SCREENING FOR CERVICAL LYMPHADENOPATHY IN LUNG CANCER

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A thesis submitted to the School of Medicine and Health Sciences, National University of Ireland Galway, in fulfilment of the degree of Doctor of Medicine (MD).

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TABLE OF CONTENTS

Declaration regarding this work

I, Mohammed Jamal Ahmed, declare that this thesis, which I submit to NUIG for examination in consideration of the award of a higher degree of Doctor of Medicine, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in NUIG or elsewhere based on this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has beencited and acknowledged within the text.

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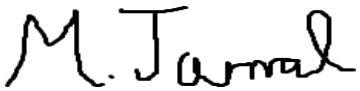

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LIST OF FIGURES

LIST OF TABLES

GLOSSARY OF ABBREVIATIONS

CT	Computerised Tomography
EBUS	Endobronchial Ultrasound
MDT	Multidisciplinary Team
FNAC	Fine Needle Aspiration Cytology
US	Ultrasound
PET	Positron Emission Tomography
MRI	Magnetic Resonance Imaging
TNM	Tumour Node Metastasis
NUS	Neck Ultrasound
CNB	Core Needle Biopsy
ENT	Ear Nose and Throat
ROSE	Rapid On Site Evaluation
FDG	Fluorodeoxyglucose
SUV	Standardised Uptake Value
NICE	National Institute of Health Care Excellence
PDL 1	Programmed Death Ligand 1
EGFR	Epidermal Growth Factor Receptor
ECOG	Eastern Oncology Cooperative Group
SD	Standard Deviation

Chapter 1: LITERATURE REVIEW

1.1 Introduction

Lung cancer is the commonest malignancy and the leading cause of cancer related deaths world-wide(1). In the United States annual deaths from lung cancer are more than those from breast, colonic, prostate and ovarian cancer combined(2). Despite recent advances in the diagnosis and management of lung cancer, there has been only a limited improvement in survival. Data from the United Kingdom showed a 1-year survival of 38% in 2016 compared to 31% in 2010(3). Most patients with lung cancer present at a late stage and in many cases due to comorbidities associated with age and smoking are not fit for radical treatment. Lung cancer screening with low dose Computerised Tomography CT does seem to improve survival but apart from the United states has not been implemented in any othercountry(4). Also, the uptake of lung cancer screening in the United States has been low and from a public health point of view this will likely reduce the effect of it on overall lung cancer survival(5). For the foreseeable future, physicians looking after lung cancer patients are likely to continue to face a significant number of cases with advanced disease that will require accurate staging in a timely manner to allow the right treatment to be started before any deterioration in patient fitness.

The principles of lung cancer staging are based on our understanding of its biological behaviour and the impact of that behaviour on clinical outcomes. Surgery provides the best chance of cure but only in patients with localised disease. Outcomes in lung cancer are associated with tumour size, tumour invasion of local structures, lymph node involvement and distant metastasis therefore the Tumour Node Metastasis system has been devised andis widely used. The 8th edition of TNM was published in 2015 using survival data from over 26,000 patients that was internally validated in a subset of over 12,000 patients(6).

Assessment of all three categories requires a multidisciplinary approach and careful planning of investigations to obtain both a stage and diagnosis ideally at the same invasive procedure. Respiratory physicians play a crucial role in the journey of patients with suspected lung cancer and, with radiologists, are required to provide a diagnosis and a stagefor surgeons and oncologists to be able to decide on treatment options that are likely to

yield the best possible outcomes for patients. In addition, respiratory physicians have an important role in assessing patient fitness and providing the necessary information to patientsso they can make informed decisions regarding treatment.

1.2 Nodal staging in lung cancer

Nodal staging is clearly associated with outcomes in patient with lung cancer regardless of the subtype. For the 8th edition of the TNM staging data with N descriptors from 38,910 patients were analysed for survival(7). For clinical N cN stage data were available in 26,326 cases out of which 2333 had N3 disease and there was clear evidence of reduced survival in association with higher N stage. Current guidelines recommend endobronchial ultrasound EBUS as the first procedure of choice in the nodal staging of patients with lung cancer(8– 10). EBUS is used to assess hilar and mediastinal lymphadenopathy and is now considered an integral part of the role of respiratory physicians as part of the multidisciplinary team MDT. Cervical lymphadenopathy is classified as N3 or M1b disease in the TNM staging system (table 1.1) but there has been limited focus on screening for cervical lymphadenopathy when compared to mediastinal lymphadenopathy in clinical practice and guidelines(8,10–12). There is also scarce literature regarding the topic. The aim of this thesisis to examine different diagnostic tools that can be utilised for screening for cervical lymphadenopathy and assess the potential benefits of performing these routinely as part oflung cancer diagnostic and staging pathway. The thesis will also examine whether respiratory physicians can extend their roles staging the mediastinum using EBUS to perform neck ultrasound and needle sampling to assess for cervical lymphadenopathy.

Stage	Description
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)*

Table 1.1: Nodal descriptors in the 8th edition of the Tumour Node Metastatsis TNM lungcancer staging system. *cervical lymph nodes located superior to the lower border of thecricoid cartilage are classified as M1b disease when involved.

1.3 Cervical lymphadenopathy in lung cancer

The 8th edition of the TNM classification for lung cancer included no changes to the Nodal (N) categories but It was also recommended that physicians record the number of lymph nodes or stations involved including the presence of skip metastasis to provide further information regarding outcomes (6). The staging is based on the anatomical lymphatic drainage from the lung into the hilar, mediastinal and supraclavicular lymph nodes in thatorder. This principle in staging is different to that used for other malignancies such as oesophageal cancer where the number of lymph nodes involved determines stage(13). Inpreparation of the 8th edition of the TNM classification the role of using the number of lymph nodes in staging was examined but was not found to significantly affect survival although this conclusion is limited by the reliability of the provided data.

In patients with lung cancer, cervical lymph node involvement is often detected, and along with the presence of contralateral mediastinal and hilar lymphadenopathy, defines N3 disease. A patient experience focused, cost-effective approach to diagnosing and staging lung cancer requires utilising the least invasive procedure that can simultaneously achieve diagnosis and final staging; fine needle aspiration cytology FNAC of suspicious cervical lymphnode fits that role. Despite this, the evidence for the role of neck imaging is lacking, and therefore is not a routine investigation in lung cancer in most institutions and national guidelines vary in their recommendations. As part of this thesis, a search for the current evidence for assessing and screening for cervical lymphadenopathy in patients with lung cancer was conducted. The literature was searched for published studies from January 1990 to December 2016 assessing the utility of neck ultrasound (US) in screening for cervical lymphadenopathy in lung cancer. Embase and Medline databases were searched for English literature. Search terms included ‘lung cancer’ and ‘supraclavicular’, ‘cervical’, ‘neck’, ‘scalene’, ‘supraclavicular’ and ‘lymph nodes’ or ‘lymphadenopathy’. The reference lists of included studies were also searched for relevant studies. A search was also conducted for studies looking at the role of palpation, computerised tomography CT and positron emissiontomography PET in the screening for cervical lymphadenopathy.

1.4 Impact of cervical lymphadenopathy on clinical outcomes

Most lung cancer patients present at an advanced stage with an average of 17% receiving surgical resection(14). N3 disease indicates at least stage IIIB according to the 8th edition ofthe TNM classification of lung cancer which defines it as involvement of supraclavicular, lower cervical, or contralateral hilar or mediastinal lymph nodes(6). Analysis of data from 962 patients with N3 disease showed a median survival of 7 months(15). The 5-year survivalfor patients with cN3 M0 and any T stage was found to be only 9% compared to 23%, 37% and 60% for cN2, cN1, cN0 respectively in the 8th TNM dataset(7). Two small studies have reported a modest survival benefit from chemotherapy and radiotherapy followed by resection for patients with N3 disease(16,17) but, based on the results of large randomised studies of surgery following chemotherapy and or radiotherapy versus chemo-radiotherapy alone for patients with N2 disease (Stage IIIA) which showed no significant survival benefit(18,19), it is widely accepted that cervical lymph node metastasis is a contraindication of curative surgery. An autopsy study of patients dying of lung cancer was positive for malignancy in the scalene lymph nodes in 37.5% of cases(20). Involvement of the higher cervical lymph nodes in lung cancer is classified as M1a indicating stage IV disease. Not all institutions or guidelines recommend the inclusion of the lower neck in initial diagnostic CT scans(8,21) as evidence for benefits of such practice is lacking. So, whilethe principle underlying lung cancer staging is to determine distant disease that may preclude localised treatment options, under the current guidelines, neck lymphadenopathy is only screened for using PET/CT in potentially curable disease.

1.5 Cervical lymphadenopathy and radiotherapy planning:

Although supraclavicular lymph node involvement in the absence of distant metastasis represents stage IIIB disease which is an indication for chemoradiotherapy with curative intent, it represents a challenge to radiation oncologists specially in the case of contralateral lymphadenopathy(22). This issue is best demonstrated looking at the definition of extensivestage small cell lung cancer that includes contralateral supraclavicular lymphadenopathy while there is no differentiation from ipsilateral disease in the TNM classification(11). It is

essential that cervical lymphadenopathy is diagnosed as once this is included in treatment planning it seems outcome are like those with N3 disease but no cervical lymphadenopathy.In a study of 204 patients with stage IIIB-N3 that received chemoradiotherapy, the presenceof cervical lymph node involvement was not associated with any significant difference in overall or progression free survival(23).

1.6 Screening for cervical lymphadenopathy in lung cancer

Different modalities have been studied for detecting metastatic cervical lymph nodes in head and neck, esophageal and lung cancers. CT is a routine investigation in the work up of these cancers. Other modalities include palpation, ultrasound and Positron emission tomography scan. Literature on the use of magnetic resonance imaging (MRI) in head and neck cancers show superior sensitivity compared to CT, but this has not been studied in lungcancer.

1.6.1 Palpation

Neck examination for palpable supraclavicular and cervical lymph nodes is considered a routine part of assessment of patients with suspected lung cancer. In one case series, Rohwedde et al reported a 13% prevalence of cervical lymph node involvement detected bypalpation alone and confirmed on cytology by fine needle aspiration(24). Later studies comparing palpation and different imaging modalities suggested the former has a significantly lower sensitivity for detecting cervical lymph node metastases. In one study thesensitivity of ultrasound was 3 times greater than for palpation, while the mean lymph nodeshort axis diameter was 13.7 mm compared to 25.2 mm for ultrasound and palpation respectively(25). The unreliability of palpation as a single method for detecting cervical lymphadenopathy is consistent with studies in esophageal and head and neck cancers(26,27).

1.6.2 Computerised Tomography

The major guidelines recommend CT thorax and upper abdomen including the adrenal glands for the staging of non-small cell lung cancer but not CT neck(8,21). Some institutions in the United Kingdom extend the CT cuts to include the lower neck and if abnormal lymph nodes are detected, neck ultrasound is performed(12). The benefits of such practice are notclear. Sensitivity of CT for detecting malignant cervical lymph nodes in lung cancer ranges from 67-83% and has a positive predictive value of 0.5-0.74(25,28,29). The relatively high false positive rate associated with CT is usually due to artefact and anatomical structures, such as vasculature, that can be difficult to differentiate from cervical lymph nodes.

Interpretation of neck CT is also made difficult by the presence of contrast in the subclavianveins. Neck CT can potentially generate delays in work up as unnecessary neck ultrasound tests will have to be performed, sometimes in patients with low pre-test probability of having malignant neck lymphadenopathy. Further studies are required to assess the impactof routine inclusion of the lower neck in CT on the work up of patients with suspected lung cancer.

1.6.3 PET-CT

PET combined with a full CT scan of the body (PET-CT) is now a routine part of staging for non-small cell lung cancer where curative treatment is being considered(8,12,21). The abilityto detect metabolic discrepancies compliments the structural abnormalities seen on other imaging. This however comes at a cost with high rates of false positive findings, which has been estimated to be 13% for mediastinal lymph nodes(30). This may result in patients being inappropriately upstaged and foregoing curative treatment options. Following the detection of avid intrathoracic lymphadenopathy, a further invasive diagnostic procedure such as EBUS or mediastinoscopy is required to clarify the question of metastasis prior to surgery. Sung et al(28) investigated the utility of PET-CT in detecting impalpable cervical lymphadenopathy in lung cancer. The study included all patients with evidence of neck

lymphadenopathy on CT or PET/CT. Among 32 patients, the rate of confirmed metastasis was 34% and the authors reported a PET-CT sensitivity of 92% and a negative predictive value of 93%. These figures are likely overestimates as the study excluded patients with no evidence of neck lymphadenopathy on CT or PET/CT. With sonographically guided FNAC used as the diagnostic standard, no significant statistical difference was detected with regards to sensitivity and diagnostic accuracy between CT and PET/CT, but the study was not sufficiently powered to exclude such a difference. A maximum SUV of 2.3 appeared to be the optimum cut off for detection of cervical lymph node metastasis. The false positive rate for PET-CT was 19% similar to findings from studies on mediastinal staging(30), and included one case with increased muscle physiological uptake and another case of tuberculous lymphadenitis. In another retrospective multicentre study, PET/CT revealed additional head and neck findings in 7% of patients leading to change in stage in only 0.5% of patients but the study was limited as only a third of the head and neck lesions were investigated further(31). Unless it is indicated as a part of routine staging of lung cancer, PET-CT does not appear to be an ideal screening modality for cervical lymph node metastasis in lung cancer as it is not superior to contrast CT and is expensive. There are no published studies prospectively comparing PET-CT to neck US. FDG avid lymph nodes on PETshould always be investigated further with US considering the relatively low positive predictive value.

1.6.4 Ultrasound

Neck US is widely used for the diagnosis of different conditions and US guided FNAC of necklesions carry a very low rate of complications and no radiation exposure to patients. The utility of US for screening and then sampling of cervical lymphadenopathy in patients with lung cancer has been the subject of 10 studies published between 1992 and 2011 (**table 1.2**). Potential points for incorporating neck ultrasound NUS in the diagnostic and staging pathway of lung cancer are illustrated in (**figure 1.1**).

The reported cervical node metastasis rate detected by ultrasound guided needle aspirationranged from 8 to 45.5%; the wide variation is explained by differing inclusion criteria. Fultz et al compared palpation, CT and US for detecting supraclavicular lymph nodes in lung

cancer among patients who presented with suspected and subsequently proven lung cancerof any stage or a proven but potentially resectable lung cancer(29). Of the 55 patients included, 22 (40%) had supraclavicular abnormalities detectable at ultrasound and/or CT. Nearly a third of patients had proven cervical lymph node metastasis, a rate similar to that of probable adrenal metastases recorded in the same study. Among these, 88% had enlarged supraclavicular lymph nodes detectable at CT. The authors suggested extending CT thorax to include the lower neck and performing neck US if there was evidence of abnormal cervical lymph nodes on CT. Van Overhagen et al compared the three modalities in 117 patients with confirmed primary lung cancer(25). Supraclavicular node metastases were diagnosed cytologically in 26% of patients. The sensitivities of US, CT and palpation fordetecting malignant nodes were 100%, 83% and 33% respectively. While the detection of cervical nodes with palpation was significantly lower than the other modalities, no significant difference was found between CT and US. TNM staging was changed in 3 out of 91 patients with NSCLC and further invasive diagnostic procedures were prevented in 11 patients.

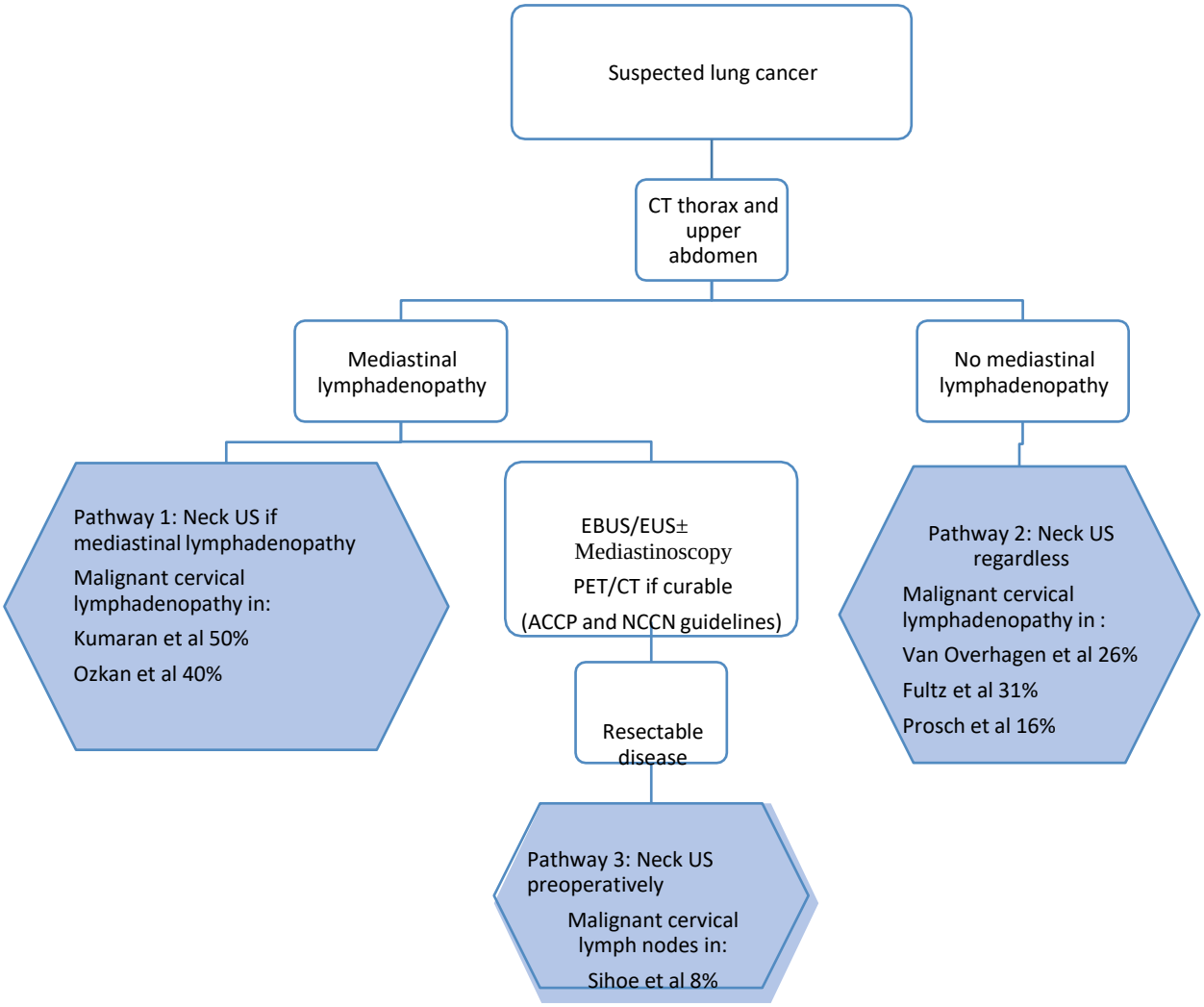

Figure 1.1: Potential points for incorporating neck ultrasound in the diagnosis and staging work up of patients with suspected lung cancer and results from previous studies. EBUS Endobronchial Ultrasound, EUS Endoscopic ultrasound, PET Positron Emission Tomography, ACCP American College of Chest Physicians, NCCN National Comprehensive Cancer Network, NICE National Institute of Health and Clinical Excellence.

Kumaran et al had different selection criteria(32). This study included 101 patients with suspected lung cancer, non-palpable cervical lymph nodes and enlarged mediastinal lymphadenopathy on CT scan. A final diagnosis of lung cancer was made in 88 patients. NeckUS was performed in all patients as the first investigation and fine needle aspiration was done if an enlarged lymph node was detected (defined by a short axis of ≥5 mm). Enlarged supraclavicular lymph nodes were detected in 62 (61.3%). Among all the patients with confirmed lung cancer,44 (50%) had a malignant FNAC. The authors estimated that 43 (50%)patients avoided further invasive diagnostic procedures and 9 out of 77 (12%) patients with non-small cell lung cancer were upstaged from N2M0 to N3M0. The same group reported a follow up retrospective study after the incorporation of neck ultrasound as a routine practice in patients with bulky mediastinal lymphadenopathy(33); 32.2% of patients with CT detected mediastinal lymphadenopathy had cytologically confirmed malignant neck lymphadenopathy. FNAC was performed in 111 patients and no complications were reported. Two studies looked at the association of cervical lymph node metastases with other imaging findings(32,34). Supraclavicular lymph node metastasis was more frequent in patients with mediastinal invasion and in patients with enlarged upper paratracheal nodal stations on thorax CT. One study showed no association between malignant cervical lymphadenopathy and T stage, distant metastasis or histological type(34) while another reported a significant association with the presence of mediastinal nodal disease or distant metastasis(32).

The criteria for recognizing abnormal cervical lymph nodes has been described in multiple studies(35–37). Different cut offs for short diameter have been used, however 5 mm is the most widely used. One study of 505 healthy individuals found 90% of normal supraclavicularLNs had a diameter of < 5 mm and no nodes were larger than 7 mm(38). Round shaped lymph nodes are associated with malignant disease and a short to a long axis diameter ratio greater than 0.5 is the best grey-scale US characteristic for differentiating malignant from benign lymph nodes (81% specificity, 75% sensitivity, and 79% overall accuracy)(37). Other features described include loss of hilar structures and absence of calcification. Doppler US toassess vascularity does not seem to add to diagnostic accuracy.

Author, Year	N	Inclusion criteria	% NSCLC	*% mediastinal lymphadenopathy	% malignant neck lymphadenopathy (95% CI)
Chang (39) 1992	51	Nonpalpable neck lymph nodes, any stage	100	27.4	12(4.4-23.8)
Sugama (40) 1992	25	Lung cancer with upper mediastinal lymph nodes on CT	100	100	33(9.9-65.1)
Van Overhagen (25) 2004	117	All lung cancer including patients with palpable neck lymph nodes	77.8	78.6	26(15.1-30.8)
Sihoe (32)(32) 2004	50	All NSCLC referred for consideration for surgery with no palpable neck lymph nodes	100	none	8(2.2-19.2)
Prosch (42) 2007	300	All lung cancer patients	83.3	NA	16(9.4-24.7)
Ozkan (43) 2009	40	Suspected lung Ca and non-palpable neck lymph nodes and mediastinal lymph nodes	NA	100	40(24.9-56.7)
Kumaran (32) 2005.	101	Suspected lung cancer and non-palpable lymph nodes and mediastinal lymph nodes	76.2	100	50(39.4-59.7)
Hoosein (33) 2011	245	Suspected lung cancer and mediastinal lymphadenopathy on CT	68.5	NA	32.2(26.4-38.5)
Kendirlinan (31) 2011	106	All lung cancer with no palpable neck lymph nodes	84.9	61.5	13.2(7.4-21.2)
Fultz (29) 2002	55	All lung cancer with no palpable neck lymph nodes	92.7	68.6	31(19.1-44.1)

Table 1.2: Studies of the use of neck ultrasound in the diagnosis and staging of patients with suspected lung cancer. NSCLC Non-small cell lung cancer. * Only one study reported N stage as a baseline characteristic, Kendirlinan et al, with 69.6% of patients staged at N2/N3.

