal staging

Although the current ESTS, ACCP and NICE guidelines differ, they all recommend invasive mediastinal nodal staging if any intrathoracic lymph node measures greater than 10mm or has FDG uptake [1–3]. Our study showed less than optimal usage of invasive mediastinal staging when it was indicated. 47% of the patients with nodal upstaging post-surgery should have undergone staging EBUS based on these criteria, however this was only performed in 13% of these patients. In addition, among all the patients with clinical N1/N2, only 32% had staging

EBUS prior to surgery. Similar experiences have been reported previously, and discrepancy in practice in comparison to guidelines may reflect varying skill levels in terms of delivering staging EBUS across a variety of centres [18–20]. Furthermore, the availability of EBUS as a less invasive alternative has resulted in a reduction in use of mediastinoscopy relative to minimally invasive procedures [21]. A recent survey of clinicians in the USA highlighted a lack of evidence for invasive mediastinal staging and inadequate expertise as barriers to adherence to guidelines[22].

We examined the factors influencing accuracy of nodal staging and undergoing a staging EBUS was independently associated with more concordant nodal staging. Simply following the recommendations regarding systematic nodal staging with EBUS will likely result in an improvement in pre-operative staging accuracy. In contrast to our findings, Heineman and colleagues showed that EBUS and EUS were not significant factors associated with the accuracy of clinical *TNM* staging after multivariate analysis in the Dutch Lung Surgery Audit, but they did not report whether a specific relationship with nodal staging alone was investigated[10].

4.3 Effect of nodal staging discordance on lung cancer specific mortality

For the first time, we have found that pre-operative under-staging is independently associated with increased risk of lung cancer specific mortality at two years in comparison with pre-operative concordant nodal staging for the same pathological nodal stage.

This is an important finding for several reasons. Principally, it confirms the relevance and importance of the recommendations of international guidelines, specifically regarding the application of invasive mediastinal staging when indicated. Two recent studies from the Netherlands highlight the importance of systematic staging to guide appropriate treatment. Bousema et al found evidence of significant unexpected N2 disease in patients with nodal imaging appearances that would indicate invasive mediastinal staging [19]. In addition, the SCORE study found that systematic mediastinal staging was more effective than targeted staging based on CT and PET-CT appearances [23].

In terms of survival, in Lung-BOOST, a post-hoc analysis of 133 patients with NSCLC, the group randomized to undergo EBUS-TBNA as their first test had an improvement in overall survival in comparison to patients undergoing conventional diagnosis and staging [24]. However, in a meta-analysis Navani and colleagues found that there was no independent association between inaccurate clinical TNM staging and *all-cause* mortality [9].

The reasons that pre-operative under-staging may lead to increased mortality remain unclear. It is possible that in centers where staging is more thorough, delivery of treatment may also be more appropriate. Typically, in patients proven to have multi-station N2 disease, patients are more appropriately treated with radical chemoradiotherapy than surgical resection. Another possible explanation is that patients with disease clearly defined with PET and mediastinal staging are more straightforward to treat in comparison with occult disease that is not demonstrated using current staging techniques. It is currently not known if patients

with occult N2 disease have a poorer prognosis in comparison to patients with clearly evident N2 disease. Alternatively, if a surgeon is aware of specific nodal involvement prior to resection then they will be more likely perform a more thorough lymphadenectomy to try and ensure complete clearance of disease.

4.4 Strengths and limitations

One of the major strengths of this study is completeness of data. Consecutive patients diagnosed with lung cancer across multiple hospital sites and treated with surgery in 2015-17 were included. However, there was a lower than recommended use of invasive staging modalities in our study - this may be representative of the variability of adherence to international guidelines on mediastinal staging outside of large teaching centres. Indeed, this is likely to explain the proportion of patients who were over-staged pre-operatively. This variability did enable us to demonstrate that staging with EBUS-TBNA is an independent predictor of pre- and post-operative intrathoracic nodal staging concordance.

