The Prevalence and Clinical Relevance of Non-expandable Lung in Malignant Pleural Mesothelioma: A Prospective, Single-Center Cohort Study of 229 Patients

Anna C Bibby[1,2], Paul Halford[1], Duneesha De Fonseka[1,2], Anna J Morley[2], Sarah Smith[2] & Nick A Maskell[1,2]

1. Academic Respiratory Unit, Bristol Medical School, University of Bristol, UK
2. North Bristol Lung Centre, North Bristol NHS Trust, Bristol, UK

Corresponding Author:
Dr Anna C Bibby
Academic Respiratory Unit, University of Bristol, 2nd Floor Learning & Research Building, Southmead Hospital, Bristol, BS10 5NB.
Email: Anna.bibby@Bristol.ac.uk
Tel: (+44) 0117 414 8049

Conflicts of Interest: No conflicts of interest declared for all authors.

Funding: No funding was received for this study.

Ethics and Consent: The research was granted ethical approval by the Research Ethics Committee South West -Central Bristol, 08/H0102/11. All patients provided written, informed consent to participate in the study.

Author Contributions: ACB and NAM conceived and designed the study. ACB cleaned & analysed the data, interpreted the results and wrote the manuscript. PH, DDF, AJM & SS helped refine the methodology, assisted with data collection & analysis, and contributed to manuscript writing. All authors reviewed and approved the final document. ACB is the guarantor for the published study, including all data and analyses.

Abstract

Rationale: Non-expandable lung is a recognised phenomenon that can create management challenges in mesothelioma. Its prevalence and clinical importance are unknown.

Objective: The aim of this study was to describe the prevalence of non-expandable lung and to evaluate whether there was any association between non-expandable lung and survival in a clinical cohort of mesothelioma patients.

Methods: This was a prospective, observational cohort of mesothelioma patients, seen in a single centre between 01/03/2008 and 03/08/2017. Baseline characteristics were collected at diagnosis. Serial chest radiographs were assessed for the presence of pleural effusions and non-expandable lung (defined as a lack of lung expansion following pleural aspiration or drainage). Patients were followed up until death or censored on 14/03/2019.

Results: Of 229 patients, 192 (82.7%) had a pleural effusion at presentation, with non-expandable lung observed in 64/192 (33.3%). Breathlessness and cough were more frequent with pleural effusions, especially with underlying non-expandable lung, whilst chest pain was more prevalent in patients without effusions. Patients with pleural effusions, both with and without underlying non-expandable lung, were more likely to have epithelioid disease, early stage disease and to receive chemotherapy than patients with no pleural effusion. Non-expandable lung was an independent risk factor for short survival, with a hazard ratio for mortality of 1.80 (95% confidence interval 1.16 to 2.80) compared with patients without non-expandable lung. The presence of a pleural effusion did not appear to be associated with a worse prognosis compared to patients with an effusion (adjusted HR 1.86, 95% confidence interval 0.93 to 3.72).

Conclusion: This is the first study to describe the prevalence and clinical implications of non-expandable lung in mesothelioma. It demonstrated that NEL is a relatively common phenomenon that is associated with significant symptomatology and shorter survival.

Malignant pleural mesothelioma (MPM) is an aggressive malignancy of the pleural surface.[1, 2] It carries a poor prognosis, with median survival of 9 to 15 months from diagnosis.[3-5] Morbidity is high and patients often experience multiple symptoms, predominantly breathlessness and chest pain, but also cough, fatigue and weight loss.[3, 6-18] Some of these symptoms are the result of pleural effusions, which are common, although the reported prevalence varies widely in the literature.[6, 12]

Non-expandable lung (NEL) is a condition in which the lung is unable to inflate fully, due to either proximal obstruction of the major bronchi or encasement of the lung by thickened pleura.[19] Pleural thickening may reflect an ongoing active and potentially reversible process, e.g. pleural infection, in which case the lung is referred to as "entrapped," or a fixed fibrotic phenomenon that persists after the active process has resolved, in which case the lung is considered "trapped." In MPM, tumour spreads circumferentially around the lung and can form a thick rind, preventing lung expansion. Whilst this is an active process, it is also permanent, and consequently the terms "trapped" or "entrapped" overlap. For the purpose of this study, the term NEL is used to describe the failure of lung re-expansion for any reason after fluid removal.