1.7 Is there a role for routine neck US and needle sampling in the diagnostic and staging pathway of lung cancer?

The previous studies do suggest a role for neck US and cervical lymph node FNAC in the diagnosis and staging of lung cancer. The potential benefits include quicker diagnosis and staging, less invasive procedures performed limiting patient's discomfort, cost savings and prevention of futile surgery and the associated morbidity. The possible limitations are potential delays waiting for neck ultrasound to be performed by a radiologist and insufficient material for subtyping and molecular analysis when required. The issue of delay awaiting an additional imaging test can be minimised if lung cancer respiratory physicians were trained to perform the procedure in the clinic setting or prior to EBUS depending on local practices. Studies of US guided FNAC of thyroid nodules performed by surgeons have shown no significant difference in diagnostic yield when compared to radiologists(44,45) and respiratory physicians are increasingly more familiar with the use of ultrasound in the management of pleural diseases and critical care patients in addition to EBUS. With regards to the adequacy of neck lymph nodes FNAC for molecular analysis, one retrospective reviewof 171 malignant neck lymph nodes in patients with lung cancer reported an adequacy rate of 85% for molecular analysis in patients with adenocarcinoma(46).

Looking at the literature, there are three dominant approaches towards incorporating NUSin the diagnostic and staging pathway of patients with probable lung cancer.

1- Screening all patients with suspected lung cancer with neck ultrasound regardless of stage on CT: this approach was examined in four studies(25,29,34,39). The diagnostic yield ranged between 12-31% with 12-20% of patients scanned avoiding a further invasive diagnostic procedure. One study reported 2.8% of patients avoided a futile thoracotomy. The two studies that utilised rapid on site evaluation (ROSE) had a higher diagnostic yield(25,29). Performing NUS for all patients with suspected lung cancer requires more resources and it reduces the diagnostic yield of the procedure leading to reduction in its cost effectiveness. This can be minimised if the neck base is included in initial CT thorax.

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2- Screening patients with enlarged mediastinal lymph nodes on CT Thorax: Kumaran et al examined 101 patients with suspected lung cancer , mediastinal lymphadenopathy on CT and no palpable cervical LNs(32). Among patients with confirmed lung cancer 50% had malignant supraclavicular LNs. Applying the results of this study to current practice it means nearly half the patients referred for EBUS will avoid the procedure potentially leading to minimising cost and reducing the pressure on centres performing EBUS.

3- Screening patients referred for surgery: This was the approach used by Sihoe et al(41). They reported 8% of the patients considered for surgery had undiagnosed malignant supraclavicular lymph nodes detected at US. It is possible that this rate would have been lower if PET scan was utilised as per the current guidelines.

Cervical lymphadenopathy is frequently detected in patients with lung cancer, especially in the presence of mediastinal lymphadenopathy. The safety, accessibility and low cost of ultrasonography is appealing. One study reported routine cervical lymph node ultrasound in patients with operable NSCLC to be a cost effective technique as one futile thoracotomy wasavoided for every 25 patients that underwent a neck US(41). Compared to other modalities US followed by FNAC provides a pathological diagnosis and stage quicker, is readily availableand is easy to learn with a minimal risk of complications. Further, investigations like PET scan and EBUS are still difficult to access in many parts of the world including some developed countries. From current evidence, a pathway utilising neck ultrasound followed by FNAC in all patients referred with suspected lung cancer and evidence of mediastinal lymphadenopathy on CT seems reasonable but further good quality studies are warranted. Previous literature regarding ultrasound performed by non-radiologists suggests that a similar approach to neck US and FNAC is feasible. Appropriately trained respiratory physicians can perform the procedure in clinic setting or prior to EBUS in the endoscopy

suite. Prospective studies comparing the standard diagnostic and staging pathway with this approach are required. The outcomes to be assessed would include time to achieving a finalstage and starting treatment, the rate and nature of invasive diagnostic procedures per patient, cost savings, the number of futile thoracotomies, the rate of insufficient FNAC samples, the rate for further sampling for subtyping or molecular analysis and patient's satisfaction.

In this thesis I aim to assess multiple diagnostic approaches for screening for cervical lymphadenopathy in lung cancer and to test whether it is feasible for respiratory physiciansto take this role as an extension of the ultrasound guided assessment of mediastinal nodal stage routinely performed by the speciality.

Chapter 2: METHODOLOGY

2.1 Rationale

The thesis aim is to answer three main questions where there is a gap in the current literature regarding cervical lymph node involvement in lung cancer.

First what is the diagnostic yield from each imaging method for the detection of cervical lymphadenopathy in patients with lung cancer and mediastinal lymphadenopathy.

Secondly, how does each imaging modality impact the diagnostic and staging pathway forpatients with lung cancer.

Finally, is it feasible for respiratory physicians to be trained to perform NUS and lymph node sampling instead of radiologists.

The role of CT, PET and US in the detection of cervical lymphadenopathy are looked at individually. Also, both a retrospective and a prospective study are conducted to look at thefeasibility of respiratory physician performed US guided cervical lymph node sampling.

2.2 Computerised tomography for the detection of cervical lymphadenopathy in lung cancer

2.2.1 Setting

In Derriford Hospital, Plymouth the lower neck is included routinely in CT for patients with suspected lung cancer while in Galway University Hospital, Ireland this is not a standard practice. This is a retrospective comparative study to assess the real-life impact of routine lower neck CT on the diagnostic and staging work up of patients with suspected lung cancer.The study protocol is included in appendix III of this thesis.

2.2.2 Patients and methods

This is a retrospective comparative double cohort study (see study protocol in appendix 1). A list of consecutive patients with a pathological diagnosis of lung cancer starting from November 2014 was obtained in both hospitals. Clinical and radiological records were reviewed to assess whether the study inclusion criteria were met. Inclusion criteria were: (1)Age > 18 years (2) pathological diagnosis of primary lung cancer and (3) N2 and or intrathoracic N3 disease on CT defined as lymph node with a short diameter > 10 mm.

2.2.4 Data collection

Baseline characteristics recorded include age, gender, clinical TNM stage based on CT, short diameter of largest mediastinal lymph node and number of mediastinal stations involved onCT. The number and type of procedures performed to obtain tissue material within 2 months after initial CT were recorded. The route of referral to the lung cancer services in each hospital was also documented.

2.2.5 Computerised Tomography

Patients in Galway university hospital underwent a CT thorax from the lung apices to the adrenal glands and the lower neck was not routinely included using a 64-slice multidetectorCT scanner (Somatom Sensation Cardiac 64, Siemens, Erlangen, Germany). All patients in Derriford hospital underwent CT scan of the lower neck, thorax, and upper abdomen with

cuts of 5 mm and intravenous contrast (add here CT scanner in Derriford). Neck lymphnodes were considered suspicious if the short diameter was > 5 mm.

2.2.6 Neck ultrasound and Fine Needle Aspiration Cytology

Neck ultrasound was done if suspicious lymph nodes were seen on CT or Positron Emission Tomography PET or when there was palpable neck lymphadenopathy. In both cohorts, neck ultrasound was performed by either radiologists or a respiratory physician trained in the procedure. Fine needle aspiration cytology (FNAC) was performed under direct ultrasound guidance using the capillary technique and a 22 G needle For each lymph node 3-4 passes were performed and samples were sent in formalin for analysis.

2.2.7 Other procedures

PET was performed in both cohorts for patients with potentially curable disease. Further diagnostic procedures were performed at the discretion of lung cancer respiratory physicians. EBUS was the first line investigation of choice in both hospitals with comparable access to the procedure under conscious sedation. Other diagnostic procedures included flexible bronchoscopy, pleural aspiration, biopsy of distant metastatic sites, transthoracic CTguided lung biopsy and mediastonoscopy.

2.2.8 Outcomes

The primary outcome of interest was the proportion of patients with pathologically confirmed metastatic cervical lymphadenopathy. The secondary outcomes were the numberof diagnostic procedures performed per patient to achieve the final diagnosis and stage within 2 months from the date of initial CT, the proportion of patients diagnosed and stagedwith one procedure and, the proportion of patients that underwent EBUS.

2.2.9 Statistical analysis

Based on existing literature it was estimated that the proportion of patients with CT evidence of intrathoracic N2-N3 disease will have evidence of neck LN malignancy in 35% ofcases in the lower neck CT group and 20% in the other group. Using a Chi-Squared test, α= 0.05(two sided) and β=0.8; a sample size of 82 patients in each cohort is required.

Categorical outcome measures are reported proportions, frequencies, and odds ratios OR with 95% confidence interval CI. Continuous outcomes are reported as mean and standarddeviations SD. Following a univariate analysis all variables with a p value < 0.20 were included in a stepwise Logistic regression model. Minitab 17 (Minitab® Statistical Software,Pennsylvania) was used to conduct the statistical analysis.

2.3 Ultrasound guided cervical lymph node sampling performed by respiratory physicians compared to radiologists

2.3.1 Patients and methods

This is a retrospective cohort study performed in the interventional respiratory unit of Galway University Hospitals over a 5-year period (March 2013-March 2018). All cases were identified from a database maintained by the unit. Patients referred to the unit who were found to have cervical adenopathy detected clinically or radiologically were included in the study including those with suspected lung cancer and evidence of bulky mediastinal lymphadenopathy on computerised tomography (CT) of the thorax. Both medical records and procedural logs were interrogated for information regarding lymph node features. Finalpathology was retrieved from the central pathology laboratory database. Adequacy of samples submitted for pathological assessment was routinely reported as a quality control measure by the examining pathologist. A record of all NUS guided lymph node samples performed by radiology regardless of indication was obtained from the pathology department. This group of patients was used as a control and adequacy of sampling was compared against samples taken by respiratory physicians.

2.3.2 Procedures

All patients with suspected cervical lymphadenopathy underwent standardised NUS. Procedures were performed using a linear ultrasound probe with a frequency of 5-12 MHz using one of two machines (Zonare Z one ultra machine (Zonare®, California) and Hitachi EUB-7500A machine (Hitachi, Ltd., Tokyo, Japan)). Patients were positioned in a semi supineposition. Initially, the thyroid isthmus was identified and once visualised the probe was moved laterally to identify the carotid artery and internal jugular vein. The probe, oriented horizontally and later vertically, was then moved cranially to assess the lower, middle and upper cervical chain to the level of the submandibular gland. The probe was then moved caudally along the posterior cervical chain until the supraclavicular fossa was identified and assessed. The procedure was then repeated to fully assess the contralateral neck.

After this initial screening assessment any visualised lymph nodes were further assessed in detail. Features including size, shape, presence of hilum, necrosis and blood flow were recorded, see **figure 2.1**. The largest accessible suspicious lymph nodes, based on US features(37) were sampled under direct visualisation following informed written consent. The area was cleaned using chlorhexidine wash and 1 or 2% lidocaine was applied intradermally and subcutaneously to provide local anaesthesia. A sterile sheath was appliedto the ultrasound probe. After sonographic identification of the node, direct sampling usinga 22g needle was performed with real-time ultrasound guidance. The first pass was used to make slides and the rest of material was sent for analysis in formalin pots. If well tolerated and technically feasible, 2-3 core needle biopsies CNBs were obtained from lymph nodes using an 18-gauge SuperCore™ needle (Aragon Medical Devices, Texas, USA).

2.3.3 Outcomes

Diagnostic yield and sampling adequacy are reported for the respiratory physician and radiologist performed neck lymph node sampling. The pathological diagnosis on lymph nodesampling is also reported including the suitability of samples for special tests for molecular and immunotherapy targets in the case of lung cancer.

2.3.4 Statistical analysis

Minitab-18 (Minitab® Statistical Software, Pennsylvania) was used to conduct the statisticalanalysis. Categorical variables are reported as frequencies and percentages and associated 95% confidence intervals while continuous variables are reported as mean and standard deviations or median and interquartile range. Chi square or Fischer exact tests were conducted for categorical variables, as appropriate. A p value of <0.05 was considered significant.

2.3.5 Ethical approval

This study was performed in accordance with the Declaration of Helsinki. This human studywas approved by Galway University Hospital Research Ethics Committee - approval: C.A.
2024

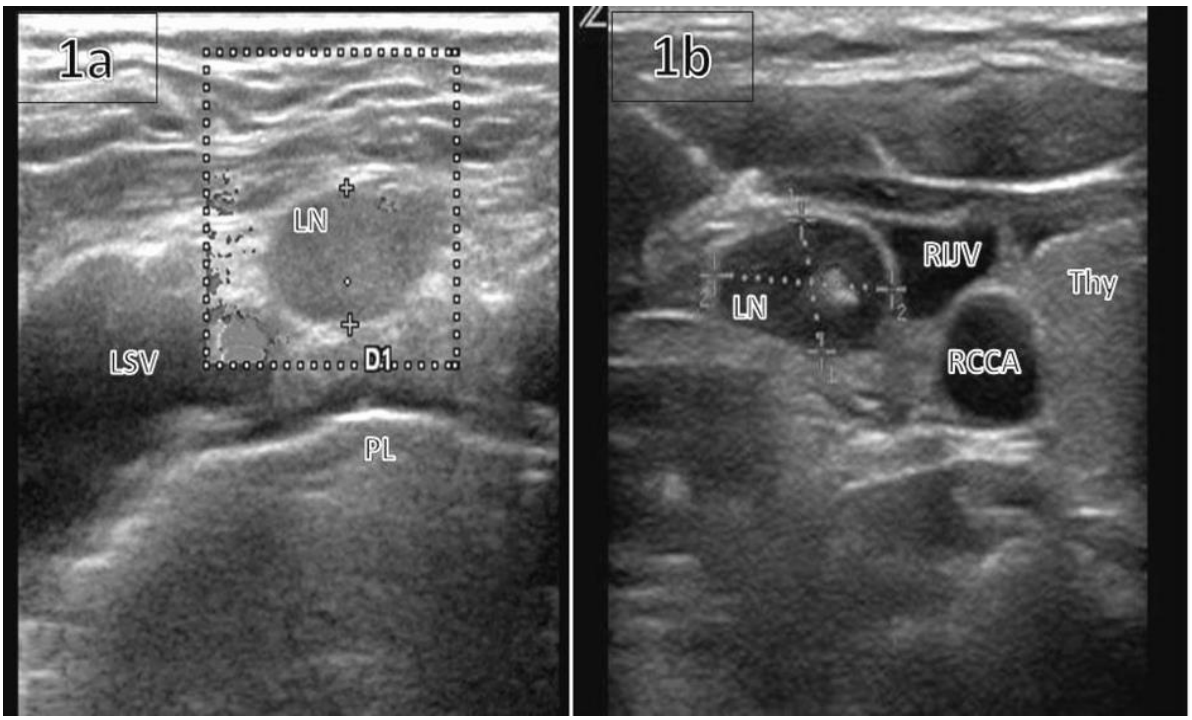

Figure 2.1: Ultrasound appearance of malignant and benign lymph nodes. Figure (1a) shows a rounded left supraclavicular lymph node with loss of hilum and some peripheral blood flow measuring 7 mm in short diameter with confirmed lung adenocarcinoma following fine needle aspiration. Figure (1b) shows a small oval lower cervical lymph node with preserved hilum, sampling showed non-caseating granulomas consistent with sarcoidosis. LN: lymph node; PL: pleura; LSV: left subclavian vein; RIJV: right internal jugular vein; RCCA: right common carotid artery

2.4 Respiratory physician performed neck ultrasound and cervical lymph node sampling in patients with lung cancer and mediastinal lymphadenopathy

2.4.1 Patients

This was a prospective study conducted in Galway University Hospital, Ireland. All consecutive patients with suspected and later confirmed primary lung cancer and evidence of mediastinal lymphadenopathy on computerised tomography CT that were referred to theinterventional respiratory unit in Galway University Hospital were approached to participatein the study. A written informed consent was obtained. Exclusion criteria included age < 18 years, history of any malignancy apart from non-melanoma skin cancer and inability to give informed consent. Mediastinal lymphadenopathy was defined as a short diameter on computerised tomography CT of ≥ 10 mm.

2.4.2 Setting

In Galway University Hospital all patients referred with suspected lung cancer are assessedin the interventional respiratory unit through a rapid access service. All patients have a CT thorax and upper abdomen with contrast followed by further work up according to CT findings but a diagnostic procedure such as bronchoscopy, EBUS or pleural fluid sampling is usually performed on the same day as CT in most patients.

2.4.3 Training respiratory physician in NUS and needle sampling

MA was trained in performing NUS as a part of a short term European Respiratory Society ERS fellowship under supervision by CD who is a respiratory physician with five-year experience in NUS and lymph node sampling. This required performing a predetermined number of normal and abnormal NUSs and achieving specified competencies requiring identification of normal and abnormal structures in the neck as outlined in **table 2.1**. As partof training MA also attended at the neck lumps clinic attended by radiologists and Ear, Noseand Throat ENT surgeons and observed procedures performed there in addition to a sessionin the pathology department to further understand the optimal sampling requirements. MAwas also trained on a gelatine-based simulation model for needle sampling and then kept a

prospective record of all NUS and needle sampling procedures he performed and recordedthe adequacy and diagnostic yield of all samples over time.

NUS training number requirements	NUS competencies to be acquired
Observing 20 NUSs Performing 20 detailed normal NUSs Performing 10 NUSs in patients with abnormal appearing lymph node Performing 10 Us guided FNAs under directsupervision	Recognition of the normal muscle anatomy Identification of carotid arteries and jugular veins using colour flow Doppler Identification of the thyroid gland Identification of the submandibular and parotid salivary glands Identification of normal appearance of lymph nodes Identification of abnormal features of lymph nodes* Measuring lymph node short and long diameters Needle aspiration of abnormal appearing lymph node

Table 2.1: Requirements for training including procedure numbers and competencies to beacquired. NUS: neck ultrasound. *Including shape, size, hilar structures, necrosis and lymphnode blood flow on Doppler.

2.4.5 Neck ultrasound

A NUS was performed in all patients included by MA. The US examination was performed with patients lying in a semi-supine position using a linear ultrasound probe with a frequency of 5-12 MHz using one of two machines (Zonare Z one ultra machine (Zonare®, California) and Hitachi EUB-7500A machine (Hitachi, Ltd., Tokyo, Japan)). Initially, the thyroid isthmus was identified and once visualised the probe was moved laterally to identifythe carotid artery and internal jugular vein. The probe was then oriented horizontally and moved to assess the anterior cervical chain and this was again repeated with the probe oriented vertically. The posterior cervical chain was then assessed before finally assessing the supraclavicular fossa. The same was repeated for the contralateral neck. The lower cricoid border was used as the landmark to differentiate N3 and M1 lymph nodes.

2.4.6 Needle sampling

If any neck lymph nodes were identified these were further assessed for size, hilar structures and necrosis. Lymph nodes with short diameter > 5 mm were considered targets for sampling and nearby vascular structures and location relative to the pleural lining were considered before proceeding. Sampling was performed under direct visualisation followinginformed written consent. The area was cleaned using chlorhexidine wash and 1 or 2% lidocaine was applied intradermally and subcutaneously to provide local anaesthesia. A sterile sheath was applied to the US probe. Around 10 minutes were allowed before sampling to give time for the local anesthesia to work. Under direct US guidance a 22g needle was used to obtain samples. The first pass was used to make slides and 2-3 further passes were performed with samples sent in a formalin container. If well tolerated and technically feasible, 2-3 CNBs were obtained from lymph nodes using an 18-gauge SuperCore™ needle (Aragon Medical Devices, Texas, USA) with all material sent in a formalin container. **Table 2.2** shows the equipment required for performing needle sampling.

2.4.7 Lung cancer work up

As this was a pilot study, all lung cancer work up was continued as standard unless the results from neck lymph node sampling came back positive before a planned diagnostic procedure in which case this was cancelled. This meant that based on the setting in GalwayUniversity Hospital it was expected that some patients will have both an EBUS and NUS guided sampling performed in the same session.

2.4.8 Outcomes

The primary outcome of interest in the study was the rate of malignant cervical lymphadenopathy defined as pathological evidence of cancer in neck lymph node samplesconsistent with a lung primary. Other outcomes of interest included adequacy of needle sampling, patient reported experience assessed by a visual analogue of discomfort associated with needle neck sampling and EBUS, and the rate of invasive procedures that could have been avoided if only NUS was performed. Patients who underwent both EBUS and NUS guided needle sampling were asked which procedure they would have preferredand why; around 10 minutes were allowed before needle sampling of neck lymph nodes to give time for the local anesthesia to work. The suitability of neck samples for molecular analysis when indicated was also reported. Potential complications of needle sampling (significant bleeding requiring prolonged compression and infection) were also recorded.

2.4.9 Statistical analysis:

Categorical variables are reported as frequencies and percentages and associated 95% confidence intervals while continuous variables are reported as mean and standard deviations or median and interquartile range. Cumulative sampling adequacy rate are reported as percentage over time. A p value of <0.05 was considered significant. Minitab-18(Minitab® Statistical Software, Pennsylvania) was used to conduct the statistical analysis. Asthis was a pilot study sample size was not calculated.

Items
Orange needles
Dressing packs
Chlorhexidine
Sterile field - rectangular
Sterile gel
Ultrasound probe sterile sheaths
Lidocaine 1% 10ml vials
Slide holder case
Formalin sample pots
Sterile gloves
Post procedure dressing (small clear dressing)
green needles
blue needles
10ml syringe
Glass slides
18ga core needle

Table 2.2: List of equipment used for ultrasound guided needle sampling of cervical lymph nodes

2.5 Positron emission tomography for the detection of cervical lymphadenopathy in patients with lung cancer and mediastinal lymphadenopathy

2.5.1 Study design and setting

This is a retrospective single centre cohort study, based in Galway University Hospital.

2.5.2 Inclusion criteria

All patients with confirmed lung cancer and evidence of mediastinal lymphadenopathy on CT as defined as short diameter > 10 mm who also underwent a NUS in the period betweenAugust 2012-August 2017 were included. Medical, laboratory and radiology records were reviewed. Procedures performed, pathology results and clinical stage were documented.

2.5.3 Procedures

2.5.3.1 Neck ultrasound and lymph node sampling

Neck US was performed in a standardised systematic way using a 5-12 MHz linear probe with patients lying supine. Abnormal lymph nodes were defined based on a short axis diameter of ≥ 5 mm. The fine needle aspiration (FNA) of lymph nodes was performed by oneof four respiratory physicians trained in the procedure. After obtaining informed written consent and using an aseptic technique, local anaesthesia was applied (1-3 mls of 1 or 2% lidocaine). Between two to four passes using a 22-gauge needle were performed under direct ultrasound guidance. Air dried and alcohol fixed glass slides were made from the first pass, while the remaining passes were placed in formalin for cell block analysis. If the lymph node was suitable, a CNB was performed using an 18-gauge SuperCore™ needle (Aragon Medical Devices, Texas, USA). Sampling adequacy was recorded by the pathology department routinely as a quality control measure. Rapid on-site evaluation ROSE was not performed for EBUS or NUS FNA.