There are well described limitations of using routine death certificate data for cause specific mortality. However, using electronic patient records we were able to establish evidence of lung cancer recurrence in all patients with lung cancer recorded as cause of death and the non-lung cancer causes of deaths were also reviewed and confirmed. In our study around a third of patients who died within 2 years of surgery were confirmed to have a cause of death other than lung cancer.

5. Conclusions

Mediastinal staging with EBUS was independently associated with pre- and post-operative staging concordance. In patients with post-operative N1 or N2 disease, pre-operative under-staging was associated with higher risk of lung cancer specific mortality in comparison to concordant pre-and post-operative nodal staging. Pre-operative nodal staging accuracy in potentially curable non-small cell lung cancer is of fundamental importance to ensure patients receive the correct first-line treatment and to improve survival.

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Competing Interests

There are no specific conflicts of interest related to this manuscript. JM has received fees for lectures and advisory boards from Astra Zeneca. JVDH has received fees for lectures and an advisory board from Astra Zeneca and for teaching and travel from Fujinon. JM has received fees for lectures and advisory boards from Astra Zeneca. The other authors have no conflicts of interest to declare.

Contributorship statement

Conception and design: AA, KB, JVDH, JM. Acquisition, analysis or interpretation of data: AA, DE, LS, JM, JVDH. Drafting and revising of manuscript: AA, DE, LS, GWC, AH, KH, KB, JVDH, JM.

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Tables

Table 1. Patient characteristics

	Total	Accurate nodal staging	Pre-operative over-staging	Pre-operative under-staging
Number of patients	973	783 (80%)	67 (7%)	123 (13%)
Mean age (SD)	69 (9)	68 (9)	69 (8)	69 (8)
Sex, n (%)				
Male	443 (46%)	360 (46%)	27 (40%)	56 (46%)
Female	530 (54%)	423 (54%)	40 (60%)	67 (54%)
Site of the tumour, n (%)				
Main bronchus	13 (1%)	7 (1%)	1 (1%)	5 (4%)
Upper lobe	586 (60%)	475 (61%)	39 (58%)	72 (58%)
Middle lobe	39 (4%)	32 (4%)	2 (3%)	5 (4%)
Lower lobe	335 (34%)	269 (34%)	25 (37%)	41 (33%)
Median (IQR) days from CT to surgery	74 (56-97)	75(56-98)	69(53-84)	70(54-96)
Surgical procedure, n (%)				
Lobectomy	836 (86%)	679 (87%)	58 (87%)	99 (80%)
Pneumonectomy	42 (4%)	18 (3%)	6 (9%)	18 (15%)
Sublobar resection	95 (10%)	86 (11%)	3 (4%)	6 (5%)
Histology, n (%)				
Squamous	337 (35%)	261 (33%)	32 (48%)	44 (36%)
Adenocarcinoma	553 (57%)	463 (60%)	29 (43%)	61 (50%)
Other	83 (9%)	59 (8%)	6 (9%)	18 (15%)
Pre-operative TNM stage, n (%)				
Stage I	655 (67%)	587 (75%)	0	68 (55%)
Stage II	227 (23%)	146 (19%)	36 (54%)	45 (37%)
Stage III	91 (9%)	50 (6%)	31 (46%)	10 (8%)
Pre-operative T stage, n (%)				
T1	528 (54%)	453 (58%)	21 (31%)	54 (44%)
T2	321 (33%)	245 (31%)	28 (42%)	48 (39%)
T3	102 (11%)	72 (9%)	14 (21%)	16 (13%)
T4	22 (2%)	13 (2%)	4 (6%)	5 (4%)
Pre-operative N stage, n (%)				
N0	800 (82%)	708 (90%)	0	92 (75%)
N1	119 (12%)	44 (6%)	44 (66%)	31 (25%)
N2	54 (6%)	31 (4%)	23 (34%)	0
2-year lung cancer mortality, n (%)				
Alive	752 (77%)	633 (81%)	52 (78%)	67 (54%)
Died due to lung cancer	146 (15%)	91 (12%)	11 (16%)	44 (36%)
Post-operative death	18 (2%)	11 (1%)	2 (3%)	5 (4%)
Died due to other causes	57 (6%)	48 (6%)	2 (3%)	7 (6%)