NEL can be diagnosed radiographically, as a lack of pleural apposition after drainage or aspiration. Alternative diagnostic approaches include pleural manometry and M-mode ultrasonography, however the clinical utility of these methods appears limited.[19-21]

The presence of NEL complicates the management of MPM. Lack of pleural apposition makes chemical pleurodesis likely to fail,[22] and whilst indwelling pleural catheters (IPC) can alleviate symptoms, care must be taken during drainages as aggressive fluid removal can cause

chest pain due to negative intra-thoracic pressure creating tension on the non-expanding lung.[23] The role of debulking surgery to release the non-expandable lung and alleviate symptoms is uncertain, and is currently under investigation in a randomised controlled trial (Meso-TRAP, NCT03412357).

The prevalence of NEL in MPM is unknown. In one retrospective series of patients undergoing diagnostic medical thoracoscopy, non-expandable lung was detected in 5 out of 40 (12.5%) patients with malignant pleural disease.[24] A randomised trial of patients with mixed malignant pleural effusions reported NEL in 41 out of 923 patients (4.4%) at screening, with a further 32/250 patients (12.5%) found to have NEL after a 10-day run-in period.[25] Whether these figures can be generalised to MPM populations, however, is not known and it is conceivable that the prevalence is higher in MPM, due to its circumferential growth pattern.

There is little data regarding the clinical implications of NEL. The British Thoracic Society emphasises the importance of 50% pleural apposition on chest radiograph as a threshold below which chemical pleurodesis is unlikely to succeed, although this figure is based on expert recommendation rather than existing evidence.[20] Logically, if the lung remains unexpanded after fluid has been removed, breathlessness is more likely than in patients with expandable lung. Equally, NEL implies visceral pleural thickening, most likely due to tumour infiltration, which has been associated with shorter survival in previous observational studies.[26]

We undertook a prospective study to describe the prevalence and clinical implications of NEL in a representative cohort of MPM patients. We used an objective radiographic definition of NEL that included any degree of pleural non-apposition, in order to maximise case

identification. The aim of the study was to determine whether NEL was associated with shorter survival. Secondary objectives of the study were to describe the natural history of NEL in MPM, symptoms associated with the condition and potential management strategies.

Methods

Participants and Setting

Patients with undiagnosed pleural disease who presented to a single centre in the United Kingdom between 01/03/2008 and 03/08/2017 were enrolled into a prospective observational study (Pleural Investigation Study, REC ref 08/H0102/11). Diagnoses were recorded, independently, by two senior clinicians, 12 months after enrolment. Cases of MPM enrolled during the specified time period were included in this study. All MPM diagnoses had been ratified by the regional multidisciplinary team meeting (MDT).

Data Collection

Baseline patient characteristics, performance status (PS) and tumour variables (laterality, histological sub-type and International Mesothelioma Interest Group (IMIG) stage [27]) were collected prospectively. The presence or absence of symptoms (breathlessness, chest pain, cough, weight loss) were recorded at presentation, prior to pleural fluid drainage. Blood tests were taken at presentation and the neutrophil lymphocyte ratio (NLR), an established prognostic marker in MPM, was calculated.[28] Treatment decisions were made by the regional mesothelioma MDT and recorded contemporaneously.

The presence and size of pleural effusions were evaluated on the baseline (i.e. prior to any pleural intervention) posterior-anterior (PA) chest radiograph by two independent clinicians, using a previously published classification system.[29] In summary, 0=no pleural fluid present, 1=blunting of the costo-phrenic angle, 2=fluid occupying up to 25% of the hemi-thorax, 3=fluid occupying between 26-50% of the hemi-thorax, 4=fluid occupying between 51-75% of the hemi-thorax, 5= fluid occupying between 76-100% of the hemi-thorax. Serial radiographs were assessed for the presence of NEL, defined as a lack of pleural apposition following pleural aspiration or drainage. The degree of NEL was assessed based on the degree of pleural non-apposition using the same criteria as above. Radiographs were performed at all clinic appointments and following any therapeutic pleural intervention, i.e. large volume thoracentesis, insertion of intercostal chest drain or indwelling pleural catheter, medical or surgical thoracoscopy.

NEL management strategy was determined from serial radiological imaging and patient records. Incidence of auto-pleurodesis, defined as spontaneous cessation of pleural fluid accumulation with no further requirement for pleural drainage, was determined based on medical records.