2.5.3.2 PET-CT

Whole body PET was performed after the injection of 370-406 MBq FDG with a standard delay time of 90 minutes. A non-contrast CT from groin to skull base was performed for attenuation correction and diagnostic interpretation. A contrast CT thorax and upper abdomen was done in all patients at baseline. Findings from PET outside the thorax weredocumented.

2.5.4 Outcome measures and definitions:

Malignant cervical lymphadenopathy was defined as presence of malignant cells at cytology or histology consistent with a diagnosis of lung cancer. FDG avidity was defined as SUV max > 2.5 and diagnostic accuracy of PET was measured against results from NUS and lymphnode sampling. Lymph node sampling was considered adequate if lymphoid material ormalignant cells were present in the samples.

2.5.5 Statistical analysis

Minitab-17 (Minitab® Statistical Software, Pennsylvania) was used to conduct the statisticalanalysis. The rate of malignant cervical lymphadenopathy is reported as proportion and 95%confidence interval (CI). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PET-CT for the detection of cervical lymphadenopathy were calculated. Man-Whitney U test was conducted to assess the relationship between standardised uptake values SUV max on PET and the possibility of false positive findings. A pvalue of <0.05 was considered significant.

2.5.6 Ethical considerations

This study was approved by the local ethics committee and patient confidentiality was maintained throughout data collection and analysis.

Chapter 3: RESULTS

3.1 Computerised tomography for the detection of cervical lymphadenopathy in lung cancer

The total number of consecutive patients that met the inclusion criteria was 192 (82 patients In Galway University Hospital diagnosed November 2014-October 2016 versus 110 patients in Derriford Hospital diagnosed November 2014-Oct 2015). Baseline characteristics are summarized in **table 3.1**. The proportion of patients with small cell lung cancer was comparable in the two cohorts while there was a higher rate of potential metastatic disease reported in the neck CT cohort predominantly due to a higher rate of M1a disease in the Plymouth cohort at 23% compared to 8% in the Galway Cohort. **Figure 3.1** shows the proportion of patients with confirmed malignant neck lymphadenopathy in each cohort. There was a higher rate of confirmed malignancy in the neck lymph nodes in neck CT cohort when compared to the no neck CT cohort (24.3% Vs. 4.8% respectively p-value< 0.001). Four patients in the no neck CT cohort had malignant neck lymph node involvement (detected by palpation in 3 cases and by PET inone case). One case had FDG avidity in the neck but was not sampled.

A statistically significant difference was detected in the proportion of patients that underwent more than one procedure to achieve a diagnosis and clinical stage. In the neckCT cohort 22.5% of patients underwent more than one diagnostic procedure compared to55.4% in the no neck CT cohort (p-value <0.001), see **table 3.2**. The mean number of procedures performed per patient was also lower in the neck CT cohort (1.2±0.45 Vs 1.67±0.65, p-value< 0.001) as shown in **table 3.2** and **figure 3.2**.

A stepwise logistic regression analysis was performed. Variables considered for the model included proportion of patients with intrathoracic N3 disease, metastatic disease, small celllung cancer, performance of PET and out of institute referrals. A statistically significant difference was noticed in favour of performing neck CT for the outcomes of the proportionof neck lymphadenopathy confirmed (OR 7.84, 95% CI 2.19-28.13) , proportion of patients undergoing more than one diagnostic procedure (OR 0.21 , 95% CI 0.11-0.41) and proportion of patients requiring EBUS (OR 0.21, 95% CI 0.01-0.47) , see **table 3.3**.

Characteristic	No neck CT (Galway Cohort) (n=82)	Neck CT (Plymouth Cohort) (n=110)
Age (SD)	67.1(9.9)	68.8(9.8)
Males%	63%	67%
Small cell %	18.1%	18.2%
N3%	38%	44.1%
Metastatic disease%	32.5%	63.4%

Table 3.1: Baseline variables across the two study cohorts.

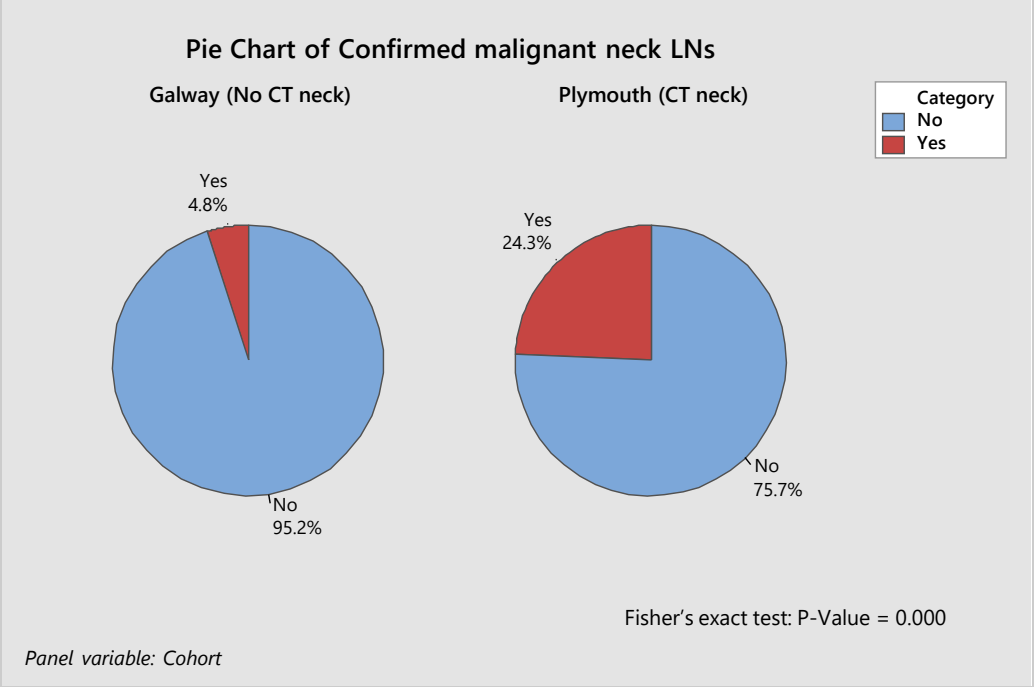

Figure 3.1: Proportion of patients with confirmed malignant lymphadenopathy followingFNAC.

FNAC: fine needle aspiration cytology.

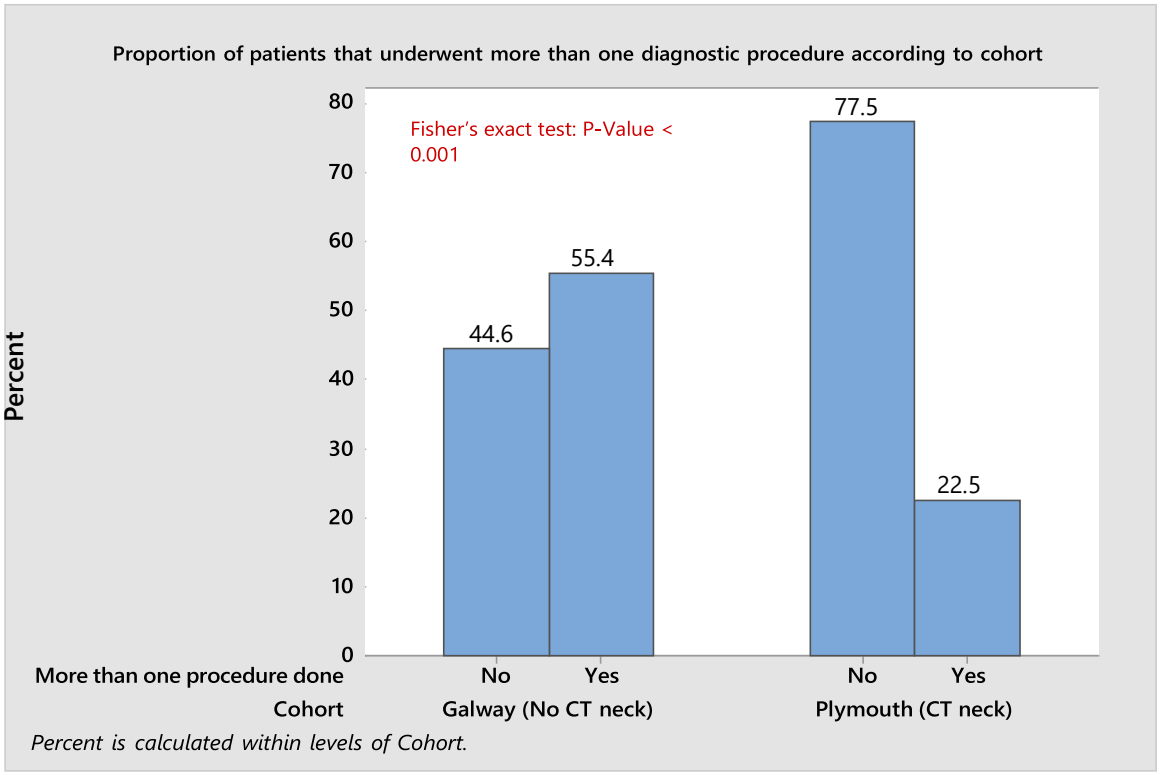

Figure 3.2: Proportion of patients that underwent >1 diagnostic procedure in each cohort.

Outcome	No neck CT (Galway) n=83	Neck CT (Plymouth) n=110	Difference (95%CI)	P Value
Confirmed malignant neck lymphadenopathy (%)	4.8	24.3	19.5 (10.3-28.7)	<0.001
Patients that underwent > one procedure (%)	55.4	22.5	32.9 (19.7-46.1)	<0.001
Number of procedures per patient	1.64 (0.65)	1.23 (0.45)	0.40 (0.24-0.57)	<0.001
Patients that underwent EBUS (%)	73.5	44.1	29.3 (16.1-42.6)	<0.001

Table 3.2: Univariate analysis comparing neck CT Vs no neck CT among patients that had mediastinal lymphadenopathy.

Outcome	OR	OR (95%CI)	P Value
Confirmed malignant neck lymphadenopathy	7.84	(2.19-28.13)	<0.001
Patients that underwent > one procedure	0.21	(0.11-0.41)	<0.001
Patients that underwent EBUS	0.21	(0.01-0.47)	<0.001

Table 3.3: Stepwise multivariate regression analysis. Variables considered in the analysis were Nodal stage, presence of metastatic disease, histological type (small cell versus non-small cell lung cancer and performance of PET. ORs reported for outcome in the CT cohortversus the no CT cohort. See appendix for summary of logistic regression models.

3.2 Ultrasound guided cervical lymph node sampling performed by respiratory physicians compared to radiologists

Over 5-year period respiratory physicians performed cervical lymph node sampling in 106 consecutive patients compared to 35 consecutive patients by radiology (**figure 3.3**). Respiratory physicians performed NUS for 306 patients and sampled 106 (34%) of those (mean age 65±16 years, 51.9% males, suspected lung cancer in 72.3%), see **table 3.4**. Neck lymph node fine needle aspiration FNA and CNB were performed in 38 patients (35.8%) andFNA only in 68 patients (64.2%). A diagnosis was achieved on lymph node sampling in 89/106 cases (84%). The most common diagnosis was lung cancer.

During the study period, the radiology department performed 35 NUS guided lymph node sampling procedures with a final diagnosis of malignancy in 10/35 cases (28.6%). CNB was performed in 5 patients (14.3%) and FNA in 30 patients (85.7%). There was no difference inmean short diameter of lymph nodes sampled by radiologists and respiratory physicians (11.75 ± 5.7 mm Vs 13.2 ± 6 mm [p = 0.203]). There was also no significant difference in adequacy of sampling in the two groups. The overall adequacy rate for respiratory physicians was 91.5% [95% CI 84.5-96%] compared to 82.9% [95% CI 66.4-93.4%] for radiologists, (p= 0.2). Results are displayed in **figure 3.4**. No significant complications were reported in either group.

Among patients assessed by respiratory physicians, neck lymph node sampling was the only procedure performed to obtain tissue in 48 cases (45.3%). The most commonly performed other procedure was EBUS in 26 patients (24.5%). Excisional lymph node biopsy was performed in 8 cases (see **table 3.5**).

Among 76 patients with suspected malignancy on cytological examination there was sufficient material for immunohistochemistry staining in 73 patients (96.1%). Further testingfor molecular analysis or programmed death ligand 1 (PDL 1) was requested in 18 samples and was possible in 17 (94.4%). In one case the percentage of tumour cells in the sample was < 10% and therefore a polymerase chain reaction PCR test for mutations was not possible. PDL 1 was requested in three cases and samples were adequate for testing in all ofthose.

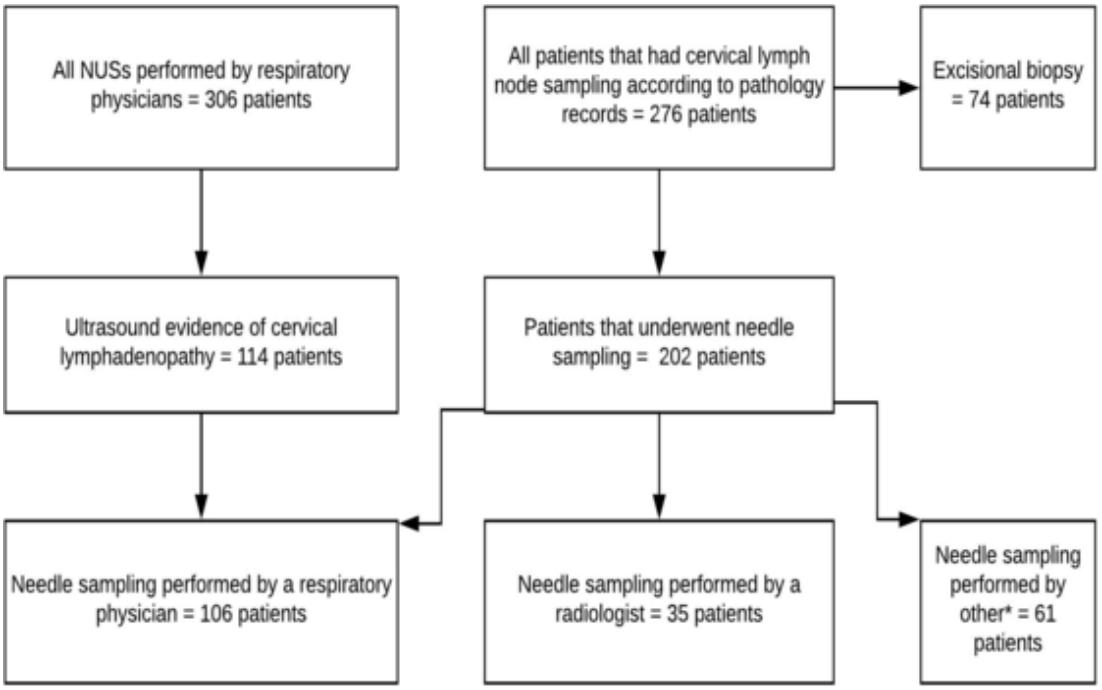

Figure 3.3: Diagram of study population. NUS: neck ultrasound; other*: includes surgeonsand pathologists that performed procedures without radiological guidance.

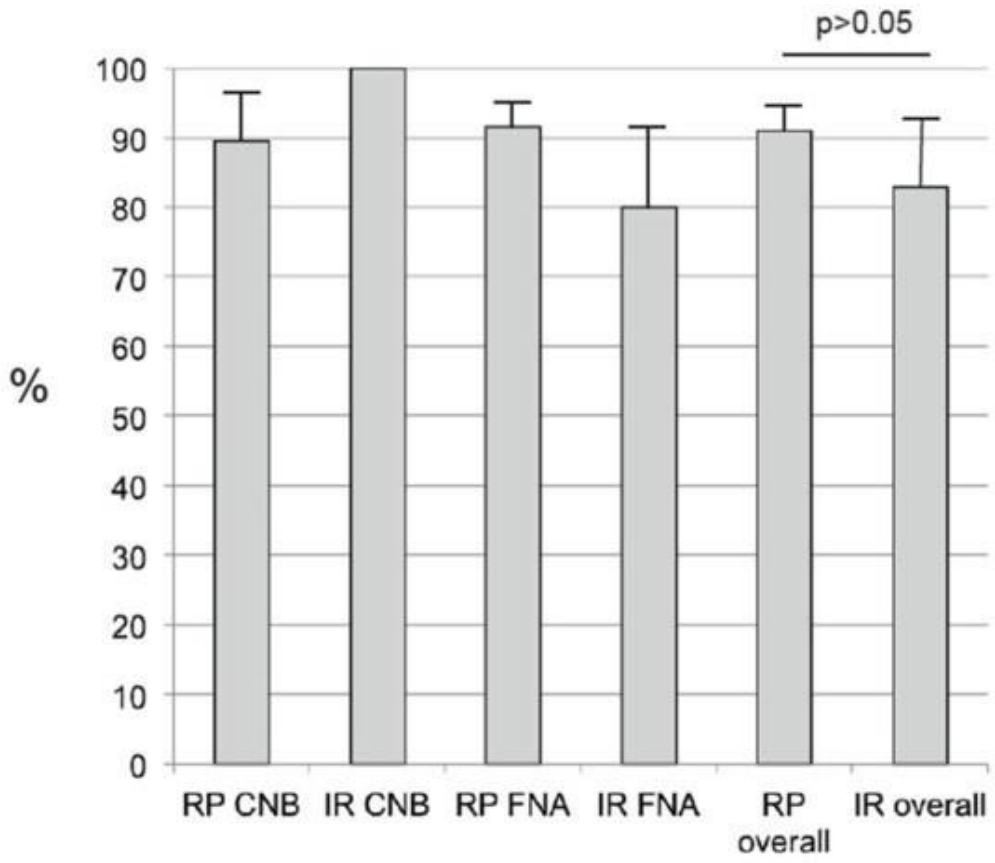

Figure 3.4: Bar chart with associated 95% upper confidence interval of adequacy of neck lymph node sampling performed by interventional radiology (IR) and respiratory physicians(RP). CNB: core needle biopsy; FNA: fine needle aspiration. 'Overall' means all procedures combined.

Characteristic	Value
Mean age (SD)	65.2 (16.1)
Males (%)	55 (51.9)
Mean short lymph node diameter mm (SD)	13.2 (6)
Diagnosis on lymph node sample (%)	
Lung cancer	69 (65.1)
Cancer other than lung	8 (7.5)
Lymphoma	4 (3.8)
Sarcoidosis	6 (5.7)
Tuberculosis	2 (1.9)
Other benign*	8 (7.5)
Inadequate sampling	9 (8.5)

Table 3.4: Characteristics of 106 patients that underwent neck lymph node sampling by respiratory physicians. SD: standard deviation. *Other benign: normal lymphoid material orevidence of reactive lymphadenopathy.

Diagnosis on needle sampling	Excisional biopsy result
Inadequate	NHL
SCLC and granulomatous inflammation	NHL
Adenocarcinoma	Adenocarcinoma
Reactive lymphadenopathy	Low grade B-cell lymphoma
NHL	NHL
Reactive lymphadenopathy	Castleman lymphadenopathy
NHL	NHL
NHL	NHL

Table 3.5: Breakdown of results of excisional lymph node biopsy performed in eight cases.NHL: Non-Hodgkin's Lymphoma

3.3 Respiratory physician performed neck ultrasound and cervical lymph node sampling in patients with lung cancer and mediastinal lymphadenopathy

Training commenced in NUS in Oct 2016 and the study was completed in May 2018. During this period, 146 NUSs were performed with 35 needle sampling procedures in 28 patients. FNA was performed in all 28 cases and CNB in 7 (25%) cases. The overall sampling adequacywas 88.6% (95% C 74.1-95.5%) (FNA 89.7 Vs CNB 85.7%, p= 0.76). **Figure 3.5** shows the cumulative overall sampling adequacy over time. No adverse events were reported for anyof the procedures.

During the second phase of the study (Feb 2017-May 2018), 44 patients meeting the inclusion criteria were identified but 30 were included in the final study analysis, see **figure 3.6.** Among those included 75.7% (n=23) were referred through the rapid access clinic while 23.3% (n=7) presented through the emergency department. **Table 3.6** shows the baseline characteristics of all patients included and the clinical stage on the initial CT. Enlarged cervical lymph nodes were detected in 14/30 (46%) patients and sampling was performed in all cases. Sampled material was adequate in 13/14 (92.9%) cases. A diagnosis of metastatic cervical lymphadenopathy from lung cancer was confirmed in 13/30 (43.3%, 95% CI 25.5-62.6%). Mean lymph node short diameter was 11±4 mm. All lymph nodes were located below the cricoid cartilage. Location of lymphadenopathy was 6/13 in the right side, 1/13 in the left side and 6/13 bilateral.

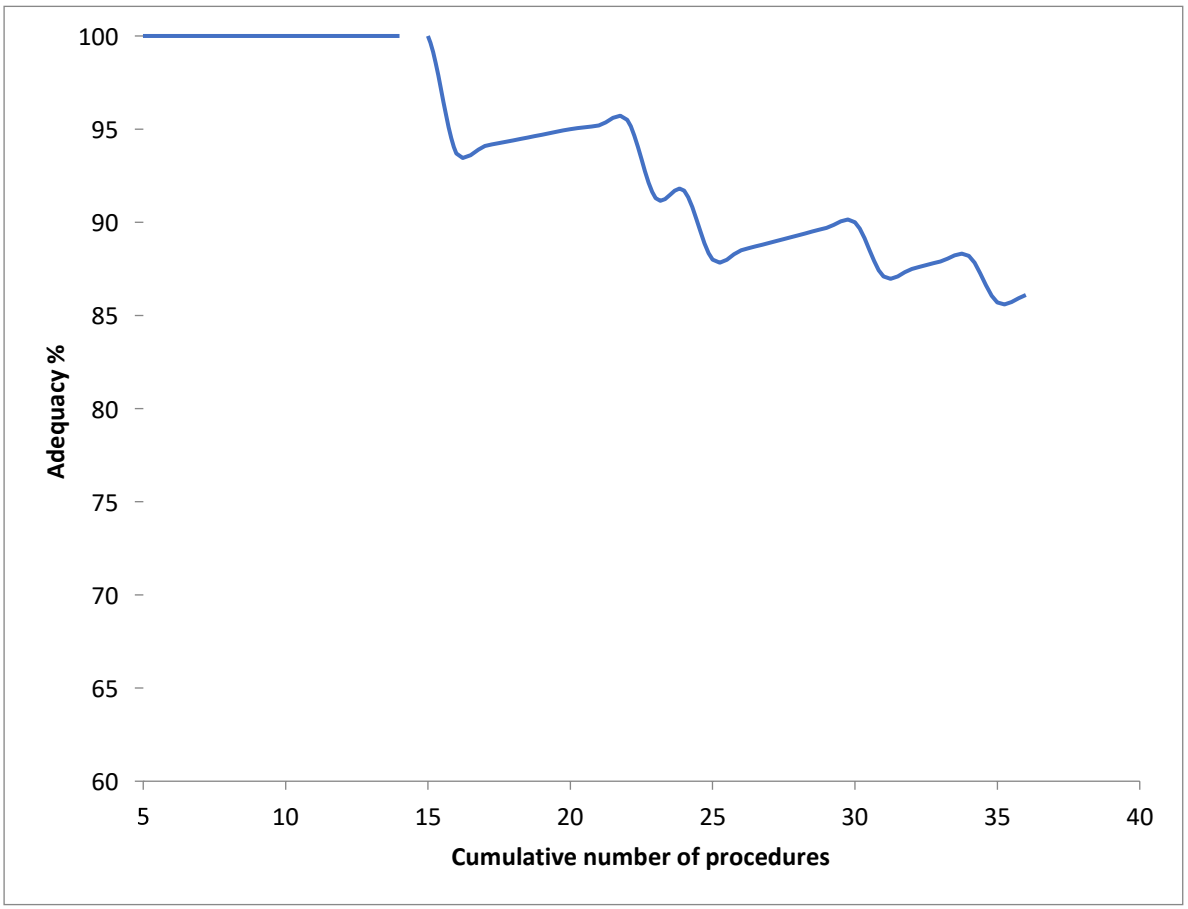

Figure 3.5: Cumulative adequacy of cervical lymph node sampling over time.