NSCLC: non-small cell lung cancer

Table 2. Agreement between clinical and pathologic nodal stage

		Post-operative N stage				
		pN0	pN1	pN2	Total	Accuracy of pre-operative staging
Pre-operative N stage	N0	708	54	38	800	89%
	N1	44	44	31	119	37%
	N2	15	8	31	54	58%
Total		767	106	100	973	

White: accurately staged, Light grey: pre-operative over-staging, Dark grey: pre-operative under-staging

Table 3. Logistic regression analysis of factors associated with discordant pre- and post-operative nodal staging in 973 patients who underwent surgical resection for non-small cell lung cancer

		Odds ratio	95% confidence interval	p-value
Pre-operative N stage	N0	1 (ref)		
	N1	11.5	7.3-18.0	<0.001
	N2	5.0	2.7-9.3	<0.001
Pre-operative T stage	T1	1 (ref)		
	T2	1.2	0.8-1.8	0.4
	T3	1.4	0.8-2.5	0.3
	T4	2.1	0.7-6.5	0.2
Waiting time until surgery		1.0	0.99-1.0	0.4
Surgical procedure	Lobectomy	1 (ref)		
	Pneumonectomy	3.4	1.5-7.5	0.002
	Sub-lobar resection	0.7	0.3-1.4	0.3
Histology	Squamous	1 (ref)		
	Adenocarcinoma	0.9	0.6-1.3	0.4
	Other	1.3	0.7-2.5	0.4

Age, sex, performance status, site of tumour and diagnosis year were not significant on univariate analysis.

Table 4: Logistic regression analysis of factors associated with discordant pre- and post-operative nodal staging in 173 patients with non-small cell lung cancer and clinical N1/N2 disease who underwent surgical resection

		Odds ratio	95% confidence interval	p-value
Age		1.05	1.01-1.09	0.02
Clinical nodal stage	N1	1 (ref)		
	N2	0.5	0.25-1.01	0.05
Staging EBUS performed	Yes	1 (ref)		
	No	2.0	1.01-4.05	<0.05

Sex, performance status, location of the primary tumour, surgical procedure, histology, waiting time until surgery and the diagnosis year were not significant on univariate analysis.

Table 5: Regression analysis of factors affecting lung cancer related mortality in patients undergoing surgery for non-small cell lung cancer

			Hazard ratio	95% confidence interval	p-value
Age			1.01	0.99-1.03	0.28
Sex		Female	1 (ref)		
		Male	1.17	0.83-1.62	0.37
Pathological T stage		T1	1 (ref)		
		T2	1.26	0.83-1.90	0.28
		T3	2.74	1.71-4.38	<0.001
		T4	7.57	4.04-14.17	<0.001
Pathological N stage by post-operative nodal staging concordance	N0	pre-operative stage concordant	1 (ref)		
		pre-operative over-staging	1.17	0.58-2.37	0.65
	N1	pre-operative stage concordant	1.79	0.85-3.78	0.13
		pre-operative over-staging	1.43	0.20-10.36	0.72
		pre-operative under-staging	2.85	1.57-5.18	<0.001
	N2	pre-operative stage concordant	2.26	1.02-4.97	0.04
		Pre-operative under-staging	5.24	3.33-8.27	<0.001
Adjuvant chemotherapy		Yes	1 (ref)		
		No	1.58	0.96-2.61	0.07

Performance status, type of surgical procedure, number of nodes sampled at surgery, time to surgery and pathological subtype were not significant.

Figure

Figure 1: Patients included in the analysis