Survival status was assessed on 14/03/19. For deceased patients, the date of death was obtained from the National Cancer Register. Patients alive on 14/03/19 were censored on that date (with a minimum follow up of 20 months). Survival was calculated from date of enrolment in the study to date of death or censoring.

Statistical Analysis

The explanatory variable was the presence of pleural effusion with NEL, hereafter referred to as NEL status. Patients were categorised as having no pleural effusion, pleural effusion without underlying NEL or pleural effusion with NEL. The primary outcome was survival.

Patient characteristics and treatments were tabulated according to NEL status and compared visually.

Absolute number of deaths and death rates per 100 person-years were tabulated according to the presence or absence of a pleural effusion and, in patients with an effusion, the presence or absence of NEL. Poisson regression was used to test for trend in event rates between groups. Cox Proportional Hazards model was used to assess the relationship between survival and NEL status. An initial univariable analysis was performed, followed by multivariable modelling, adjusted for the presence of an effusion, age category, sex, WHO performance status, tumour laterality, tumour stage, non-epithelioid histology, NLR, effusion size and whether the patient received chemotherapy.

A separate analysis was performed to evaluate the relationship between symptoms and survival. *A priori* subgroup analysis was undertaken in patients with NEL to determine whether there was any relationship with NEL size and survival. Statistical analyses were undertaken using STATA v14.2 (STATACorp LLP, Texas, USA) with an α value of ≤ 0.05.

Results

Participant Characteristics

Two hundred and twenty-nine participants were enrolled during the study period, 196 (85.6%) of whom were male. Mean age was 64 years (range 40-93, standard deviation (SD) 8.4) and the majority of participants were PS 0 or 1 (62; 27.1% and 111; 48.5% respectively). Right-sided tumours were more common than left (134; 58.5% *vs* 94; 41.1%) with 1 participant (0.4%) having bilateral disease. One hundred and forty six patients (63.8%) had epithelioid disease, 45 (19.7%) sarcomatoid or desmoplastic, and 18 (7.9%) biphasic, whilst for 20 participants (8.7%) histological subtype was not specified (NOS). Staging information was available for 186 patients, of whom 65/186 (35%) were stage I, 8 (4.3%) were stage II, 72 (38.7%) stage III and 41 (22%) stage IV. Median NLR for the 197 patients in whom it was available was 4.37 (IQR 2.99 to 6.37). 167 participants (72.9%) were offered chemotherapy and 98 (42.8%) ultimately received it.

Breathlessness was the most common symptom at presentation, occurring in 183 participants (79.9%), followed by chest pain, which occurred in 100 participants (43.7%). Weight loss was reported by 90 patients (39.3%), and cough by 88 (38.4%). Ten patients (4.4%) were asymptomatic at presentation.

Pleural Effusion and NEL

One hundred and ninety-two participants (192/229; 83.8%) had a pleural effusion at presentation, the majority of which occupied over 25% of the hemi-thorax (130/192; 67.7%).

Of 192 patients with pleural effusions, 64 (33.3%) had NEL, with 49/64 (76.6%) demonstrating preserved pleural apposition over at least 50% of the hemithorax (Table 1). For most patients with NEL (38/64, 59%), the degree of NEL was smaller than the size of the overlying pleural effusion.

Right-sided tumours were more frequently associated with pleural effusions and with underlying NEL, whilst left-sided tumours were more common in patients without effusions (Table 1). The NEL group had a higher proportion of men compared with the effusion without NEL group and the no effusion group (96.9% *vs* 81.3 % *vs* 81.1%). Breathlessness was more frequently reported in patients with NEL compared with patients with effusions but no NEL, who in turn, were more likely to be breathless than patients without effusions (90.6% *vs* 82% *vs* 54.1%). A similar pattern was seen with cough (51.6% *vs* 37.5% *vs* 21.6%). In contrast, chest pain was most common in patients without effusions and least common in patients with NEL (64.9% *vs* 42.2% *vs* 34.4%).

NEL was usually diagnosed at presentation or within 14 days of receiving a diagnosis of MPM (53/64; 82.8%). The median time between diagnosis with MPM and detection of NEL was -4.5 days, with an upper limit of 818 days. NEL was managed with an IPC in 31/64 patients (48.4%). The remaining 33 patients were managed conservatively, i.e. did not undergo any further pleural intervention. This was usually because the degree of NEL was small and reaccumulation of fluid filled the resultant space but did not result in a large pleural effusion, or because aspiration of fluid yielded no symptomatic benefit. Five patients (2.2%) in the conservatively managed group died within 6 weeks of being diagnosed with NEL. Interestingly,

in 18/64 patients with NEL (28.1%), subsequent disease progression led to obliteration of the pleural space and auto-pleurodesis.