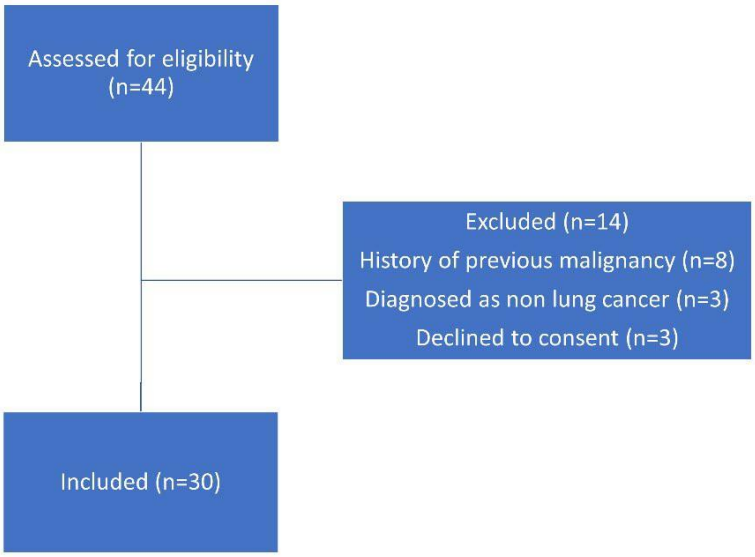

Figure 3.6: Participation flowchart detailing breakdown of patients assessed for inclusion inthe second phase of the study.

Characteristic N=30	Value
Age (SD)	12.8 (5.9)
Male gender (%)	18 (60)
Presentation	
Outpatient Emergency	23 (76.7)
admission	7 (23.3)
ECOG PS	
0	6 (20)
1	15 (50)
2	8 (26.7)
3	1 (3.3)
Nodal stage	
N2	20 (66.7)
N3	10 (33.3)
Metastatic disease	12 (40)
Cancer subtype	
Small cell lung cancer (%)	6 (20)
Adenocarcinoma (%)	16 (53.3)
Squamous cell carcinoma (%)	8 (26.7)
NSCLC NOS (%)	0

Table 3.6: Baseline characteristics of all patients included. NSCLC NOS: Non small cell lungcancer not otherwise specified; ECOG: Eastern Cooperative Oncology Group; SD: Standarddeviation.

Immunohistochemistry was possible in all samples. No significant complications were reported after any of the procedures. PET-CT was performed in 13/30 (43.3%). In this group that had PET-CT 6/13 had evidence of cervical lymphadenopathy and 4/6 were confirmed on

US guided FNA with a false positive rate for PET of 33.3%. PET-CT was not associated withany false negatives.

Molecular analysis was requested on six samples from patients with adenocarcinoma andwas possible in all cases. Testing for Programmed Death Ligand-1 (PDL-1) was also requested and performed in three cases.

Performing NUS lead to upstaging the clinical nodal status from cN2 to cN3 in four cases (13.3%). Overall NUS guided lymph node sampling was the only procedure performed to obtain tissue in 7/30 (23.3%) cases, but 4/7 (57.1%) in those presenting through the emergency department. Other procedures to obtain tissue samples were performed in 23/30 (76.7%) patients including EBUS in 17 cases, bronchoscopy in 5 cases, pleural tap aspiration in one case and mediastinoscopy followed by surgical resection in one case.

Data on patient experience was available for only six patients who underwent both neck lymph node sampling and EBUS in the same session. When asked in the recovery room which procedure would the patient prefer, four chose neck lymph node sampling comparedto two that picked EBUS. All patients reported they will definitely be willing to return for both procedures if required.

3.4 Positron emission tomography for the detection of cervical lymphadenopathy in patients with lung cancer and mediastinal lymphadenopathy

Between August 2012 and Aug 2017, 223 patients were assessed with NUS in the interventional respiratory unit and 149 patients were diagnosed with lung cancer. Of those,123 patients had mediastinal lymphadenopathy. Baseline characteristics are shown in table
3.7. Endobronchial US (EBUS) was performed in 83/123 patients (68%).

The number of patients with enlarged cervical lymphadenopathy on NUS was 69/123 (56.1%). The mean (SD) cervical lymph node short diameter was 12.8 (5.9) mm. Needle sampling was technically feasible and therefore performed in 57/123 patients (46.3%). Findings are summarized in table 3.8. Overall, 49/123 patients (39.8% (95% CI 31.1-49.1%))had confirmed malignant cervical lymphadenopathy on pathological evaluation. When FNAwas compared to CNB, there was no significant difference in sampling adequacy (94.7% versus 92.8% p=0.80). Immunohistochemistry was possible in 48/49 (98%) samples. A sample was considered sufficient for molecular analysis when tumour cells represented > 10% of population. Molecular analysis was requested in 17 neck lymph node samples and was successfully performed in 14 cases (82.4%, 95%CI 56.6-96.2). There was no significant association between the presence of cervical lymphadenopathy and lung cancer subtype

In total, 45/123 (36.6%) patients with mediastinal lymphadenopathy had potentially curabledisease and underwent PET/CT and NUS. FDG avid cervical lymph nodes were detected in 14/45 (31%) patients and following NUS the number of false positives was 7/14 (50%). The breakdown of the ultrasound findings in this group is shown in table 3.9. Overall, PET had a specificity of 81.1%, sensitivity of 87.5%, NPV of 96.8% and PPV of 50% for the detection of cervical lymphadenopathy in this group with potentially curable disease. PET did not add any additional staging information in the assessment of the neck region when compared to NUS alone. PET provided additional overall clinical stage information in four (8.9%) patients and led to a change in management in one (2.2%) patient. No relationship was detected between SUV max and true or false positive PET findings in the neck with median SUV max

for true positive cases of 7.0 (IQR 4-11) versus median SUV max for false positive cases of 3.7 (IQR 3-9) (p=0.11), see figure 3.7. The highest false positive FDG uptake was due to lymphoma which was evident on cytology and confirmed later by surgical excision.

Characteristic	Value
Gender	
Male	70 (56.9)
Female	53 (43.1)
Age (SD)	67.4 (11.2)
Small cell lung cancer (%)	27 (22)
Non-small cell lung cancer (%)	101 (78)
Adenocarcinoma (%)	56 (45.5)
Squamous cell carcinoma (%)	32 (26)
Other* (%)	8 (6.5)

Table 3.7: Baseline characteristics of 123 patients with confirmed lung cancer and mediastinal lymphadenopathy that underwent a neck ultrasound. Data reported as n (percentage) or mean (standard deviation). *Other: neuroendocrine and poorly differentiated lung cancer.

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Characteristic	Value
Short diameter (SD) cm	12.8 (5.9)
Enlarged lymph nodes (%)	69 (56.1)
Needle sampling	57 (46.3)
FNA alone	43 (35)
FNA and CNB	14 (11.4)
Sampling adequacy	
FNA %	94.7
CNB %	92.8
Malignant cervical lymphadenopathy	49 (39.8)
Small cell lung cancer (%)	13 (26.5)
Adenocarcinoma (%)	20 (40.8)
Squamous cell carcinoma (%)	12 (24.5)
Other (%)	4 (8.2)

Table 3.8: Results of neck US and needle sampling of 57 patients with suspicious cervical lymphadenopathy on neck US. Data reported as n (percentage) or mean (standard deviation). FNA: fine needle aspiration; CNB: core needle biopsy.

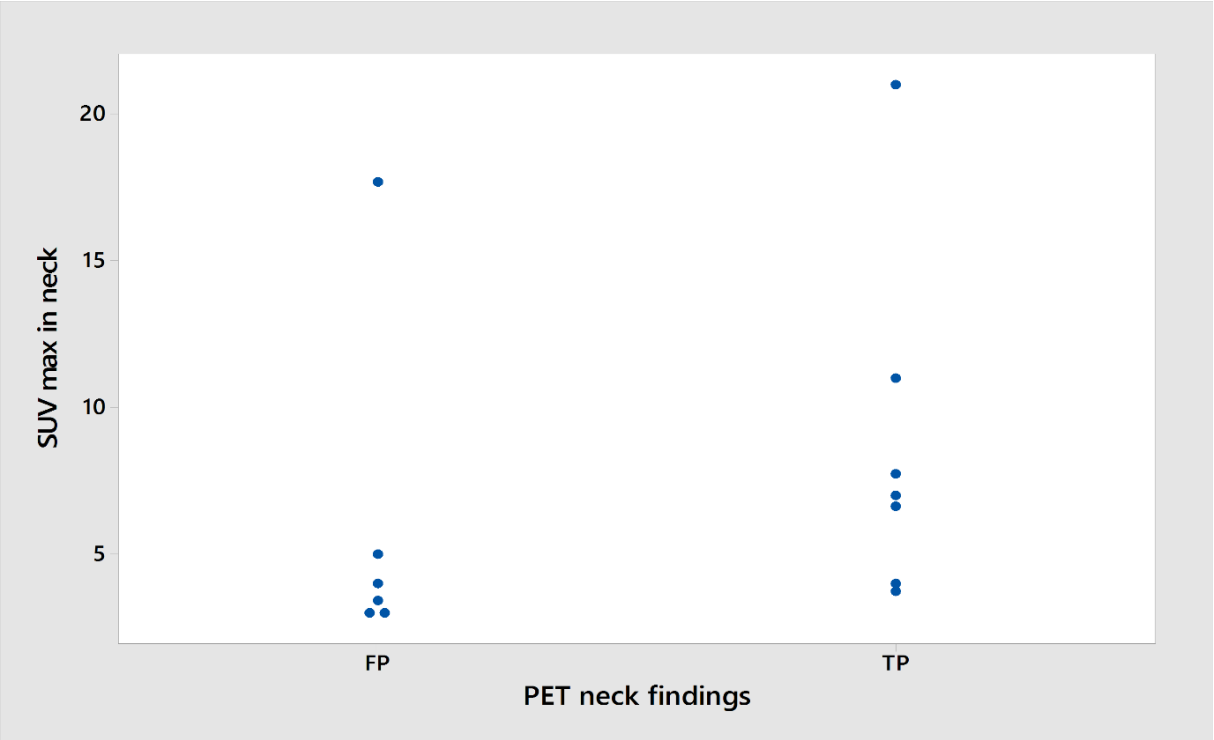

Figure 3.7: Individual SUV max values in true and false positive neck nodes. Median SUV max for TP 7.0 (IQR 4-11) Vs. median SUV max for FP 3.7 (IQR 3-9) (p=0.11, Mann Whitney test). FP = False positive; TP = True Positive; SUV = standardized uptake values; IQR Interquartile range.

Case	SUV Max	Neck US findings	LN short diameter (mm)	Cytology results
1	17.7	Bilateral cervical LNs	14	Lymphoma
2	3	No lymphadenopathy		
3	4.2	Left cervical LN	10	Nonspecific lymphadenitis
4	5	No lymphadenopathy		
5	4	No lymphadenopathy		
6	3	No lymphadenopathy		
7	3.4	Bilateral enlarged LNs	12	Lymphoma

Table 3.9: Results of positron emission tomography PET, neck ultrasound NUS and cytology in all 7 patients that were considered to have false positive PET findings in the neck. Lymph node short diameter reported for the largest lymph node as measure on US LN: Lymph node; SUV: standardised uptake values; LN: lymph node. Two cases of lymphoma on cytology were later confirmed on surgical excisional biopsy.

Chapter 4: DISCUSSION

We conducted four studies to look at the best way to screen for cervical lymphadenopathy in patients with lung cancer. Previous studies have suggested that for this approach to yield significant benefits, patients will have to be appropriately selected. The strongest predictor of the presence of neck lymph node involvement in lung cancer is the presence of mediastinal lymphadenopathy on CT scan(25,32). In current practice patients are frequentlyinvestigated by CT once lung cancer is suspected even before they are reviewed in the clinic.This provides an opportunity to plan investigations ahead with time and cost saving benefits. The principles of lung cancer diagnosis and staging require choosing the right procedure that is least invasive and provides a diagnosis and a stage at the same time. This approach is now further complicated by the increasing need for performing further sophisticated molecular studies in these tissue samples. Moreover, a lot of these diagnostic investigations happen in a setting where there's increasing pressures on these tests. Considering the current body of literature, we hypothesised that routine screening for cervical lymphadenopathy is associated with less invasive investigations in addition to potential time and cost savings. To investigate this hypothesis further we conducted thisseries of studies to look at different modalities for screening for cervical lymph lymphadenopathy; namely CT, PET-CT and ultrasound.

Another question addressed by this thesis is whether neck ultrasound and lymph node sampling can be performed by respiratory physicians. This is widely in practice among other non-radiologist specialities such as ear nose and throat surgeons and endocrinologists. In fact, The Royal College of Radiologists has published guidelines for the use of ultrasound my medical and surgical specialties(47). Respiratory physicians are increasingly familiar with theuse of ultrasound. Thoracic ultrasound is now a basic skill included in training off respiratory physicians in most jurisdictions and is a critical skill in the field of pleural medicine. In addition, lung cancer physicians and interventional pulmonologist frequently use endobronchial ultrasound. Finally, NUS is used in critical care units for the insertion of central venous catheter. In a prospective study supported by a short-term fellowship from the European Respiratory Society I trained to perform NUS and lymph node needle sampling according to pre-set criteria. These criteria included both a predetermined numberof procedures and a selection of competencies.

In the first study we assessed the real-life impact of routinely including the lower neck in initial CT for patients with suspected lung cancer compared to the standard practice recommended by most guidelines. The results suggest that lower neck CT performed at referral leads to higher rate of detection of neck lymphadenopathy and reduces the numberof procedures performed per patient to achieve a diagnosis and a stage among patients withmediastinal lymphadenopathy on CT. This practice also was associated with a reduced need for EBUS. The analysis was limited to patients with CT evidence of N2 or intrathoracic N3 disease for two reasons. First , this is the subgroup of patients with highest prevalence of malignant neck lymphadenopathy according to previous studies(48,48–50). Second, this specification reduces the chance of confounding bias by limiting the analysis to this group; the strongest known variable associated with the presence of neck lymphadenopathy in lung cancer is the presence of mediastinal lymphadenopathy. Results from the cohort in Plymouth showed 8.3% of patients with lung cancer had evidence of neck lymphadenopathythat was later on confirmed to be malignant. This result can be put in context considering the prevalence of adrenal metastases detected on initial CT is 1.6-3.5% according to literature(51,52) and yet it is currently standard practice to include the adrenal glands but not the lower neck. . Over the study period the proportion of patients with evidence of N2- N3 disease and stage IV was comparable to each other and to the findings generally reported in the literature (reference NLCA and IASLC 8th edition) indicating the two study cohorts had similar characteristics compared to other hospitals in the UK and other countries. The study is limited by its retrospective design. Potential unmeasured confounders were not accounted for in the analysis and the design. The difference in the presence of metastatic disease between the two cohort was predominantly driven by higher rate of M1a stage in the Plymouth cohort which might be explained by a higher background rate of indeterminate lung nodules. Because the study was restricted to patients with evidence of N2 and intrathoracic disease to limit confounding bias, the results can only be read with caution before generalising the findings to all patientswith suspected lung cancer referred for assessment. Routine inclusion of the lower neck in patients with suspected lung cancer is associated with increased rate of detection of malignant neck lymph nodes, reduced number of procedures done to achieve a diagnosis and a stage and lower need for EBUS. Further prospective studies are required to confirm these findings.

In another study we report our results of respiratory physician led NUS guided sampling of adenopathy. Our results demonstrate this can be performed with a high level of adequacy

and safety by respiratory physicians trained in this procedure. Our sampling inadequacy rate(8.5%) was comparable to results from a previous systematic review of US guided sampling of neck lesions where the inadequacy rate was 9.6% for radiologists and 11% for clinicians without Rapid On Site Evaluation ROSE(53). Importantly in 14/15 (93.3%) cases confirmed asa primary lung adenocarcinoma, further mutational analysis was possible in 93.3% of samples. This demonstrates that adequate material is available in these cases for additional testing which is becoming increasingly important in the modern oncological management ofthis patient population consistent with a previous study where molecular analysis was possible in 85% of the cases (46). Incorporating respiratory led NUS as a point of care diagnostic test in the suspected lung cancer clinic and respiratory procedural environment impacts significantly on the patient pathway. This safe, quick procedure provides early confirmation of cancer type and stage, whilst potentially preventing more invasive and expensive diagnostic and staging investigations. Such an impact, explored in diagnostic algorithms may also have a positive effect on not only individual patient pathway time, but the wider patient cohort flow undergoing investigation by freeing interventional radiology and EBUS lists with likely cost benefits. We believe that this hypothesis is worth further assessment in a prospective study in lung cancer patients. US as performed by non- radiologists has become increasingly common over the last decade. Adequate training guidance in NUS for the use in this setting, has historically, been an area of uncertainty.

However the Royal College of Radiologists (RCR) in the UK now have published guidelines for procedures performed by non-radiologists(54). The guidelines recommend experience inNUS for level 2 training in pleural ultrasound acknowledging the potential benefits of such a skill for respiratory physicians. An inadequate sampling rate of < 15% was recommended for level 2 training in head and neck ultrasound – a metric achieved in our practice. However, for further advancement of NUS as skill for respiratory physicians we propose separate tailored guidelines and training recommendations should be developed. This study has a few inherent limitations. Firstly, this is a retrospective cohort and most cases were identifiedwith adenopathy either by careful clinical examination or radiological assessment of the neck; however, the indications for neck imaging in the first place were heterogeneous introducing an element of selection bias which might be associated with a higher diagnostic yield. In addition, all procedures were performed by one of four chest physicians with varying degrees of experience in NUS and sampling including core biopsy of neck nodes. It is

unclear how much experience is required to achieve a high level of sampling adequacy. Further prospective studies should be undertaken to elucidate the role of training respiratory physicians in NUS guided lymph node sampling. This study demonstrates that neck ultrasound can be performed by respiratory physicians with accuracy in patients with identified adenopathy by clinical examination or imaging of the neck. Subsequent samplingof nodes under direct sonographic guidance was associated with a high level of accuracy and diagnostic yield. Guidelines need to be developed to allow training of respiratory physicians particularly those with a special interest in lung cancer diagnosis and management

We next conducted a prospective study and we showed a significant proportion of patients with lung cancer and mediastinal lymphadenopathy also had cervical lymph node involvement when neck ultrasound was performed routinely by a trained respiratory physician. The proportion of patients that had cervical lymph node involvement in the studywas 43.3% consistent with similar previous studies. Kumaran et al performed routine neck ultrasounds in 101 patients with suspected and later on confirmed lung cancer and found evidence of cervical lymph node involvement in 50% of cases(32). That study also showed 9/101 patients were upstaged from N2M0 to N3M0. All procedures were performed by radiologists. Another study compared routine neck CT, US and palpation for the detection of cervical lymphadenopathy in patients with lung cancer regardless of nodal stage on CT. The authors included 50 patients and confirmed malignant cervical lymphadenopathy in 40% of those. US guided cervical lymph node sampling is appealing as a procedure to be embedded in the diagnostic and staging pathway for lung cancer patients specially if done by respiratory physicians. Such a procedure can be performed in the clinic, does not require sedation with the logistic implications of a recovery time and is cheaper compared to other nodal staging procedures such as endobronchial ultrasound and mediastinoscopy. Within this study six patients underwent both EBUS and NUS guided FNA in the same session and there was no difference in the level of discomfort reported for the two procedures and the level for willingness to return for a repeat procedure was high although the study was not powered to detect a difference in patient reported outcomes between the two procedures.The 8th TNM edition for lung cancer staging does not differentiate between ipsilateral and contralateral supraclavicular lymphadenopathy and labels both as N3 disease despite the

potential implications for radiotherapy treatment planning(7). In the case of small cell lung cancer, the presence of contralateral supraclavicular lymphadenopathy is not consistent with limited stage disease. Performing routine neck ultrasounds among patients with high likelihood of cervical lymph node involvement will add to our knowledge of the impact of the presence of cervical lymphadenopathy on the response to chemoradiotherapy in patients with locally advanced disease. Such information should be collected prospectively and considered in the data analysis for future TNM staging updates. Further molecular studies were possible in all cervical lymph node samples when this was required (9 cases). A previous retrospective study was performed on 171 cervical lymph node samples from patients with lung cancer and showed further molecular studies were feasible in 85% of cases(46). We did not attempt to assess whether neck lymph node sampling provided sufficient tissue for molecular analysis if required but one study suggested > 80% of FNAC from malignant neck lymph nodes in patients with lung cancer provide enough material for EGFR/Alk analysis(55). In this prospective study we showed that it is feasible to train a respiratory physician to perform US guided cervical lymph node needle sampling and maintain an acceptable level of sampling adequacy. At no stage did the cumulative samplingadequacy fall beyond 85% which is the recommendation made by the Royal College of Radiologist for non-radiologists performing US guided neck sampling(54). The overall sampling adequacy was 88.6% and 89.7% for FNAs. The cumulative sampling adequacy did not seem to improve over time. The study had some limitations. As this was a study with one operator, it is not possible to say whether the results were generalisable. Factors that might affect sampling adequacy such as lymph node size were not accounted for. The study was not designed to assess the impact of routine neck ultrasound on the average time to a final diagnosis/stage and this will need to be examined prospectively in a randomised study. This study demonstrates the feasibility of training respiratory physicians to perform US guided cervical lymph node sampling to an acceptable standard. It also shows that when thiswas embedded routinely in the work up pathway of patients with mediastinal lymphadenopathy nearly four in ten patients had evidence of cervical lymphadenopathy andhad the potential of avoiding a more invasive and costly diagnostic procedure.

Finally, we conducted a retrospective study to examine the role of PET in the detection ofcervical lymphadenopathy in patients with lung cancer. While PET had a high NPV for the

detection of malignant cervical lymphadenopathy, it was associated with a high rate of falsepositive findings. The diagnostic accuracy of PET for malignant neck lymphadenopathy in lung cancer has previously been studied; Sung et al reported on 32 patients with cervical lymphadenopathy detected at PET and/or CT and found a false positive rate of 19% (28).

The authors reported an SUV max of 2.3 to be the optimum cut off for differentiating true and false positive findings. A smaller study of 12 patients with lung cancer and FDG avid cervical lymphadenopathy showed supraclavicular metastases from lung cancer in 10 cases;one case showed evidence of sarcoidosis and another evidence of metastatic breast cancer(56). Mean SUV max in in this study was 6.3 (range 3.7-12.2). In our study NUS was performed by respiratory physicians trained in the procedure and, while it can be argued there could have been a failure to detect some malignant neck lymphadenopathy, the high sampling adequacy rate of 94.7% in this cohort would be inconsistent with such an argument. In this cohort, 39.8% of patients with lung cancer and mediastinal lymphadenopathy had confirmed malignant cervical lymphadenopathy following NUS. These findings are consistent with the results reported by Kumaran et al who investigated the role of routine neck US in 101 patients with suspected and later confirmed lung cancer that had evidence of mediastinal lymphadenopathy (32). The authors reported that 50% of patients had malignant neck lymph nodes. Similarly, a study of 40 patients with non- palpable neck lymph nodes confirmed 40% had supraclavicular lymph nodes metastases(43). The presence of supraclavicular lymphadenopathy in non-small cell lung cancer indicates N3 disease consistent with at least stage IIIB(6). Such cN3 disease is associated with a median survival of 7 months in patients with non-small cell lung cancer(15). The National Institute of Health and Care Excellence (NICE) guidelines recommend routine NUS in patients with bulky mediastinal lymphadenopathy or blind transbronchial needle aspiration TBNA mostly based on a cost-effectiveness analysis although the level of evidence is weak(12) . The findings from our study support this recommendation – potentially identifying nodal disease in the neck region in about 40% of patients. This can significantly streamline investigations and prevent the need for more invasive tests potentially reducing futile treatments and time to definitive diagnosis and clinical stage. If these findings are supported by further well-designed prospective studies ofroutine NUS in patients with mediastinal lymphadenopathy it will have a significant impact on the diagnostic and staging pathway in lung cancer considering the feasibility and safety

of performing NUS even in the office. In this paper we report that PET offered no additionalstaging value in the neck when NUS was also performed in this cohort. In addition, it only changed M stage in 8.8% of patients from finding disease in other sites which lead to a change in management in only 2.2% of cases. Similar results were seen in a multicentre retrospective study of 1059 patient who underwent PET scanning for suspected lung cancer(31). In this population, additional extra-thoracic findings were detected in 15.8% butmanagement changed in only 1.2% of all patients that underwent PET. The results from thisstudy and our study suggest PET/CT has only a limited additional staging value once NUS is performed and the mediastinum is properly staged. However, a recommendation regardingthe benefit of PET when NUS is negative cannot be made based on this study as the sample size of this subgroup was small (38 patients). This study is limited by its retrospective designand the possibility of selection bias. Only patients that underwent a NUS were assessed for inclusion in the study which might have led to confounding by indication bias. Also, this is a single centre study which might affect the generalisability of its findings. In this cohort of patients with lung cancer and mediastinal lymphadenopathy, routine neck ultrasound performed revealed malignant cervical lymphadenopathy in 39.8% of cases. Once neck US was performed, PET did not add any staging value in the neck and only limited additional staging value elsewhere with change in management in just 2.2% of cases.

Apart from NICE guidance that recommends lower neck CT in all patients with suspected lung cancer(57), the current guidelines have no specific recommendations regarding screening for cervical lymphadenopathy in lung cancer although there is guidance regardingscreening for involvement in liver, bone, adrenal glands, brain and intrathoracic lymphadenopathy. PET is the only test that can be used to assess for cervical lymphadenopathy according to the pathway that is widely used in clinical practice. There are two main limitations of this approach. First, PET is only performed in patients with localised disease that are considered candidates for curative treatment and therefore no screening is done in patients with advanced disease who are frequently less fit for more invasive procedures and where neck lymph node sampling can be a more suitable test to perform than EBUS or CT guided lung biopsy readily providing material for analysis to guide treatment option without delay specially when performed in the outpatients or at the bedside by respiratory physicians which was shown to be feasible in this thesis. Secondly,

PET was also shown in this thesis to be associated with a false positive rate of 50% and therefore cannot be relied on solely to confirm cervical lymph node involvement and therefore NUS will be required in these cases anyway.

CHAPTER 5: FUTURE DIRECTIONS

Overall, in the thesis we showed that cervical lymphadenopathy is frequently present in patients with lung cancer and mediastinal lymphadenopathy on CT to a degree that justifies screening for it routinely. We have shown that lower neck CT done routinely in patients withlung cancer reduced the need for the number of invasive procedures needed and was associated with a higher rate of detection of cervical lymphadenopathy. We have also shown that in a single centre where respiratory physicians frequently performed cervical lymph node needle sampling that adequacy was acceptable and comparable to radiologists performing the procedure. We have also prospectively shown that it is feasible to train a respiratory physician to perform NUS and needle sampling to an acceptable standard by a respiratory consultant with experience in the procedure with support from radiology. We replicated the current literature regarding the rate of cervical lymphadenopathy in patients with lung cancer and mediastinal lymphadenopathy when NUS was performed by respiratory physicians compared to radiologists in the previous literature. Finally, we showed that in patients with lung cancer and mediastinal lymphadenopathy that are candidates for curative treatment based on staging CT, PET was associated with an unacceptably high false positive rate for neck lymph nodes and had only minimum impact on treatment planning when NUS was routinely performed. At this stage further research is required to assess the impact of a pathway that includes routine NUS in patients with lung cancer and mediastinal lymphadenopathy versus routine inclusion of the lower neck on the initial staging CT in all patients with suspected lung cancer. We also recommend another multicentre study to assess whether the feasibility of training respiratory physicians on NUS can be replicated in different settings and therefore generalised. A structured approach to training respiratory physicians in NUS is needed and must be developed by stakeholders to maintain an acceptable level of competency and safety.

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APPENDIX

Appendix I: Consent form for prospective study of neck ultrasound in patients with suspected lung cancer and mediastinal lymphadenopathy

INFORMED CONSENT

Title of study: **Pilot study assessing the role of routine neck ultrasound performed by respiratory physicians in lung cancer**

I,_____(Full name)

of_____(Address)

I hereby fully and freely consent to participate in the above named study.

I have been given adequate information regarding the details of the study including a patient information leaflet on the underlying condition and associated procedures.

I acknowledge the purpose of the study and any risks involved in the study procedures. I understand that I may withdraw my consent at any stage in the study. I understand that data relating to this study may be securely stored and used for future publications. I agree that the study investigators can access my medical records for the purpose of the study.

I agree that my general practitioner may be notified of my participation in the study and that he/she may release information on my past medical history. I have informed the investigator of any drugs that I am presently taking.

DECLARATION BY THE PARTICIPANT

The nature and purpose of such procedures has been described to me in the Information Sheet and has been explained to me and I have discussed these matters with him/her to my satisfaction.

Signed:_____

Date: _____

DECLARATION BY THE INVESTIGATOR

I confirm that I have provided an Information Sheet and explained the nature and effect of the procedures to the participant and that his/her consent has been given freely and voluntarily.

Signed:_____

Status:_____Date: _____

Appendix II: Patient information leaflet for prospective study of neck ultrasound in patients with suspected lung cancer and mediastinal lymphadenopathy

Pilot study assessing the role of routine neck ultrasound performed by respiratory physicians in lung cancer

You are being invited to participate in a research study to help us gain further understanding the role of ultrasound guided sampling of neck lymph glands that might be affected by your disease. Before you decide whether or not to take part, it is important for you to understand why this research is being done and what it involves. Through research, It is hoped that our understanding of how to best manage the disease will be improved. This form explains the study, including the risks and benefits of participation. Please take time to read the following information carefully and discuss it with the research staff if you so wish. If anything is not clear to you or you would like more information, please do not hesitate to ask. Thank you for reading this information sheet.

What is the purpose of this study?

Lung cancer is the commonest malignancy worldwide and its management depend on obtaining a tissue diagnosis to identify the type of tumour. Outcome and choice of treatment depend on a process called staging. It involves multiple tests to assess whether the tumour is present outside the lung tissue. These tests include imaging and very frequently invasive procedures to obtain samples. Neck lymph glands represent a site that can be potentially involved and they are readily accessible. Small lymph glands are difficult to detect by palpating the neck and ultrasound has been used extensively for this purpose. Ultrasound also makes sampling these glands a safer procedure compared to other invasive tests. The study aims to further investigate the role of this procedure specifically in the context of lung cancer.

Do I have to take part?

It is up to you to decide whether or not you would like to take part in this study. We will describe the study and go through this information sheet which we will then give to you to read in your own time. We will then ask you to sign a consent form to show you have agreed to take part. If you choose not to participate in the study, this will not in any way affect the clinical care you receive. You are free to withdraw from the study at any time and do not have to provide us with a reason for doing so if you do not wish to. This will not affect your treatment or follow-up in any way.

What will happen if I take part in this research study?

The research in this study will take place in Galway University and Merlin Park Hospitals. A neck ultrasound will be performed by one of the researchers. If abnormal appearing lymph glands are detected a sample will be obtained from these glands using a needle. You can ask us to stop at any time during the procedure. This will normally take 5-15 minutes to be performed. You will otherwise receive the same routine care and investigations you would have received if you did not participate in the study.

Potential Benefits and Discomforts:

Your participation in this study will aid our understanding of the role of this minimally invasive test in the staging and diagnosis of patients with lung cancer. It is hoped that it will eventually lead to improvements in the diagnosis, staging and experience of patients with lung cancer. It is theoretically possible that participation in the study would lead to you avoiding some further invasive procedures. Although this study may have no direct benefits to you on an individual basis, it is hoped that the results may benefit patients like you in the future.

The ultrasound test is safe and non-invasive. Unlike X-Ray it is not associated with risk of radiation. If lymph gland sampling is required this can be associated with complications like bleeding or infection but these are rare.

Thank you for taking the time to read this information. We would ask that if you have any further questions, please feel free to ask the investigators at any time. Please be aware that you are under no obligation to enrol in this study if you do not wish to do so and can withdraw from the study at any time. This will not affect your treatment or follow-up in any way.

Appendix III: Study protocol; retrospective comparative study of routine lower neck CT in the staging and diagnosis of lung cancer across two cohorts

Retrospective comparative study of routine lower neck CT in the staging and diagnosis of lung cancer across two cohorts

V1.0; 6th Jun 2017

GLOSSARY OF ABBREVIATIONS

CI	Chief Investigator
CT	Computed Tomography
EBUS	Endobronchial Ultrasound
FNAC	Fine Needle Aspiration Cytology
GCP	Good Clinical Practice
NHS	National Health Service
NRES	National Research Ethics Service
PET	Positron Emission Tomography
PI	Principal Investigator
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SD	Standard Deviation
SOP	Standard Operating Procedure
TNM	Tumour Node Metastasis
TSG	Trials Steering Group
US	Ultrasound
VATS	Video-assisted Thoracoscopy

KEYWORDS

lower neck CT, staging, diagnosis, lung cancer, neck, lymphadenopathy

STUDY SUMMARY

TITLE Retrospective comparative study of routine lower neck CT in the staging and diagnosis of lung cancer across two cohorts

DESIGN Retrospective comparative study

AIMS To assess the impact of routine lower neck CT on the rate of detection of malignant neck lymphadenopathy among patients with lung cancer

OUTCOME MEASURES Proportion of pathologically confirmed malignant supraclavicular lymph node

POPULATION Patients initially seen with suspected lung cancer

ELIGIBILITY *Inclusion Criteria*

- Male or female age > 18 years
- Pathologically confirmed primary lung cancer
- Intrathoracic N2 and or N3 disease on CT defined as lymph node with short diameter > 10 mm

Exclusion Criteria

- None

DURATION 1 year

1. INTRODUCTION

1.1 BACKGROUND AND RATIONALE FOR CURRENT STUDY

Lung cancer is the leading cause of cancer related deaths among males world-wide and among females in most developed countries[1]. Initial prognosis and management depend on disease stage which in non-small cell lung cancer is defined by the Tumour Node Metastasis (TNM) classification system. Cervical lymph node involvement is often detected, and is defined as N3 or M1a disease depending on anatomical location. Pathologically confirmed N3 disease (pN3) is associated with poor outcome with only 3-5% 5 year survival[2] and is generally considered incurable[3].

A cost-effective approach to diagnosing and staging lung cancer requires utilizing the least invasive procedure that can simultaneously achieve diagnosis and final staging; fine needle aspiration of suspicious cervical lymph node fits that role. Despite this, neck imaging is not a routine investigation in lung cancer in most institutions. The American College of Chest Physicians ACCP and the National Comprehensive Cancer Network NCCN guidelines recommend CT thorax and upper abdomen for the staging of non-small cell lung cancer but not CT neck[4,5]. However, the National Institute of Clinical Excellence NICE lung cancer guidelines recognize that many centres in the United Kingdom include the lower neck when performing CT scans for the diagnosis of lung cancer and advises that patients with supraclavicular lymphadenopathy on CT undergo neck ultrasound. It also recommends neck US or blind TBNA in all patients with bulky mediastinal lymphadenopathy based on a cost-effectiveness analysis[6]. Sensitivity of CT for detecting malignant cervical lymph nodes in lung cancer ranges from 67-83% and has a positive predictive value of 0.5-0.74[7,8]. Two practices currently exist regarding the role of lower neck CT in patients with suspected lung cancer but with little evidence for either. Routine lower neck CT is potentially associated with benefits of higher detection of neck lymphadenopathy leading to better staging, less invasive procedure with positive implications for patients experience and care. The potential harms are delay in diagnosis due to false positive findings and radiation exposure. There is limited evidence in this area so this study will potentially provide evidence to inform health policy decisions based on the risk benefit balance.

In Derriford Hospital, Plymouth the lower neck is included routinely in CT for patients with suspected lung cancer while in Galway University Hospital, Ireland this is not a standard practice. This is a retrospective comparative study to assess the real-life impact of routine lower neck CT on the diagnostic and staging work up of patients with suspected lung cancer.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To assess the impact of routine lower neck CT on the rate of detection of malignant neck lymphadenopathy among patients with lung cancer

2.2 SECONDARY OBJECTIVES

1- Assess the prevalence of neck lymph node involvement among patients with lung cancer as detected by CT and confirmed by Ultrasound guided Fine Needle Aspiration Cytology FNAC

2- Assess the impact of routine lower neck CT on the number of procedures performed per patient

3- Assess the impact of routine lower neck CT on the proportion of patients with mediastinal lymphadenopathy that underwent Endobronchial Ultrasound (EBUS)

3. STUDY DESIGN

This is a retrospective comparative study of two cohorts of patients with confirmed lung cancer in two centres with different practice regarding routine lower neck CT in patients with suspected lung cancer.

3.1 STUDY POPULATION

Starting from Nov 2014 patients with a diagnosis of primary lung cancer will be screened for those meeting the inclusion criteria until the target sample size of 82 patients in each cohort is reached.

3.2 STUDY OUTCOME MEASURES

Primary outcome:

1- Proportion of pathologically confirmed malignant supraclavicular lymph node

Secondary outcomes:

1- Number of diagnostic procedures performed per patient

2- Proportion of patients who underwent more than one diagnostic procedures

3- Proportion of patients who underwent Endobronchial Ultrasound (EBUS)

3.3 INCLUSION CRITERIA

1. Male or female age > 18 years

2. Pathologically confirmed primary lung cancer

3. Intrathoracic N2 and or N3 disease on CT defined as lymph node with short diameter > 10 mm

3.4 EXCLUSION CRITERIA

None

4 STUDY PROCEDURES AND GUIDELINES

4.1 CLINICAL ASSESSMENTS

Initial data collection will take the form of an audit conducted at Galway University Hospital (Eire) and Plymouth Hospitals NHS Trust (UK). The extracted data will be anonymised before any data comparisons are made, no patient identifiable data will leave either hospital.

4.1.1 Concomitant Medications

For this study concomitant medications will not be reported considering the observational retrospective design.

4.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded.

4.1.3 Medical History

Relevant medical history, including history of current disease will be recorded.

4.1.4 Radiology records

Variables will be extracted from radiology records. The investigations that will be looked at include CT, PET and US. Results will be reported as true positives, true negatives, false positives and false negatives based on results from US guided FNAC.

4.1.5 Pathology records

Information about adequacy of sampling and final pathological diagnoses and stage will be recorded

4.1.6 Diagnostic procedures

For each patient, the number and type of diagnostic procedure used to obtain a pathological diagnosis will be recorded. These include Endobronchial Ultrasound EBUS, Bronchoscopy, CT guided biopsy, mediastinoscopy, pleural fluid aspiration, Video-assissted Thoracoscopy VATS and neck FNAC.

5. END OF STUDY

This is defined as the date of the primary outcome analysis of the study data.

6. STATISTICS AND DATA ANALYSIS

6.1 DESCRIPTION OF STATISTICAL METHODS

Sample size calculation: based on existing literature it is estimated that the proportion of patients with CT evidence of intrathoracic N2-N3 disease will have evidence of neck LN malignancy in 35% of cases in the lower neck CT group and 20% in the other group. Using a Chi-Squared test for categorical variables, $\alpha = 0.05$(two sided) and $\beta = 0.8$; a sample size of 82 patients in each cohort is required.

Statistical analysis plan: Categorical outcome measures will be reported as proportions, frequencies, and odds ratios OR with 95 confidence interval CI. Continuous outcomes will be reported as mean and standard deviations SD. Multivariate logistic regression will be used to adjust for potential confounders. Minitab 17 will be used to conduct the statistical analysis.

6.2 THE LEVEL OF STATISTICAL SIGNIFICANCE

In all cases, p-values of less than 0.05 will be considered significant.

6.3 PROCEDURE FOR ACCOUNTING FOR MISSING, UNUSED, AND SPURIOUS DATA.

The research team will check completed datasets for missing data or obvious errors prior to any analysis. Data will be monitored centrally for quality and completeness by the research team and every effort will be made to recover data from incomplete data sets where possible.

7. ARCHIVING

Following the closure of the study, the research team will liaise with the study Sponsor to arrange the archiving of the study documentation (essential documents) and the trial database. Local study Files will be archived according to the local archiving SOP. The Study documentation will be archived for a minimum of 5 years after completion of the trial. Destruction of essential documents at the end of the archive period will require authorisation from the Sponsor.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Chief Investigator in EIRE and the UK will obtain approval from an approprite Research Ethics Committee. The Chief Investigators will ensure that this study is conducted in full conformity with relevant regulations and the principles of the Declaration of Helsinki.

8.2 CONSENT

The study is utilising anonymised audit data so consent is not required.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of the participants records used in the study and will comply with the Data Protection Act (1998).

8.4 DATA PROTECTION AND PATIENT CONFIDENTIALITY

The investigators and trial site staff will comply with the requirements of National Data Protection legislation with regards to the collection, storage, processing and disclosure of personal information and will uphold the required core principles.

Participants' records will be converted to unique identifiers for use in the study, and the original list used for conversion will be kept locally and separate to the rest of the study data on the Chief Investigator's password protected network drive within Plymouth Hospitals NHS Trust or Galway University Hospitals. The name and any other identifying detail will NOT be included in any study data electronic file. At the end of the anonymised study the data will be burnt to disc, password protected and archived locally in the hospitals secure archive facility for a minimum of 5 years after which with the sponsor's permission it will be securely deleted/destroyed.

8.5 ACCESS TO DATA

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

9.0 INDEMNITY

This is an NHS-sponsored research study. If an individual suffers negligent harm as a result of participating in the study, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an ex-gratia payment may be considered in the event of a claim.

10 SPONSOR

Galway University Hospital will act as the main sponsor for this study. Delegated responsibilities (such as monitoring) will be assigned to Plymouth Hospital NHS Trust taking part in this study.

11 FUNDING

None

12 MONITORING

The study may be subject to audit by Galway University Hospital under their remit as sponsor. Local study monitoring will follow the partcipants hospital SOP to ensure adherence to the principles of GCP. The level of monitoring will be determined by a risk assessment, or on a for cause basis. The study may also be audited / inspected by regulatory bodies to ensure compliance with national regulations.

13. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through name in Eire and in the UK by name.

14. PUBLICATION POLICY

The final results of the study will be disseminated via presentations at appropriate scientific meetings and conferences and publication in appropriate peer-reviewed journals.

12. REFERENCES

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APPENDIX 1-RISK ASSESSMENT

Risks associated with trial interventions

☒ **LOW ≡ Comparable to the risk of standard medical care**

☐ MODERATE ≡ Somewhat higher than the risk of standard medical care

☐ HIGH ≡ Markedly higher than the risk of standard medical care

Justification: Briefly justify the risk category selected and your conclusions below (where the tableis completed in detail the detail need not be repeated, however a summary should be given):

This is retrospective observational study. Only risk is an unlikely breach of data protection.

What are the key risks related to therapeutic interventions you plan to monitor in this trial? **No therapeutic intervention**		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
N/A	N/A	N/A	N/A	N/A

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)

Study will be monitored locally and this would identify any potential study issues.

Appendix IV: Publications related to this thesis

List of publications related to this thesis

1. Ahmed M, Daneshvar C, Breen D. Routine neck ultrasound by respiratory physicians in the diagnosis and staging of patients with lung cancer and mediastinal lymphadenopathy: a prospective pilot study. ERJ Open Res [Internet]. 2020 Jan 1 [cited 2020 Jun 7];6(1). Available from: https://openres.ersjournals.com/content/6/1/00180-2019

2. Ahmed M, Flannery A, Daneshvar C, Breen D. PET and Neck Ultrasound for the Detection of Cervical Lymphadenopathy in Patients with Lung Cancer and Mediastinal Lymphadenopathy. Respir Int Rev Thorac Dis. 2018;96(2):138–43.