Survival

Median survival was 11.1 months, with 15 patients (6.6%) alive at the time of analysis. Follow-up for living patients ranged from 20 months to 123 months.

A similar proportion of patients died in each group (94.6 vs 93.8 vs 92.3% in patients with no pleural effusion, pleural effusion without NEL and pleural effusion with NEL respectively – see Table 2). Event rates for death were also comparable across the groups, and unadjusted survival analysis demonstrated no convincing association between the presence of NEL and mortality. However, in the adjusted model, the presence of NEL was associated with an increased risk of dying compared with patients without NEL (HR 1.80, 95% CI 1.16 to 2.80). The multivariable model controlled for the presence or absence of a pleural effusion, suggesting the relationship between NEL and survival was an independent association related to lung expansion rather than presence of pleural fluid. In fact, the presence of a pleural effusion was not associated with survival in either unadjusted (HR 1.02, 95% CI 0.70 to 1.46) or adjusted (HR 1.86, 95% CI 0.93 to 3.72) models. Full results of the survival model are shown in Appendix A.

Chest pain was associated with shorter survival (HR 1.89, 95% CI 1.26 to 2.83), but other symptoms were not markers of poor prognosis (see Appendix B).

Sub-group analysis of patients with NEL showed no association between the degree of NEL and survival (HR=0.85, 95% CI 0.66 to 1.10, p=0.213), nor between the presence of clinically relevant NEL (defined as NEL with a lack of pleural apposition affecting >25% of the hemithorax)

and survival (HR 0.78, 95% CI 0.45 to 1.33, p=0.362). However, with only 64 patients in the sub-group, the analysis was unlikely to have had sufficient power to detect a relationship.

Discussion

This is the first study to report the prevalence of non-expandable lung (NEL) in malignant pleural mesothelioma (MPM), and it does so using data from a prospective, clinical cohort in a high incidence country. This study demonstrated that NEL is a relatively common phenomenon and that it is associated with significant symptomatology and shorter survival.

The prevalence of NEL in this cohort of MPM patients was higher than has been reported in general malignant pleural effusion (MPE) populations (33% vs 12.5%).[24, 25] There are several potential explanations for this. The first is that the MPE studies evaluated the presence of NEL at a single time-point, early in the disease course, and could have missed patients who developed NEL as a late phenomenon. The current paper assessed serial chest radiographs throughout the disease course and is therefore will have detected a greater number of cases of NEL. An alternative explanation is that NEL is more common in patients with MPM compared with MPE. This hypothesis is plausible, given the circumferential growth pattern of MPM tumours, which is more likely to result in lung encasement and subsequent NEL.

This study demonstrated that NEL was an independent predictor of poor prognosis. Instinctively, one may think that this is a reflection of bulky, advanced-stage tumours being more likely to cause NEL, however the relationship between NEL and survival persisted after

adjustment for tumour stage. In fact, patients with pleural effusions (with and without NEL) were more likely to present with early stage disease than patients without pleural effusions. This is in contrast to most other cancer types, in which the presence of a pleural effusion reflects metastatic spread, and consequently a higher disease stage. However, because MPM is a primary malignancy of the pleural surface, pleural effusions may be present in early disease, as seen here, and do not influence disease staging. Previous studies have suggested pleural effusions are a poor prognostic factor in MPM, but this has not been consistently demonstrated, and our data do not support this hypothesis.[6, 7] It is possible that the previously observed relationship between pleural effusions and shorter survival in MPM was due to underlying NEL, as lung expansion was not reported or adjusted for in that study.[6]

As well as earlier disease stage, NEL was associated with other positive prognostic factors, including a greater proportion of epithelioid tumours and higher chemotherapy treatment rates. These differences in patient characteristics explain the discrepancy between the crude and adjusted hazard ratios for death. The favourable characteristics attenuated the negative outcomes associated with NEL, thus introducing confounding to the unadjusted result. However, based on the fully adjusted model, NEL was an independent predictor of short survival in MPM. This finding may reflect tumour-specific biological factors and growth pathways, the evaluation of which were outside the scope of this study. Future research could focus on proteomic and metabolomic evaluation of tumour samples and pleural fluid in patients with NEL to explore this hypothesis further.