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Appendix IV: Logistic regression model for CT neck double cohort study

Binary Logistic Regression: More than one procedure versus PET done?, M stage, Tumour Type

Method

Link function	Logit
Categorical predictor coding	(1, 0)
Rows used	191
Rows unused	3

Response Information

Variable	Value	Count	
More than one procedure done	Yes	69	(Event)
	No	122	
	Total	191	

Deviance Table

Source	DF	Adj Dev	Adj Mean	Chi-Square	P-Value
Regression	3	15.282	5.0940	15.28	0.002
PET done?	1	0.480	0.4803	0.48	0.488
M stage	1	0.347	0.3472	0.35	0.556
Tumour Type	1	12.880	12.8804	12.88	0.000
Error	187	234.599	1.2545		
Total	190	249.881			

Model Summary

Deviance R-Sq	Deviance R-Sq(adj)	AIC
6.12%	4.92%	242.60

Coefficients

Term	Coef	SE Coef	VIF
Constant	-0.326	0.302	
PET done?			
1	0.241	0.347	1.18
M stage			
1	-0.200	0.339	1.17
Tumour Type			
SCLC	-1.710	0.558	1.01

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI
PET done?			
1	0	1.2720	(0.6447, 2.5099)
M stage			
1	0	0.8191	(0.4219, 1.5905)
Tumour Type			
SCLC	NSCLC	0.1808	(0.0606, 0.5397)

Odds ratio for level A relative to level B

Regression Equation

P(Yes) = exp(Y')/(1 + exp(Y'))

Y' = -0.326 + 0.0 PET done?_0 + 0.241 PET done?_1 + 0.0 M stage_0 - 0.200 M stage_1
     + 0.0 Tumour Type_NSCLC - 1.710 Tumour Type_SCLC

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	187	234.60	0.010
Pearson	187	191.29	0.400
Hosmer-Lemeshow	2	0.52	0.772

Fits and Diagnostics for Unusual Observations

Obs	Observed Probability	Fit	Resid	Std Resid	
61	1.0000	0.0965	2.1623	2.19	R
99	1.0000	0.0965	2.1623	2.19	R
130	1.0000	0.1423	1.9747	2.02	R
161	1.0000	0.1154	2.0782	2.11	R

R Large residual

Binary Logistic Regression: More than one pr versus PET done?, M stage, Tumour Type, Cohort

Method

Link function	Logit
Categorical predictor coding	(1, 0)
Rows used	191
Rows unused	3

Response Information

Variable	Value	Count	
More than one procedure done	Yes	69	(Event)
	No	122	
	Total	191	

Deviance Table

Source	DF	Adj Dev	Adj Mean	Chi-Square	P-Value
Regression	4	39.271	9.818	39.27	0.000
PET done?	1	1.973	1.973	1.97	0.160
M stage	1	1.409	1.409	1.41	0.235
Tumour Type	1	13.646	13.646	13.65	0.000
Cohort	1	23.989	23.989	23.99	0.000
Error	186	210.609	1.132		
Total	190	249.881			

Model Summary

Deviance R-Sq	Deviance R-Sq(adj)	AIC
15.72%	14.12%	220.61

Coefficients

```
Term           Coef  SE Coef   VIF
Constant      0.193    0.334
PET done?
  1           0.531    0.379  1.21
M stage
  1           0.462    0.393  1.37
Tumour Type
  SCLC       -1.848    0.581  1.03
Cohort
  Plymouth   -1.719    0.370  1.22


Odds Ratios for Categorical Predictors

Level A      Level B  Odds Ratio       95% CI
PET done?
  1          0            1.7003  (0.8087, 3.5749)
M stage
  1          0            1.5873  (0.7341, 3.4322)
Tumour Type
  SCLC       NSCLC        0.1575  (0.0505, 0.4917)
Cohort
  Plymouth   Galway       0.1792  (0.0867, 0.3701)

Odds ratio for level A relative to level B


Regression Equation

P(Yes)  =  exp(Y')/(1 + exp(Y'))


Y' = 0.193 + 0.0 PET done?_0 + 0.531 PET done?_1 + 0.0 M stage_0 + 0.462 M stage_1
     + 0.0 Tumour Type_NSCLC - 1.848 Tumour Type_SCLC + 0.0 Cohort_Galway
     - 1.719 Cohort_Plymouth


Goodness-of-Fit Tests

Test              DF  Chi-Square  P-Value
Deviance         186      210.61    0.104
Pearson          186      200.53    0.221
Hosmer-Lemeshow    5        5.21    0.390


Fits and Diagnostics for Unusual Observations

        Observed                    Std
Obs  Probability     Fit   Resid  Resid
 61       1.0000  0.0515  2.4355   2.46  R
 99       1.0000  0.0515  2.4355   2.46  R

R  Large residual
```

Binary Logistic Regression: Malignant neck LNs versus PET done?, M stage, Tumour Type, Cohort

```
Method

Link function                 Logit
Categorical predictor coding  (1, 0)
Rows used                     191
Rows unused                   3
```

Response Information

Variable	Value	Count	
Malignant neck LNs	1	30	(Event)
	0	161	
	Total	191	

Deviance Table

Source	DF	Adj Dev	Adj Mean	Chi-Square	P-Value
Regression	4	41.578	10.3944	41.58	0.000
PET done?	1	21.389	21.3890	21.39	0.000
M stage	1	0.153	0.1533	0.15	0.695
Tumour Type	1	0.072	0.0725	0.07	0.788
Cohort	1	17.027	17.0268	17.03	0.000
Error	186	124.507	0.6694		
Total	190	166.084			

Model Summary

Deviance R-Sq	Deviance R-Sq(adj)	AIC
25.03%	22.63%	134.51

Coefficients

Term	Coef	SE Coef	VIF
Constant	-2.681	0.640	
PET done?			
1	-3.35	1.07	1.07
M stage			
1	-0.213	0.545	1.20
Tumour Type			
SCLC	-0.148	0.552	1.00
Cohort			
Plymouth	2.363	0.687	1.15

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI
PET done?			
1	0	0.0349	(0.0043, 0.2865)
M stage			
1	0	0.8078	(0.2777, 2.3501)
Tumour Type			
SCLC	NSCLC	0.8627	(0.2925, 2.5445)
Cohort			
Plymouth	Galway	10.6257	(2.7628, 40.8663)

Odds ratio for level A relative to level B

Regression Equation

P(1) = exp(Y')/(1 + exp(Y'))

Y' = -2.681 + 0.0 PET done?_0 - 3.35 PET done?_1 + 0.0 M stage_0 - 0.213 M stage_1
+ 0.0 Tumour Type_NSCLC - 0.148 Tumour Type_SCLC + 0.0 Cohort_Galway
+ 2.363 Cohort_Plymouth

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	186	124.51	1.000
Pearson	186	157.85	0.934
Hosmer-Lemeshow	4	2.53	0.639

Fits and Diagnostics for Unusual Observations

Obs	Observed Probability	Fit	Resid	Std Resid	
2	1.0000	0.3857	1.3804	1.46	X
4	1.0000	0.3857	1.3804	1.46	X
10	0.0000	0.3857	-0.9872	-1.04	X
21	1.0000	0.0248	2.7192	2.75	R
125	1.0000	0.0641	2.3441	2.37	R
129	1.0000	0.0641	2.3441	2.37	R
167	1.0000	0.0641	2.3441	2.37	R

R Large residual
X Unusual X

Binary Logistic Regression: Confirmed ma versus PET done?, Tumour Type, M stage, ...

Method

Link function	Logit
Categorical predictor coding	(1, 0)
Rows used	191
Rows unused	3

Response Information

Variable	Value	Count	
Confirmed malignant neck LNs	Yes	30	(Event)
	No	161	
	Total	191	

Deviance Table

Source	DF	Adj Dev	Adj Mean	Chi-Square	P-Value
Regression	5	48.098	9.6195	48.10	0.000
PET done?	1	17.931	17.9309	17.93	0.000
M stage	1	1.054	1.0539	1.05	0.305
Tumour Type	1	0.443	0.4434	0.44	0.505
Cohort	1	14.721	14.7212	14.72	0.000
Nodal stage	1	6.520	6.5199	6.52	0.011
Error	185	117.987	0.6378		
Total	190	166.084			

Model Summary

Deviance R-Sq	Deviance R-Sq(adj)	AIC
28.96%	25.95%	129.99

Coefficients

Term	Coef	SE Coef	VIF
Constant	-3.003	0.671	
PET done?			
1	-3.27	1.09	1.10
M stage			
1	-0.605	0.593	1.37
Tumour Type			
SCLC	-0.381	0.580	1.04
Cohort			
Plymouth (CT neck)	2.292	0.704	1.17
Nodal stage			
3	1.253	0.506	1.14

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI
PET done?			
1	0	0.0380	(0.0045, 0.3242)
M stage			
1	0	0.5458	(0.1707, 1.7450)
Tumour Type			
SCLC	NSCLC	0.6833	(0.2192, 2.1305)
Cohort			
Plymouth (CT neck)	Galway (No CT neck)	9.8905	(2.4866, 39.3399)
Nodal stage			
3	2	3.4992	(1.2969, 9.4417)

Odds ratio for level A relative to level B

Regression Equation

P(Yes) = exp(Y')/(1 + exp(Y'))

Y' = -3.003 + 0.0 PET done?_0 - 3.27 PET done?_1 + 0.0 M stage_0 - 0.605 M stage_1
+ 0.0 Tumour Type_NSCLC - 0.381 Tumour Type_SCLC + 0.0 Cohort_Galway (No CT neck)
+ 2.292 Cohort_Plymouth (CT neck) + 0.0 Nodal stage_2 + 1.253 Nodal stage_3

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	185	117.99	1.000
Pearson	185	161.04	0.898
Hosmer-Lemeshow	7	3.30	0.856

Fits and Diagnostics for Unusual Observations

Obs	Observed Probability	Fit	Resid	Std Resid	
2	1.0000	0.2511	1.6624	1.75	X
3	1.0000	0.6320	0.9580	1.01	X
4	1.0000	0.5399	1.1103	1.19	X
8	0.0000	0.6320	-1.4140	-1.49	X
10	0.0000	0.5399	-1.2461	-1.34	X
21	1.0000	0.0183	2.8287	2.86	R
125	1.0000	0.0473	2.4705	2.50	R
129	1.0000	0.1479	1.9549	2.02	R
167	1.0000	0.1479	1.9549	2.02	R

R Large residual
X Unusual X

Binary Logistic Regression: More than on versus PET done?, Tumour Type, M stage, ...

Method

Link function	Logit
Categorical predictor coding	(1, 0)
Rows used	191
Rows unused	3

Stepwise Selection of Terms

α to enter = 0.15, α to remove = 0.15

Response Information

Variable	Value	Count	
More than one procedure done	Yes	69	(Event)
	No	122	
	Total	191	

Deviance Table

Source	DF	Adj Dev	Adj Mean	Chi-Square	P-Value
Regression	2	36.83	18.415	36.83	0.000
Tumour Type	1	15.48	15.476	15.48	0.000
Cohort	1	22.89	22.891	22.89	0.000
Error	188	213.05	1.133		
Total	190	249.88			

Model Summary

Deviance R-Sq	Deviance R-Sq(adj)	AIC
14.74%	13.94%	219.05

Coefficients

Term	Coef	SE Coef	VIF
Constant	0.538	0.252	
Tumour Type			
SCLC	-1.941	0.578	1.02
Cohort			
Plymouth (CT neck)	-1.552	0.337	1.02

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI
Tumour Type			
SCLC	NSCLC	0.1436	(0.0462, 0.4460)
Cohort			
Plymouth (CT neck)	Galway (No CT neck)	0.2118	(0.1095, 0.4097)

Odds ratio for level A relative to level B

Regression Equation

P(Yes) = exp(Y')/(1 + exp(Y'))

Y' = 0.538 + 0.0 Tumour Type_NSCLC - 1.941 Tumour Type_SCLC + 0.0 Cohort_Galway (No CT neck)
- 1.552 Cohort_Plymouth (CT neck)

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	188	213.05	0.102
Pearson	188	202.34	0.225
Hosmer-Lemeshow	7	5.82	0.561

Fits and Diagnostics for Unusual Observations

Obs	Observed Probability	Fit	Resid	Std Resid	
61	1.0000	0.0495	2.4518	2.47	R
99	1.0000	0.0495	2.4518	2.47	R
117	0.0000	0.1974	-0.6631	-0.68	X
118	0.0000	0.1974	-0.6631	-0.68	X
126	0.0000	0.1974	-0.6631	-0.68	X
130	1.0000	0.1974	1.8015	1.85	X
133	0.0000	0.1974	-0.6631	-0.68	X
134	0.0000	0.1974	-0.6631	-0.68	X
135	0.0000	0.1974	-0.6631	-0.68	X
136	0.0000	0.1974	-0.6631	-0.68	X
152	0.0000	0.1974	-0.6631	-0.68	X
159	0.0000	0.1974	-0.6631	-0.68	X
160	0.0000	0.1974	-0.6631	-0.68	X
161	1.0000	0.1974	1.8015	1.85	X
162	0.0000	0.1974	-0.6631	-0.68	X
163	0.0000	0.1974	-0.6631	-0.68	X
164	0.0000	0.1974	-0.6631	-0.68	X

R Large residual
X Unusual X

Binary Logistic Regression: More than on versus PET done?, Tumour Type, M stage, ...

Method

Link function	Logit
Categorical predictor coding	(1, 0)
Rows used	191
Rows unused	3

Stepwise Selection of Terms

α to enter = 0.15, α to remove = 0.15

Response Information

Variable	Value	Count	
More than one procedure done	Yes	69	(Event)
	No	122	
	Total	191	

Deviance Table

Source	DF	Adj Dev	Adj Mean	Chi-Square	P-Value
Regression	2	36.83	18.415	36.83	0.000
Tumour Type	1	15.48	15.476	15.48	0.000
Cohort	1	22.89	22.891	22.89	0.000
Error	188	213.05	1.133		
Total	190	249.88			

Model Summary

Deviance R-Sq	Deviance R-Sq(adj)	AIC
14.74%	13.94%	219.05

Coefficients

Term	Coef	SE Coef	VIF
Constant	0.538	0.252	
Tumour Type			
SCLC	-1.941	0.578	1.02
Cohort			
Plymouth (CT neck)	-1.552	0.337	1.02

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI
Tumour Type			
SCLC	NSCLC	0.1436	(0.0462, 0.4460)
Cohort			
Plymouth (CT neck)	Galway (No CT neck)	0.2118	(0.1095, 0.4097)

Odds ratio for level A relative to level B

Regression Equation

P(Yes) = exp(Y')/(1 + exp(Y'))

Y' = 0.538 + 0.0 Tumour Type_NSCLC - 1.941 Tumour Type_SCLC + 0.0 Cohort_Galway (No CT neck)
- 1.552 Cohort_Plymouth (CT neck)

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	188	213.05	0.102
Pearson	188	202.34	0.225
Hosmer-Lemeshow	7	5.82	0.561

Fits and Diagnostics for Unusual Observations

Obs	Observed Probability	Fit	Resid	Std Resid	
61	1.0000	0.0495	2.4518	2.47	R
99	1.0000	0.0495	2.4518	2.47	R
117	0.0000	0.1974	-0.6631	-0.68	X
118	0.0000	0.1974	-0.6631	-0.68	X
126	0.0000	0.1974	-0.6631	-0.68	X
130	1.0000	0.1974	1.8015	1.85	X
133	0.0000	0.1974	-0.6631	-0.68	X
134	0.0000	0.1974	-0.6631	-0.68	X
135	0.0000	0.1974	-0.6631	-0.68	X
136	0.0000	0.1974	-0.6631	-0.68	X
152	0.0000	0.1974	-0.6631	-0.68	X
159	0.0000	0.1974	-0.6631	-0.68	X
160	0.0000	0.1974	-0.6631	-0.68	X
161	1.0000	0.1974	1.8015	1.85	X
162	0.0000	0.1974	-0.6631	-0.68	X
163	0.0000	0.1974	-0.6631	-0.68	X
164	0.0000	0.1974	-0.6631	-0.68	X

R Large residual
X Unusual X

Binary Logistic Regression: More than on versus PET done?, Tumour Type, M stage, ...

Method

Link function	Logit
Categorical predictor coding	(1, 0)
Rows used	191
Rows unused	3

Response Information

Variable	Value	Count	
More than one procedure done	Yes	69	(Event)
	No	122	
	Total	191	

Deviance Table

Source	DF	Adj Dev	Adj Mean	Chi-Square	P-Value
Regression	5	39.271	7.8543	39.27	0.000
PET done?	1	1.940	1.9396	1.94	0.164
M stage	1	1.355	1.3553	1.36	0.244
Tumour Type	1	13.641	13.6411	13.64	0.000
Cohort	1	23.782	23.7825	23.78	0.000
Nodal stage	1	0.000	0.0001	0.00	0.993
Error	185	210.609	1.1384		
Total	190	249.881			

Model Summary

Deviance R-Sq	Deviance R-Sq(adj)	AIC
15.72%	13.72%	222.61

Coefficients

Term	Coef	SE Coef	VIF
Constant	0.193	0.346	
PET done?			
1	0.530	0.383	1.24
M stage			
1	0.463	0.401	1.43
Tumour Type			
SCLC	-1.848	0.581	1.03
Cohort			
Plymouth (CT neck)	-1.719	0.372	1.23
Nodal stage			
3	-0.003	0.375	1.13

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI
PET done?			
1	0	1.6996	(0.8031, 3.5970)
M stage			
1	0	1.5884	(0.7237, 3.4861)
Tumour Type			
SCLC	NSCLC	0.1575	(0.0505, 0.4917)
Cohort			
Plymouth (CT neck)	Galway (No CT neck)	0.1792	(0.0865, 0.3714)
Nodal stage			
3	2	0.9968	(0.4776, 2.0805)

Odds ratio for level A relative to level B

Regression Equation

P(Yes) = exp(Y')/(1 + exp(Y'))

Y' = 0.193 + 0.0 PET done?_0 + 0.530 PET done?_1 + 0.0 M stage_0 + 0.463 M stage_1
+ 0.0 Tumour Type_NSCLC - 1.848 Tumour Type_SCLC + 0.0 Cohort_Galway (No CT neck)
- 1.719 Cohort_Plymouth (CT neck) + 0.0 Nodal stage_2 - 0.003 Nodal stage_3

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	185	210.61	0.095
Pearson	185	200.57	0.206
Hosmer-Lemeshow	7	7.74	0.356

Fits and Diagnostics for Unusual Observations

Obs	Observed Probability	Fit	Resid	Std Resid	
61	1.0000	0.0515	2.4360	2.46	R
99	1.0000	0.0515	2.4360	2.46	R

R Large residual

Binary Logistic Regression: More than one pr versus PET done?, Cohort, M stage, Nodal stage

Method

Link function	Logit
Categorical predictor coding	(1, 0)
Rows used	191
Rows unused	3

Response Information

Variable	Value	Count	
More than one procedure done	Yes	69	(Event)
	No	122	
	Total	191	

Deviance Table

Source	DF	Adj Dev	Adj Mean	Chi-Square	P-Value
Regression	4	25.630	6.4076	25.63	0.000
PET done?	1	3.754	3.7540	3.75	0.053
M stage	1	1.709	1.7095	1.71	0.191
Cohort	1	22.867	22.8669	22.87	0.000
Nodal stage	1	0.005	0.0049	0.00	0.944
Error	186	224.250	1.2056		
Total	190	249.881			

Model Summary

Deviance R-Sq	Deviance R-Sq(adj)	AIC
10.26%	8.66%	234.25

Coefficients

Term	Coef	SE Coef	VIF
Constant	-0.190	0.316	
PET done?			
1	0.704	0.367	1.22
M stage			
1	0.496	0.383	1.40
Cohort			
Plymouth (CT neck)	-1.637	0.359	1.23
Nodal stage			
3	-0.025	0.362	1.13

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI
PET done?			
1	0	2.0225	(0.9860, 4.1487)
M stage			
1	0	1.6413	(0.7749, 3.4767)
Cohort			
Plymouth (CT neck)	Galway (No CT neck)	0.1945	(0.0962, 0.3930)
Nodal stage			
3	2	0.9749	(0.4796, 1.9815)

Odds ratio for level A relative to level B

Regression Equation

P(Yes) = exp(Y')/(1 + exp(Y'))

Y' = -0.190 + 0.0 PET done?_0 + 0.704 PET done?_1 + 0.0 M stage_0 + 0.496 M stage_1
+ 0.0 Cohort_Galway (No CT neck) - 1.637 Cohort_Plymouth (CT neck) + 0.0 Nodal stage_2
- 0.025 Nodal stage_3

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	186	224.25	0.029
Pearson	186	189.61	0.413
Hosmer-Lemeshow	6	5.78	0.449

Fits and Diagnostics for Unusual Observations

Obs	Observed Probability	Fit	Resid	Std Resid	
20	1.0000	0.1386	1.9882	2.01	R

R Large residual

Binary Logistic Regression: More than on versus PET done?, Cohort, M stage, Nodal stage, ...

Method

Link function	Logit
Categorical predictor coding	(1, 0)
Rows used	191
Rows unused	3

Stepwise Selection of Terms

α to enter = 0.2, α to remove = 0.2

Response Information

Variable	Value	Count	
More than one procedure done	Yes	69	(Event)
	No	122	
	Total	191	

Deviance Table

Source	DF	Adj Dev	Adj Mean	Chi-Square	P-Value
Regression	2	36.83	18.415	36.83	0.000
Cohort	1	22.89	22.891	22.89	0.000
Tumour Type	1	15.48	15.476	15.48	0.000
Error	188	213.05	1.133		
Total	190	249.88			

Model Summary

Deviance R-Sq	Deviance R-Sq(adj)	AIC
14.74%	13.94%	219.05

Coefficients

Term	Coef	SE Coef	VIF
Constant	0.538	0.252	
Cohort			
Plymouth (CT neck)	-1.552	0.337	1.02
Tumour Type			
SCLC	-1.941	0.578	1.02

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI
Cohort			
Plymouth (CT neck)	Galway (No CT neck)	0.2118	(0.1095, 0.4097)
Tumour Type			
SCLC	NSCLC	0.1436	(0.0462, 0.4460)

Odds ratio for level A relative to level B

Regression Equation

P(Yes) = exp(Y')/(1 + exp(Y'))

Y' = 0.538 + 0.0 Cohort_Galway (No CT neck) - 1.552 Cohort_Plymouth (CT neck)
+ 0.0 Tumour Type_NSCLC - 1.941 Tumour Type_SCLC

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	188	213.05	0.102
Pearson	188	202.34	0.225
Hosmer-Lemeshow	7	5.82	0.561

Fits and Diagnostics for Unusual Observations

Obs	Observed Probability	Fit	Resid	Std Resid	
61	1.0000	0.0495	2.4518	2.47	R
99	1.0000	0.0495	2.4518	2.47	R
117	0.0000	0.1974	-0.6631	-0.68	X
118	0.0000	0.1974	-0.6631	-0.68	X
126	0.0000	0.1974	-0.6631	-0.68	X
130	1.0000	0.1974	1.8015	1.85	X
133	0.0000	0.1974	-0.6631	-0.68	X
134	0.0000	0.1974	-0.6631	-0.68	X
135	0.0000	0.1974	-0.6631	-0.68	X
136	0.0000	0.1974	-0.6631	-0.68	X
152	0.0000	0.1974	-0.6631	-0.68	X
159	0.0000	0.1974	-0.6631	-0.68	X
160	0.0000	0.1974	-0.6631	-0.68	X
161	1.0000	0.1974	1.8015	1.85	X
162	0.0000	0.1974	-0.6631	-0.68	X
163	0.0000	0.1974	-0.6631	-0.68	X
164	0.0000	0.1974	-0.6631	-0.68	X

R Large residual
X Unusual X

Binary Logistic Regression: Confirmed ma versus PET done?, Cohort, M stage, Nodal stage, ...

Method

Link function	Logit
Categorical predictor coding	(1, 0)
Rows used	191
Rows unused	3

Stepwise Selection of Terms

α to enter = 0.2, α to remove = 0.2

Response Information

Variable	Value	Count	
Confirmed malignant neck LNs	Yes	30	(Event)
	No	161	
	Total	191	

Deviance Table

Source	DF	Adj Dev	Adj Mean	Chi-Square	P-Value
Regression	3	46.695	15.5651	46.70	0.000
PET done?	1	17.151	17.1510	17.15	0.000
Cohort	1	14.033	14.0332	14.03	0.000
Nodal stage	1	5.338	5.3377	5.34	0.021
Error	187	119.389	0.6384		
Total	190	166.084			

Model Summary

Deviance R-Sq	Deviance R-Sq(adj)	AIC
28.12%	26.31%	127.39

Coefficients

Term	Coef	SE Coef	VIF
Constant	-3.234	0.648	
PET done?			
1	-2.95	1.05	1.01
Cohort			
Plymouth (CT neck)	2.059	0.652	1.01
Nodal stage			
3	1.075	0.475	1.02

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI
PET done?			
1	0	0.0524	(0.0067, 0.4067)
Cohort			
Plymouth (CT neck)	Galway (No CT neck)	7.8411	(2.1861, 28.1247)
Nodal stage			
3	2	2.9307	(1.1541, 7.4423)

Odds ratio for level A relative to level B

Regression Equation

P(Yes) = exp(Y')/(1 + exp(Y'))

Y' = -3.234 + 0.0 PET done?_0 - 2.95 PET done?_1 + 0.0 Cohort_Galway (No CT neck)
+ 2.059 Cohort_Plymouth (CT neck) + 0.0 Nodal stage_2 + 1.075 Nodal stage_3

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	187	119.39	1.000
Pearson	187	178.20	0.666
Hosmer-Lemeshow	6	2.19	0.901

Fits and Diagnostics for Unusual Observations

Obs	Observed Probability	Fit	Resid	Std Resid	
21	1.0000	0.0159	2.8776	2.90	R
125	1.0000	0.0379	2.5585	2.58	R
129	1.0000	0.1035	2.1299	2.17	R
167	1.0000	0.1035	2.1299	2.17	R

R Large residual

Binary Logistic Regression: EBUS versus PET done?, Cohort, M stage, Nodal stage, Tumour Type

Method

Link function	Logit
Categorical predictor coding	(1, 0)
Rows used	191
Rows unused	3

Stepwise Selection of Terms

α to enter = 0.2, α to remove = 0.2

Response Information

Variable	Value	Count	
EBUS	1	110	(Event)
	0	81	
	Total	191	

Deviance Table

Source	DF	Adj Dev	Adj Mean	Chi-Square	P-Value
Regression	4	73.726	18.431	73.73	0.000
PET done?	1	26.749	26.749	26.75	0.000
M stage	1	4.945	4.945	4.95	0.026
Cohort	1	16.013	16.013	16.01	0.000
Tumour Type	1	4.560	4.560	4.56	0.033
Error	186	186.636	1.003		
Total	190	260.362			

Model Summary

Deviance R-Sq	Deviance R-Sq(adj)	AIC
28.32%	26.78%	196.64

Coefficients

Term	Coef	SE Coef	VIF
Constant	1.249	0.367	
PET done?			
1	2.132	0.449	1.15
M stage			
1	-0.865	0.387	1.13
Cohort			
Plymouth (CT neck)	-1.559	0.405	1.20
Tumour Type			
SCLC	-0.952	0.453	1.03

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI
PET done?			
1	0	8.4281	(3.4963, 20.3163)
M stage			
1	0	0.4210	(0.1971, 0.8991)
Cohort			
Plymouth (CT neck)	Galway (No CT neck)	0.2103	(0.0950, 0.4656)
Tumour Type			
SCLC	NSCLC	0.3858	(0.1588, 0.9375)

Odds ratio for level A relative to level B

Regression Equation

P(1) = exp(Y')/(1 + exp(Y'))

Y' = 1.249 + 0.0 PET done?_0 + 2.132 PET done?_1 + 0.0 M stage_0 - 0.865 M stage_1
+ 0.0 Cohort_Galway (No CT neck) - 1.559 Cohort_Plymouth (CT neck)
+ 0.0 Tumour Type_NSCLC - 0.952 Tumour Type_SCLC

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	186	186.64	0.473
Pearson	186	211.41	0.097
Hosmer-Lemeshow	6	3.20	0.783

Fits and Diagnostics for Unusual Observations

Obs	Observed Probability	Fit	Resid	Std Resid		
21	0.0000	0.8607	-1.9855	-2.01	R	
39	0.0000	0.8607	-1.9855	-2.01	R	
40	0.0000	0.8607	-1.9855	-2.01	R	
42	0.0000	0.8607	-1.9855	-2.01	R	
67	0.0000	0.5009	-1.1789	-1.23		X
106	1.0000	0.5009	1.1759	1.23		X
107	1.0000	0.5009	1.1759	1.23		X
170	0.0000	0.9671	-2.6129	-2.62	R	
187	0.0000	0.9671	-2.6129	-2.62	R	

R Large residual
X Unusual X

Appendix VI: First author publications from this thesis

ORIGINAL ARTICLE
LUNG CANCER

Routine neck ultrasound by respiratory physicians in the diagnosis and staging of patients with lung cancer and mediastinal lymphadenopathy: a prospective pilot study

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ABSTRACT

Introduction: Cervical lymphadenopathy in lung cancer indicates advanced disease. The presence of mediastinal lymphadenopathy is commonly associated with involvement of neck lymph nodes and some studies suggest routine neck ultrasound (NUS) in this group of patients. We conducted a two-phase study looking at training a respiratory physician to perform ultrasound-guided neck lymph node aspiration in patients with suspected lung cancer.

Methods: In the first phase of the study, one of the authors underwent training in NUS according to predetermined criteria. The adequacy of sampling was prospectively recorded. In the second phase, consecutive patients with suspected lung cancer and mediastinal lymphadenopathy underwent NUS and sampling of abnormal lymph nodes. The outcomes were the adequacy of samples for pathological analysis and molecular analysis, prevalence of cervical lymphadenopathy, and change in stage.

Results: Following the period of training, 35 patients underwent neck node sampling with an overall adequacy of 88.6% (95% CI 78.1–99.1%). Cervical lymph node involvement was confirmed in 13 out of 30 patients with lung cancer (43.3%, 95% CI 25.5–62.6%). Further immunohistochemistry and molecular studies were possible in all patients when it was required (nine cases). NUS led to nodal upstaging in four out of 30 (13.3%) cases.

Conclusion: Training a respiratory physician to perform NUS and needle sampling to an acceptable level is feasible. Benefits of embedding this procedure in lung cancer diagnosis and pathway staging need to be explored in further studies.

@ERSpublications
It is feasible to train respiratory physicians to perform ultrasound-guided sampling of cervical lymph nodes. In lung cancer patients with mediastinal lymphadenopathy, 43% had cervical lymph node involvement with reduction in the number requiring EBUS. http://bit.ly/33LekBa

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This study is registered at ClinicalTrials.gov with identifier number NCT03970564.

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Introduction

Lung cancer prognosis and mortality remain poor, as currently >60% of patients present with advanced disease (stage IIIB or IV), where the only treatment options are noncurative systemic drug therapies and/or radiotherapy [1]. Accurate staging is required to inform on management, with respiratory physicians being the key interface, as the receivers of referrals and as part of the multidisciplinary teams. Furthermore, an expedited diagnostic and staging process is needed to avoid any deterioration in the functional status of patients rendering them unfit for treatment. To achieve such an expedited pathway where possible, the safest, highest yield diagnostic procedure should be performed to achieve both a diagnosis and a stage while providing enough tissue for analysis for targeted treatments such as immunotherapy and tyrosine kinase inhibitors [2].

Cervical lymph nodes are frequently involved in lung cancer [3]. The presence of cervical lymphadenopathy in patients with lung cancer is consistent with N3 or M1b disease depending on which level is involved, with significant impact on prognosis [4]. Clinical examination is unreliable, while staging computed tomography (CT) scans may not include the full neck in some centres [5]. Ultrasound examination confers the optimal assessment. Among patients with mediastinal lymphadenopathy, cervical lymph nodes were found to be involved in up to 50% of cases [6], leading to some guidelines recommending neck ultrasound (NUS) in patients with suspected lung cancer and bulky mediastinal lymphadenopathy [2]. Cervical node disease might also impact the radiotherapy planning fields and their involvement should therefore be accurately determined in such circumstances.

Needle sampling of cervical lymph nodes under direct ultrasound guidance is a safe and low-cost option. However, access to radiology for such a procedure might limit its time-saving value as a part of the diagnostic pathway. The literature supports the performance of such procedures by nonradiologists [7, 8], but no prospective studies have been performed for respiratory physicians and nor is training standardised. In this study, we aimed to prospectively assess the feasibility of training a respiratory physician to perform routine NUS and subsequent needle sampling of lymph nodes among patients with suspected lung cancer and mediastinal lymphadenopathy before endobronchial ultrasound (EBUS).

Methods

This was a prospective study conducted in Galway University Hospital (Galway, Ireland). The study was conducted in two phases. In the first phase, one of the authors (M.A.) was trained in performing NUS and cervical lymph node sampling, and sampling adequacy was recorded prospectively. This author had Level 1 Royal College of Radiologists training and limited experience performing EBUS when the study was commenced. In the second phase, a prospective study of NUS in patients with suspected lung cancer and mediastinal lymphadenopathy was conducted.

Phase 1: training the respiratory physician in NUS and needle sampling

Training in NUS and lymph node sampling was performed in a tertiary lung cancer centre (University Hospitals Plymouth NHS Trust, Plymouth, UK) supported by a fellowship from the European Respiratory Society under supervision of a respiratory physician (C.D.) with 5 years of experience in NUS and lymph node sampling.

The training structure was divided into five blocks. 1) Supervised NUS examination, including a predetermined number of normal and abnormal NUSs and achieving specified competencies requiring identification of normal and abnormal structures in the neck as outlined in table 1. 2) Attendance at the neck lumps clinic led by radiologists and ear, nose and throat surgeons, and observing procedures. 3) A period of observation in the pathology department to further understand the optimal sampling requirements. 4) Use of simulation tools (gelatine model with node-like structures for real-time ultrasound guidance practice). 5) Supervised neck node sampling with use of needle/core needle handling further supported by D.B.

The duration of training was 8 h per week for 10 weeks. Competencies listed in table 1 were assessed at the end of the training period. A prospective record of all NUS and needle sampling procedures performed was kept, including the adequacy and diagnostic yield of all samples over time.

Phase 2

Setting

In Galway University Hospital, all patients referred with suspected lung cancer are assessed in the interventional respiratory unit through a rapid access service. All patients have thorax and upper abdomen CT with contrast followed by further workup according to CT findings, but a diagnostic procedure such as bronchoscopy, EBUS or pleural fluid sampling is usually performed on the same day as CT in most patients. Positron emission tomography (PET) was done for patients with evidence of potentially curable disease on initial CT.

TABLE 1 Requirements for neck ultrasound (NUS) training: procedure numbers and competencies to be acquired

NUS training number requirements
Observing 20 NUSs
Performing 20 detailed normal NUSs
Performing 10 NUSs in patients with abnormal appearing lymph nodes
Performing 10 ultrasound-guided fine-needle aspirations under direct supervision
NUS competencies to be acquired
Recognition of normal muscle anatomy
Identification of carotid arteries and jugular veins using colour flow Doppler
Identification of the thyroid gland
Identification of the submandibular and parotid salivary glands
Identification of normal appearance of lymph nodes
Identification of abnormal features of lymph nodes[#]
Measuring lymph node short and long diameters
Needle aspiration of abnormal appearing lymph node

[#]: including shape, size, hilar structures, necrosis and lymph node blood flow on Doppler.

Patients

All consecutive patients with suspected and later confirmed primary lung cancer and evidence of mediastinal lymphadenopathy on CT that were referred to the interventional respiratory unit in Galway University Hospital were approached to participate in the study. Written informed consent was obtained. Exclusion criteria included age <18 years, history of any malignancy apart from nonmelanoma skin cancer and inability to give informed consent. Mediastinal lymphadenopathy was defined as a short diameter on CT of ⩾10 mm.

Procedures

Neck ultrasound

A NUS was performed in all patients included. The ultrasound examination was performed with patients lying in a semisupine position using a linear ultrasound probe with a frequency of 5–12 MHz using one of two machines: Zonare Z.One Ultra (Zonare, Mountain View, CA, USA) or Hitachi EUB-7500A (Hitachi, Tokyo, Japan). Initially, the thyroid isthmus was identified and, once visualised, the probe was moved laterally to identify the carotid artery and internal jugular vein. The probe was then oriented horizontally and moved to assess the anterior cervical chain, and this was again repeated with the probe oriented vertically. The posterior cervical chain was then assessed before finally assessing the supraclavicular fossa. The same was repeated for the contralateral neck. The lower cricoid border was used as the landmark to differentiate N3 and M1 lymph nodes.

Needle sampling

If any neck lymph nodes were identified, these were further assessed for size, shape, hilar structures and necrosis. Lymph nodes with a short axis >5 mm were considered targets for sampling, and nearby vascular structures and location relative to the pleural lining were considered before proceeding. Sampling was performed under direct ultrasound visualisation following informed written consent. The equipment used in the sampling kit is outlined in table 2. The area was cleaned using chlorhexidine wash and 1% or 2%

TABLE 2 List of equipment used for ultrasound-guided needle sampling of cervical lymph nodes

Orange needles	Formalin sample pots
Dressing packs	Sterile gloves (large)
Chlorhexidine	Post-procedure dressing (small clear dressing)
Sterile field (rectangular)	Green needles
Sterile gel	Blue needles
Ultrasound probe sterile sheaths	10 mL syringe
Lidocaine 1% 10 mL vials	Glass slides
Slide holder case	18G core needle

lidocaine was applied intradermally and subcutaneously to provide local anaesthesia. A sterile sheath was applied to the ultrasound probe. Under direct ultrasound guidance, a 22G needle was used to obtain samples. The first pass was used to make slides and two or three further passes were performed with samples sent in a formalin container. If well tolerated and technically feasible, two or three core needle biopsies (CNBs) were obtained from lymph nodes using an 18G SuperCore needle (Aragon Medical Devices, Frisco, TX, USA) with all material sent in a formalin container.

Lung cancer workup

As this was a pilot study, all lung cancer workup was continued as standard unless the results from neck lymph node sampling came back positive before a planned diagnostic procedure, in which case this was cancelled. This meant that based on the setting in Galway University Hospital it was expected that some patients would have both EBUS- and NUS-guided sampling performed in the same session.

Outcomes

The primary outcomes of interest in the study were 1) the diagnostic yield of malignant cervical lymphadenopathy defined as pathological evidence of cancer in neck lymph node samples consistent with a lung primary and 2) adequacy of needle sampling. Secondary outcomes included 1) patient-reported experience assessed by a visual analogue of discomfort associated with needle neck sampling and EBUS, and 2) the proportion of patients that had nodal upstaging. Patients who underwent both EBUS- and NUS-guided needle sampling were asked which procedure they preferred and why. The suitability of neck samples for molecular analysis when indicated was also reported. Potential complications of needle sampling (significant bleeding requiring prolonged compression and infection) were also recorded.

Statistical analysis

Categorical variables are reported as frequencies and percentages with associated 95% confidence intervals; continuous variables are reported as mean and standard deviations or median and interquartile range. Cumulative sampling adequacy rate is reported as percentage over time. A p-value of <0.05 was considered significant. Minitab 18 (Minitab, State College, PA, USA) was used to conduct the statistical analysis. As this was a pilot study, sample size was not calculated.

Ethics and trial registration

The study was approved by the Galway University Hospital research ethics committee (approval 54/08) and registered at ClinicalTrials.gov with identifier number NCT03970564.

Results

Training commenced in NUS in October 2016 and the study was completed in May 2018. During this period, 146 NUSs were performed with 35 needle sampling procedures in 28 patients. Fine-needle aspiration (FNA) was performed in all 28 cases and CNB in seven (25%) cases. The overall sampling adequacy was 88.6% (95% CI 74.1–95.5%) (FNA 89.7% *versus* CNB 85.7%; p=0.76). Figure 1 shows the cumulative overall sampling adequacy over time. No adverse events were reported for any of the procedures.

During the second phase of the study (February 2017–May 2018), 44 patients meeting the inclusion criteria were identified; 30 were included in the final study analysis (figure 2). Among those included, 76.7% (n=23) were referred through the rapid access clinic, while 23.3% (n=7) presented through the emergency department. Table 3 shows the baseline characteristics of all patients included and the clinical stage on the initial CT.

Enlarged cervical lymph nodes were detected in 14 out of 30 (46%) patients and sampling was performed in all cases. Sampled material was adequate in 13 out of 14 (92.9%) cases. A diagnosis of metastatic cervical lymphadenopathy from lung cancer was confirmed in 13 out of 30 (43.3%, 95% CI 25.5–62.6%) cases. Mean lymph node short diameter was 11±4 mm. All lymph nodes were located below the cricoid cartilage. Location of lymphadenopathy in the 13 cases was right side in six cases, left side in one case and bilateral in six cases. Immunohistochemistry was possible in all samples. No significant complications were reported after any of the procedures. PET-CT was performed in 13 out of 30 (43.3%) cases. In this group that had PET-CT, six out of 13 cases had evidence of cervical lymphadenopathy and four out of six cases were confirmed on ultrasound-guided FNA with a false-positive rate for PET of 33.3%. PET-CT was not associated with any false negatives.

Molecular analysis was requested on six samples from patients with adenocarcinoma and was possible in all cases. Testing for programmed death ligand-1 was also requested and performed in three cases.

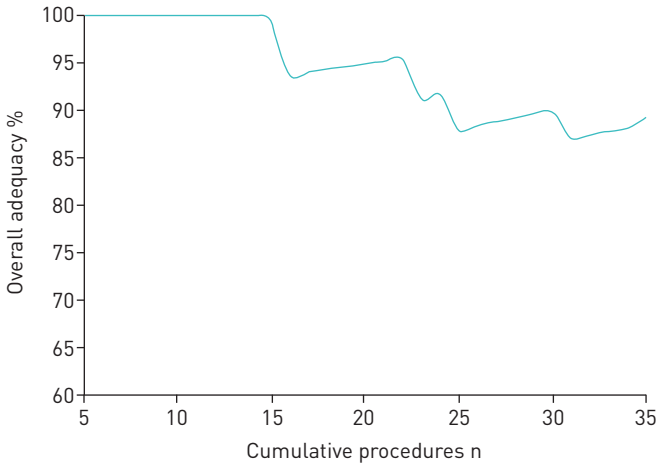

FIGURE 1 Cumulative adequacy of cervical lymph node sampling over time.

Performing NUS led to upstaging the clinical nodal status from cN2 to cN3 in four cases (13.3%). Overall, NUS-guided lymph node sampling was the only procedure performed to obtain tissue in seven out of 30 (23.3%) cases, but four out of seven (57.1%) in those presenting through the emergency department. Other procedures to obtain tissue samples were performed in 23 out of 30 (76.7%) patients, including EBUS in 17 cases, bronchoscopy in five cases, pleural tap in one case and mediastinoscopy followed by surgical resection in one case.

Data on patient experience were available for only six patients who underwent both neck lymph node sampling and EBUS in the same session. When asked in the recovery room which procedure would the patient prefer, four picked neck lymph node sampling compared with two that picked EBUS. All patients reported they would definitely be willing to return for both procedures if required.

Discussion

In this prospective study, we showed that it is feasible to train a respiratory physician to perform ultrasound-guided cervical lymph node needle sampling and maintain an acceptable level of sampling adequacy. At no stage did the cumulative sampling adequacy fall below 85%, which is the recommendation made by the Royal College of Radiologists for nonradiologists performing ultrasound-guided neck sampling [9]. The overall sampling adequacy was 88.6% and adequacy for FNAs was 89.7%. Sampling adequacy did seem to fall initially, likely due to sampling of more challenging lymph nodes over time.

The study showed a significant proportion of patients with lung cancer and mediastinal lymphadenopathy also had cervical lymph node involvement when NUS was performed routinely by a trained respiratory physician. The proportion of patients that had cervical lymph node involvement in the study was 43.3%, consistent with similar previous studies. Kumaran *et al.* [6] performed routine NUS conducted by radiologists in 101 patients with suspected and later on confirmed lung cancer, and found evidence of cervical lymph node involvement in 50% of cases, with nine out of 101 (9%) patients upstaged from radiographical N2M0 to N3M0 disease. A comparison of routine neck CT, ultrasound and palpation for

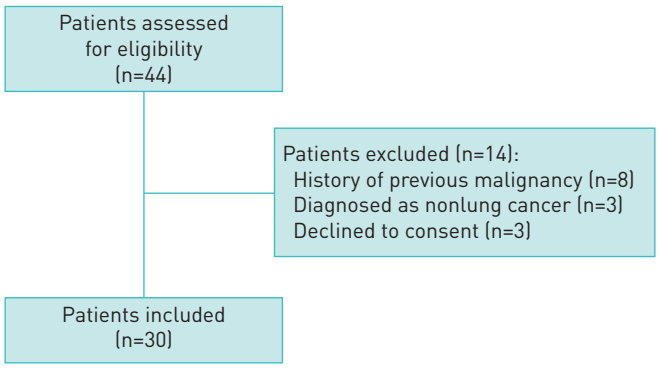

FIGURE 2 Participation flowchart detailing breakdown of patients assessed for inclusion in the second phase of the study.

TABLE 3 Baseline characteristics of all patients included in the second phase of the study

Patients	30
Age years	68.9±9.6
Male	18 (60.0)
Presentation	
Outpatient	23 (76.7)
Emergency admission	7 (23.3)
ECOG Performance Status	
0	6 (20.0)
1	15 (50.0)
2	8 (26.7)
3	1 (3.3)
Nodal stage#	
N2	20 (66.7)
N3	10 (33.3)
Metastatic disease	12 (40.0)
Cancer subtype	
Small cell lung cancer	6 (20.0)
Adenocarcinoma	16 (53.3)
Squamous cell carcinoma	8 (26.7)
NSCLC NOS	0

Data are presented as n, mean±SD or n (%). ECOG: Eastern Cooperative Oncology Group; NSCLC NOS: nonsmall cell lung cancer not otherwise specified. #: nodal stage defined by computed tomography.

the detection of cervical lymphadenopathy in 50 patients with lung cancer regardless of nodal stage on CT confirmed malignant cervical lymphadenopathy in 40% [3].