This study demonstrated breathlessness was more common in the context of pleural effusions and NEL whilst chest pain was more prevalent in “dry MPM”. This is almost certainly a

result of reduced respiratory capacity due to lung compression and compromised diaphragmatic function due to the presence of fluid.[30] Notably, in NEL, reduced lung capacity cannot be reversed by fluid drainage, although removal of fluid may improve respiratory dynamics and ameliorate symptoms.[19, 30] The higher incidence of cough in patients with NEL is a novel observation, and is likely to reflect negative intra-thoracic pressures stimulating highly sensitive cough receptors on the visceral pleura.[31, 32]

The management of NEL is poorly evidenced, and a recent international review statement concluded that clinical trials are required to elucidate the optimal treatment strategy.[19] IPCs have been shown to be effective at controlling symptoms, but our results revealed that conservative management may also be appropriate in the right setting.[30, 33] The observation that NEL was a pre-terminal event in a small number of patients, alongside the finding that over a quarter of patients with NEL subsequently pleurodesed, supports a symptom-based approach to management.

Strengths and Weaknesses

Prospective data collection from consecutive MPM patients minimised the risk of selection bias and enhanced the generalisability of the study findings. The external validity of the results is supported by the similarity between our patients' characteristics and existing cohorts, specifically with respect to age, male to female ratio, distribution of histological sub-types and prevalence of pleural effusions.[6, 7, 9-14, 16] Survival was similar to national figures, and the relationship of certain known prognostic variables with survival, e.g. sarcomatoid histology, tumour stage, NLR, was replicated.[3-5, 34-36]

Previous research into NEL has been complicated by different definitions of NEL and varying thresholds in the degree of lung non-expansion considered clinically relevant.[19] A strength of this study was the use of a robust definition for NEL that identified patients with any degree of lung non-expansion, with additional data collected on the extent of NEL based on the degree of pleural non-apposition. Exploratory sub-group analysis of patients with NEL failed to elucidate what degree of NEL is clinically relevant in terms of survival. However, patient numbers were small and type II errors possible. Future studies would require larger numbers of patients to evaluate the relationship between the degree of NEL and clinically important outcomes such as symptoms and survival.

This study used chest radiographs to detect NEL and determine the degree of non-expandable lung, as this investigation is readily available and easily interpretable. It is acknowledged that there is no validated system for measuring the size of NEL, hence we employed an existing score previously used in pleural effusions.[29] Computed tomography (CT) may be more sensitive in detecting NEL and is likely to yield more accurate information about the degree of pleural apposition. Additionally, CT could enable volumetric quantification of NEL, which may provide further prognostic information. Future research could explore the correlation between NEL size on chest radiograph and size on CT, to determine whether either are associated with survival.

Imaging was undertaken based on clinical practice, rather than on a pre-defined study schedule. It is possible, therefore, that some NEL cases may have been missed due to imaging not being performed at the relevant time-point. This would have resulted in an underestimation of NEL prevalence and may have affected outcomes as these patients would

be more likely to be asymptomatic. However, most patients underwent some form of imaging every few months and therefore the likelihood of missing NEL in the brief periods between radiographs was small.

This study did not have the capacity to ascertain symptom severity nor to collect serial data on symptom evolution throughout the disease process. A multi-centre, prospective, observational study is currently underway in the UK collecting this data, using repeat-measure patient-reported symptom scores and quality of life questionnaires alongside serial radiological imaging (ASSESS-meso, ISRCTN 61861764). The results are awaited with interest.

Conclusion

In summary, NEL affected one third of MPM patients with effusions and was associated with breathlessness and cough. The presence of NEL was an independent predictor of poor survival, even after adjustment for tumour stage, presence of effusion and treatment received.

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Table 1: The characteristics of patients presenting without pleural effusion, with pleural effusion but no non-expandable lung, and pleural effusion with non-expandable lung.

		No pleural effusion n=37	Pleural effusion without NEL n=128	Pleural effusion with NEL n=64
Male, n (%)		30 (81.1)	104 (81.3)	62 (96.9)
Age, mean (SD)		74 (7.33)	73 (8.83)	74 (7.97)
	Aged <65	2 (5.4)	18 (14.8)	6 (9.4)
	Aged 65-69	9 (24.3)	25 (19.5)	15 (23.4)
	Aged 70-74	8 (21.6)	30 (23.4)	14 (21.8)
	Aged 75-79	9 (24.3)	27 (21.1)	9 (14.1)
	Aged 80+	9 (24.3)	27 (21.1)	20 (31.3)
Performance status, n (%)	0	11 (30.6)	34 (26.6)	17 (26.6)
	1	17 (47.2)	65 (50.8)	29 (45.3)
	2	8 (22.2)	13 (10.2)	10 (15.3)
	3	0 (0)	12 (9.4)	8 (12.5)
	4	0 (0)	1 (0.8)	0 (0)
	Not recorded	1 (2.7)	3 (2.3)	0 (0)
Laterality, n (%)	Left	21 (56.8)	51 (39.8)	22 (34.4)
	Right	15 (40.5)	77 (60.2)	42 (65.6)
	Bilateral	1 (2.7)	0 (0)	0 (0)
Histology, n (%)	Epithelioid	19 (51.4)	84 (65.6)	43 (67.2)
	Sarcomatoid/Desmoplastic	9 (24.3)	23 (18.0)	13 (20.1)
	Biphasic	4 (10.8)	7 (5.5)	7 (10.9)
	NOS	5 (13.5)	14 (10.9)	1 (1.6)
Stage, n (%)	I	5 (13.5)	38 (29.7)	22 (34.4)
	II	1 (2.7)	4 (3.1)	3 (4.7)
	III	13 (35.1)	42 (32.8)	17 (26.6)
	IV	13 (35.1)	20 (15.6)	8 (12.5)
	Not recorded	5 (13.5)	24 (18.8)	14 (21.9)
Received chemotherapy, n (%)		12 (33.3)	53 (42.7)	33 (53.2)
Neutrophil Lymphocyte Ratio, median (IQR)		4.6 (3.0-6.8)	4.3 (2.9-6.3)	4.3 (3.2-6.3)
Size of effusion, n (%)				
	Blunting of costophrenic angle		14 (10.9)	2 (3.1)
	Fluid occupying ≤25% of hemithorax		38 (29.7)	8 (12.5)
	Fluid occupying 25-50% of hemithorax	-	37 (28.9)	14 (21.9)
	Fluid occupying 50-75% of hemithorax		31 (24.2)	24 (37.5)
	Fluid occupying >75% of hemithorax		8 (6.3)	16 (25.0)
Size of NEL, n (%)				
Lack of pleural apposition affecting:				
	Costophrenic angle only			3 (4.7)
	≤25% of hemithorax			18 (28.1)
	25-50% of hemithorax	-	-	28 (43.8)
	50-75% of hemithorax			12 (18.8)

	>75% of hemithorax			3 (4.7)
Symptoms, n (%)	Breathlessness	20 (54.1)	105 (82.0)	58 (90.6)
	Chest pain	24 (64.9)	54 (42.2)	22 (34.4)
	Weight loss	17 (46.0)	47 (36.7)	26 (40.6)
	Cough	8 (21.6)	48 (37.5)	33 (51.6)
	Asymptomatic	2 (5.4)	6 (4.7)	2 (5.4)

HP – hydropneumothorax, IQR – interquartile range, NEL – non-expandable lung, NOS – not otherwise specified, SD – standard deviation.

Table 2: Total number of deaths, event rate for death and hazard ratios for death in patients with and without a pleural effusion and, in patients with an effusion, with and without NEL.

	No. of patients	No. of deaths (%)	Person-years	Event rate, per 100 person years (95% CI)	p	Crude HR for death (95% CI)	p	Adjusted HR for death (95% CI)	p
No pleural effusion	37	35 (94.6)	46.1	75.9 (54.5-105.7)	0.988	1	0.935	1	0.081
Pleural effusion	192	179 (93.2)	235.1	76.1 (65.7 to 88.1)		1.02 (0.70 to 1.46)		1.86 (0.93 to 3.72)	
In whom: **No NEL**	128	120 (93.8)	157.2	76.3 (63.8-91.3)	0.952	1	0.911	1	0.008
NEL	64	59 (92.3)	78.0	75.6 (58.6-97.6)		1.02 (0.67-1.56)		1.80 (1.16 to 2.80)	

CI – confidence interval, HR – hazard ratio, NEL – non-expandable lung