Ultrasound-guided cervical lymph node sampling is appealing as a procedure to be embedded in the diagnostic and staging pathway for lung cancer patients, especially if done by respiratory physicians. This can be considered as a test of choice following discussion at a diagnostic multidisciplinary team meeting when planning investigations for patients with suspected lung cancer on an individual basis, especially in cases with borderline performance status. Such a procedure can be performed in the clinic, does not require sedation with the logistic implications of a recovery time and is cheaper compared with other nodal staging procedures, *e.g.* EBUS and mediastinoscopy. In addition, a previous study showed PET-CT had only limited added staging benefit when done following NUS in patients with at least N2 disease on CT scan [10].

Within this study, six patients underwent both EBUS- and NUS-guided FNA in the same session, and there was no difference in the level of discomfort reported for the two procedures or the level of willingness to return for a repeat procedure was high (although the study was not powered to detect a difference in patient-reported outcomes between the two procedures). Further molecular studies were possible in all cervical lymph node samples when this was required, supporting the findings in a previous retrospective study of 171 cervical lymph nodes sampled from patients with lung cancer where further molecular studies were feasible in 85% of cases [11].

The study had some limitations. As this was a study with one operator, it is not possible to say whether the results were generalisable. Factors that might affect sampling adequacy such as lymph node size were not accounted for. The study was not designed to assess the impact of routine NUS on the average time to a final diagnosis/stage and this will need to be examined prospectively in a randomised study.

This study demonstrates the feasibility of training respiratory physicians to perform ultrasound-guided cervical lymph node sampling to an acceptable standard. Based on this study and previous literature, we recommend considering NUS through a multidisciplinary meeting in a selected group of patients, but not routinely. At this time PET-CT would likely be part of that decision making. Embedding routine NUS performed by respiratory physicians in the pathway of investigating patients with suspected lung cancer can potentially lead to more accurate staging in addition to time and cost savings, but this will need to be examined in further studies, which will likely include PET-CT as part of the algorithm

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Conflict of interest: None declared.

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Clinical Investigations

Respiration

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PET and Neck Ultrasound for the Detection of Cervical Lymphadenopathy in Patients with Lung Cancer and Mediastinal Lymphadenopathy

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Keywords
Lung cancer · Cervical lymphadenopathy · Ultrasound · Positron emission tomography

Abstract
Background: Cervical lymph nodes are frequently involved in patients with lung cancer and indicate inoperability. Some guidelines recommend neck ultrasound (NUS) in patients with bulky mediastinal lymphadenopathy. Positron emission tomography (PET) is indicated for patients with potentially curable disease. ***Objectives:*** We aimed to assess the diagnostic yield of NUS and the diagnostic accuracy of PET for cervical lymphadenopathy in this group with a high pre-test probability of N3 disease. ***Methods:*** Records of all patients with lung cancer who underwent an NUS over a consecutive 5-year period were reviewed. Only patients with mediastinal lymphadenopathy on computerised tomography (CT) were included. The diagnostic accuracy of PET was assessed with NUS-guided fine needle aspiration cytology used as the reference test. ***Results:*** During the study period, 123 patients met the inclusion criteria. Malignant cervical lymphadenopathy was confirmed in 49/123 (39.8% [95% CI 31.1–49.1]). PET-CT had a specificity of 81.1%, sensitivity of 87.5%, negative predictive value of 96.8% and positive predictive value of 50% for the detection of cervical lymphadenopathy, and it contributed no additional staging information in the neck area. Overall, PET led to a change in management in only 2.2% of cases. ***Conclusion:*** A significant proportion of patients with lung cancer and mediastinal lymphadenopathy have cervical lymphadenopathy detected by NUS. In this group of patients, PET offers minimal additional value in staging and management.

Introduction

Patients with lung cancer frequently present at an advanced stage [1]. Decisions regarding treatment depends on accurate staging that should be performed using non-invasive investigations followed by selection of suitable sites for tissue sampling. Presence of lower cervical lymphadenopathy indicates N3 disease corresponding to at least stage IIIB, and upper cervical lymphadenopathy represents M1b disease – stage IV lung cancer [2]. Neck ultrasound (NUS) routinely performed in patients with mediastinal lymphadenopathy has been shown to reveal metastases to neck lymph nodes in 40–50% of cases [3, 4].

Positron emission tomography (PET) is indicated when computerised tomography (CT) of the thorax and

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upper abdomen shows evidence of potentially curable disease. For staging of the mediastinum, PET-CT consistently shows a significant rate of false-positive findings. A systematic review of 45 studies on the diagnostic accuracy of PET for mediastinal lymphadenopathy in lung cancer showed significant heterogeneity and evidence of significant bias. The summary sensitivity and specificity was 77.4% (95% confidence interval [CI] 65.3–86.1) and 90.1% (95% CI 85.3–93.5) when increased uptake against background was used to define fluorodeoxyglucose (FDG) avidity [5]. Patients with FDG-avid mediastinal lymphadenopathy should have lymph node sampling to pathologically confirm that the nodes are involved. Currently, this is most frequently performed by endobronchial ultrasound (EBUS) or other procedures depending on the site of accessible disease. If samples from EBUS are negative for malignancy, the guidelines recommend performing mediastinoscopy before proceeding to surgical resection [6].

Only limited literature is available regarding the diagnostic yield of PET-CT for cervical lymphadenopathy in lung cancer. One study demonstrated that PET-CT was associated with false-positive findings in the neck in 19% of cases [7]. More studies were performed on the role of PET-CT for the detection of neck lymphadenopathy in head and neck cancer, and within this patient population, PET-CT had a positive predictive value (PPV) of 60–87% and a specificity of 65–70% [8, 9].

While some guidelines recommend routine NUS in patients with lung cancer and bulky mediastinal lymphadenopathy, the evidence level in the literature is poor and other guidelines do not endorse such a recommendation [6, 10]. The aim of this study was to investigate the role and diagnostic accuracy of PET-CT compared to NUS for the detection of malignant cervical lymphadenopathy in patients with lung cancer and mediastinal lymphadenopathy on CT.

Materials and Methods

Study Design and Setting

This is a retrospective single centre cohort study, based in Galway University Hospital, where, since 2012, the Interventional Respiratory Unit has routinely performed NUS in patients with suspected lung cancer who have bulky mediastinal lymphadenopathy on CT.

Inclusion Criteria

All patients with confirmed lung cancer and evidence of mediastinal lymphadenopathy on CT defined as a short-axis diameter >10 mm who also underwent an NUS in the period between August 2012 and August 2017 were included. Medical, laboratory and radiology records were reviewed. Procedures performed, pathology results and clinical stage were documented.

Procedures

NUS and Lymph Node Sampling

NUS was performed in a standardised systematic way using a 5- to 12-MHz linear probe with patients in the supine position. Abnormal lymph nodes were defined based on a short-axis diameter of ≥5 mm. The fine needle aspiration (FNA) of lymph nodes was performed by 1 of 4 respiratory physicians trained in the procedure. After obtaining informed written consent and using an aseptic technique, local anaesthesia was applied (1–3 mL of 1 or 2% lidocaine). Between 2 and 4 passes using a 22-gauge needle were performed under direct US guidance. Air-dried and alcohol-fixed glass slides were made from the first pass, while the remaining passes were placed in formalin for cell block analysis. If the lymph node was suitable, a core needle biopsy was performed using an 18-gauge SuperCore™ needle (Aragon Medical Devices, TX, USA). Sampling adequacy was routinely recorded by the pathology department as a quality control measure. Rapid on-site evaluation was not performed for EBUS or NUS FNA.

Positron Emission Tomography-Computerised Tomography

Whole-body PET was performed after the injection of 370–406 MBq FDG with a standard delay time of 90 min. A non-contrast CT from groin to skull base was performed for attenuation correction and diagnostic interpretation. PET-CT was stored and analysed in the Picture Archiving and Communication System (PACS) and reported by 1 of 2 radiologists with more than 10 years' experience. A contrast CT of the thorax and upper abdomen was done in all patients at baseline and was used for correlation. Findings from PET outside the thorax were documented. The maximum standardised uptake value (SUV_{max}) was routinely reported for all abnormal findings, and a 2.5-cut-off was used to define FDG avidity for cervical lymph nodes.

Outcome Measures and Definitions

Malignant cervical lymphadenopathy was defined as the presence of malignant cells at cytology or histology consistent with a diagnosis of lung cancer. Diagnostic accuracy of PET was measured against results from NUS and lymph node sampling. Lymph node sampling was considered adequate if lymphoid material or malignant cells were present in the samples.

Statistical Analysis

Minitab-17 (Minitab® Statistical Software, State College, PA, USA) was used to conduct the statistical analysis. Normally distributed data are described as means (standard deviations), while all other data are described as medians (interquartile ranges) or proportions and 95% CI. Analysis was performed using Mann-Whitney *U* test or Fisher's exact test. A p value of <0.05 was considered significant. The sensitivity, specificity, PPV and negative predictive value (NPV) of PET-CT for the detection of cervical lymphadenopathy were calculated.

Ethical Considerations

This study was approved by the local ethics committee, and patient confidentiality was maintained throughout data collection and analysis.

Results

Between August 2012 and August 2017, 223 patients were assessed with NUS in the interventional respiratory unit and 149 patients were diagnosed with lung cancer. Of those, 123 patients had mediastinal lymphadenopathy. Baseline characteristics are shown in Table 1. EBUS was performed in 83/123 patients (68%).

NUS and Cervical Lymphadenopathy

The number of patients with enlarged cervical lymphadenopathy on NUS was 69/123 (56.1%). The mean (standard deviation) cervical lymph node short diameter was 12.8 (5.9) mm. Needle sampling was technically feasible and therefore performed in 57/123 patients (46.3%). Findings are summarised in Table 2. Overall, 49/123 patients (39.8% [95% CI 31.1–49.1]) had confirmed malignant cervical lymphadenopathy on pathological evaluation. When FNA was compared to core needle biopsy, there was no significant difference in sampling adequacy (94.7 vs. 92.8%; $p = 0.80$). Immunohistochemistry was possible in 48/49 (98%) samples. A sample was considered sufficient for molecular analysis when tumour cells represented >10% of the population. Molecular analysis was requested in 17 neck lymph node samples and was successfully performed in 14 cases (82.4% [95% CI 56.6–96.2]). There was no significant association between the presence of cervical lymphadenopathy and lung cancer subtype.

PET for Patients with Potentially Curable Disease

In total, 45/123 (36.6%) patients with mediastinal lymphadenopathy had potentially curable disease and underwent PET/CT and NUS. FDG-avid cervical lymph nodes were detected in 14/45 (31%) patients, and following NUS, the number of false positives was 7/14 (50%). The breakdown of the US findings in this group is shown in Table 3. Overall, PET had a specificity of 81.1%, sensitivity of 87.5%, NPV of 96.8% and PPV of 50% for the detection of cervical lymphadenopathy in this group with potentially curable disease. PET did not add any additional staging information in the assessment of the neck region when compared to NUS alone. PET provided additional overall clinical stage information in 4 (8.9%) patients and led to a change in management in 1 (2.2%) patient. No relationship was detected between SUV_{max} and true- or false-positive PET findings in the neck with a median SUV_{max} for true-positive cases of 7.0 (IQR 4–11) versus a median SUV_{max} for false-positive cases of 3.7 (IQR 3–9; $p = 0.11$; Fig. 1). The highest false-positive FDG uptake was due to lymphoma which was evident on cytology and confirmed later by surgical excision.

Table 1. Baseline characteristics of 123 patients with confirmed lung cancer and mediastinal lymphadenopathy that underwent a neck ultrasound

Gender	
Male	70 (56.9)
Female	53 (43.1)
Age, years	67.4±11.2
Small cell lung cancer	27 (22)
Non-small cell lung cancer	96 (78)
Adenocarcinoma	56 (45.5)
Squamous cell carcinoma	32 (26)
Other[a]	8 (6.5)

Data are shown as *n* (%) or means ± standard deviations. [a] "Other" includes neuroendocrine and poorly differentiated lung cancer.

Table 2. Results of NUS and needle sampling of 57 patients with suspicious cervical lymphadenopathy on NUS

Short diameter, cm	12.8±5.9
Enlarged lymph nodes	69 (56.1)
Needle sampling	57 (46.3)
FNA alone	43 (35)
FNA and CNB	14 (11.4)
Sampling adequacy, %	
FNA	94.7
CNB	92.8
Malignant cervical lymphadenopathy	49 (39.8)
Small cell lung cancer	13 (26.5)
Adenocarcinoma	20 (40.8)
Squamous cell carcinoma	12 (24.5)
Other	4 (8.2)

Data are reported as *n* (%) or means ± standard deviations, unless otherwise stated. NUS, neck ultrasound; FNA, fine needle aspiration; CNB, core needle biopsy.

Discussion

In this cohort, 39.8% of patients with lung cancer and mediastinal lymphadenopathy had confirmed malignant cervical lymphadenopathy following NUS. These findings are consistent with the results reported by Kumaran et al. [4] who investigated the role of routine NUS in 101 patients with suspected and later confirmed lung cancer

Table 3. Results of PET, NUS and cytology in all 7 patients that were considered to have false-positive PET findings in the neck

Case	SUV_{max}	NUS findings	LN short diameter, mm[a]	Cytology findings
1	17.7	bilateral cervical LNs	14	lymphoma
2	3	no lymphadenopathy		
3	4.2	left cervical LN	10	non-specific lymphadenitis
4	5	no lymphadenopathy		
5	4	no lymphadenopathy		
6	3	no lymphadenopathy		
7	3.4	bilateral enlarged LNs	12	lymphoma

Two cases of lymphoma on cytology were later confirmed on surgical excisional biopsy. PET, positron emission tomography; NUS, neck ultrasound; SUV_{max}, maximum standardised uptake value; LN, lymph node.
[a] LN short diameter is reported for the largest LN as measured on US.

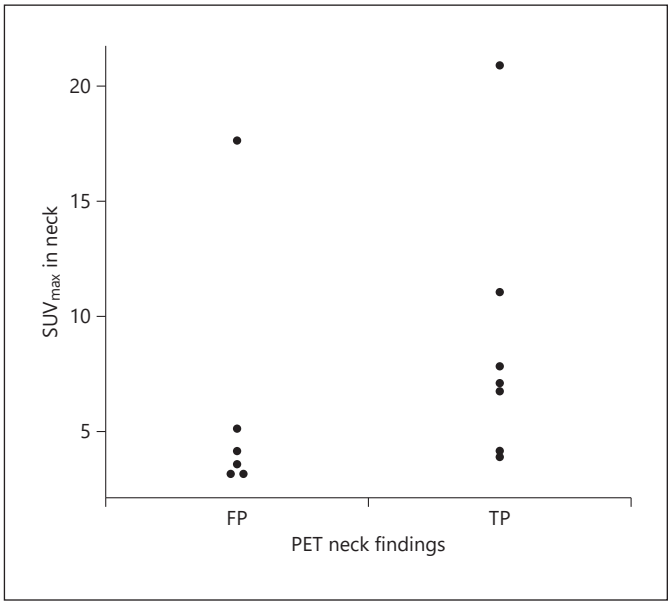

Fig. 1. Comparison of FDG uptake in patients with true- and false-positive findings in the neck on PET-CT. SUV_{max}, maximum standardised uptake value; FP, false positive; TP, true positive; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

that had evidence of mediastinal lymphadenopathy. The authors reported that 50% of patients had malignant neck lymph nodes. Similarly, a study of 40 patients with non-palpable neck lymph nodes confirmed that 40% had supraclavicular lymph nodes metastases [11].

The presence of supraclavicular lymphadenopathy in non-small cell lung cancer indicates N3 disease consistent with at least stage IIIB [12]. Such cN3 disease is associated with a median survival of 7 months in patients with non-small cell lung cancer [13]. The National Institute of Health and Care Excellence (NICE) guidelines recommend routine NUS in patients with bulky mediastinal lymphadenopathy or blind transbronchial needle aspiration mostly based on a cost-effectiveness analysis, although the level of evidence is weak [10]. The findings from our study support this recommendation – potentially identifying nodal disease in the neck region in about 40% of patients. This can significantly streamline investigations and prevent the need for more invasive tests, potentially reducing futile treatments and time to definitive diagnosis and clinical stage. If these findings are supported by further well-designed prospective studies of routine NUS in patients with mediastinal lymphadenopathy, they will have a significant impact on the diagnostic and staging pathway in lung cancer considering the feasibility and safety of performing NUS even in the office.

While PET had a high NPV for the detection of malignant cervical lymphadenopathy, it was associated with a high rate of false-positive findings. The diagnostic accuracy of PET for malignant neck lymphadenopathy in lung cancer has previously been studied; Sung et al. [7] reported on 32 patients with cervical lymphadenopathy detected on PET and/or CT and found a false-positive rate of 19%. The authors reported an SUV_{max} of 2.3 to be the optimum cut-off for differentiating true- and false-positive findings. A smaller study of 12 patients with lung cancer and FDG-avid cervical lymphadenopathy showed supraclavicular metastases from lung cancer in 10 cases; 1 case showed evidence of sarcoidosis and another evidence of metastatic breast cancer [14]. Mean SUV_{max} in

this study was 6.3 (range 3.7–12.2). In our study, NUS was performed by respiratory physicians trained in the procedure and, while it can be argued that there could have been a failure to detect some malignant neck lymphadenopathy, the high sampling adequacy rate of 94.7% in this cohort would be inconsistent with such an argument.

In this paper, we report that PET offered no additional staging value in the neck when NUS was also performed in this cohort. In addition, it only changed M stage in 8.8% of patients from finding disease in other sites, which led to a change in management in only 2.2% of cases. Similar results were seen in a multicentre retrospective study of 1,059 patients who underwent PET scanning for suspected lung cancer [15]. In this population, additional extra-thoracic findings were detected in 15.8%, but management changed in only 1.2% of all patients that underwent PET. The results from this study and our study suggest that PET/CT has only a limited additional staging value once NUS is performed and the mediastinum is properly staged. However, a recommendation regarding the benefit of PET when NUS is negative cannot be made based on this study as the sample size of this subgroup was small (38 patients).

This study is limited by its retrospective design and the possibility of selection bias. Only patients that underwent an NUS were assessed for inclusion in the study, which might have led to confounding by indication bias. Also, this is a single centre study, which might affect the generalisability of its findings.

Conclusions

In this cohort of patients with lung cancer and mediastinal lymphadenopathy, routine NUS performed by respiratory physicians revealed malignant cervical lymphadenopathy in 39.8% of cases. Once NUS was performed, PET did not add any staging value in the neck and only limited additional staging value elsewhere with change in management in just 2.2% of cases. Further prospective studies in this subgroup of patients with suspected lung cancer is required to further assess the role of PET in the staging algorithm once NUS is incorporated as a routine investigation.

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Disclosure Statement

The authors declare no competing interests.

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Research Article

Ultrasound-Guided Cervical Lymph Node Sampling Performed by Respiratory Physicians

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What Is It about?

Some respiratory diseases such as lung cancer and sarcoidosis are associated with neck lymphadenopathy. Sampling of neck lesions is frequently done by non-radiologists. In this study we retrospectively looked at the adequacy of ultrasound-guided sampling of neck lymph nodes performed by respiratory physicians compared to radiologists and found no difference. Respiratory physicians were able to obtain enough material for analysis in 91% of cases and a diagnosis was made based on these samples in 84% of cases.

Keywords

Adenopathy · Ultrasound · Biopsy · Lung cancer diagnosis

Abstract

Background: A variety of disease processes investigated by respiratory physicians can lead to cervical lymphadenopathy. Ultrasound (US) has revolutionised respiratory investigations, and neck ultrasound (NUS) is increasingly recognised as an additional important skill for respiratory physicians. ***Objectives:*** We aimed to assess the feasibility of NUS performed by respiratory physicians in the workup of patients with mediastinal lymphadenopathy. ***Methods:*** This is a single-centre retrospective cohort study. All patients that underwent US-guided cervical lymph node sampling were included. The diagnostic yield is reported, and specimen adequacy is compared for respiratory physicians and radiologists. ***Results:*** Over 5 years, 106 patients underwent NUS-guided lymph node sampling by respiratory physicians compared to 35 cases performed by radiologists. There was no significant difference in the adequacy of sampling between the two groups (respiratory physicians 91.5% [95% CI 84.5–96%] compared to 82.9% [95% CI 66.4–93.4%] for radiologists [p = 0.2]). In the respiratory physician group, a diagnosis was achieved based on lymph node sampling in 89 cases (84%). Neck lymph node

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sampling was the only procedure performed to obtain tissue in 48 cases (45.3%). ***Conclusion:*** NUS and sampling performed by respiratory physicians are feasible and associated with an adequacy rate comparable to that of radiologists. It can reduce the number of invasive procedures performed in a selected group of patients. Guidelines for training and competency assessment are required.

Introduction

Endobronchial ultrasound (EBUS) has revolutionised the assessment of intrathoracic lymphadenopathy but is relatively expensive and in many jurisdictions remains difficult to access in routine clinical practice. Cervical lymph nodes are frequently involved by the same pathological processes associated with hilar and mediastinal lymphadenopathy. In lung cancer, for instance, patients with mediastinal lymphadenopathy have been reported to have cervical lymph node involvement in 40–50% of cases when neck ultrasound (NUS) was routinely performed [1, 2]. The presence of metastatic disease within the supraclavicular lymph nodes represents N3 disease and M1b disease if the upper cervical lymph nodes are involved with a major impact on treatment decisions [3]. The clinical and radiological assessment of neck adenopathy can suggest involvement; however, sampling of the nodes is necessary to definitively confirm involvement. In addition, the basic principles of cancer assessment advise sampling the site of disease that provides the most clinical information regarding staging and diagnosis in a single clinical setting [4]. Moreover, other conditions frequently investigated by respiratory physicians such as sarcoidosis, tuberculosis, mediastinal lymphadenopathy due to metastatic extrapulmonary malignancy, and lymphoma are also associated with neck adenopathy [5, 6].

Respiratory physicians are increasingly familiar with the use of ultrasound (US). It is now an integral component in the assessment of the pleural space and EBUS is by far the greatest advance in lung cancer staging over the last two decades. Finally, NUS is also frequently performed by respiratory physicians in working critical care units to guide central line insertion.

In this paper we report our experience with NUS-guided lymph node sampling performed by respiratory physicians and compare it to the results obtained from procedures performed by radiologists within the same institution.

Methods

This is a retrospective cohort study performed in the interventional respiratory unit of Galway University Hospitals over a 5-year period (March 2013–March 2018). All consecutive cases were identified from a database maintained by the unit. Patients referred to the unit who were found to have cervical adenopathy detected clinically or radiologically were included in the study including those with suspected lung cancer and evidence of bulky mediastinal lymphadenopathy on computerised tomography of the thorax. Both medical records and procedural logs were interrogated for information regarding lymph node features. Final pathology was retrieved from the central pathology laboratory database. Adequacy of samples submitted for pathological assessment was routinely reported as a quality control measure by the examining pathologist. A record of all NUS-guided lymph node samples performed by radiology regardless of indication was obtained from the pathology department. This group of patients was used as a control and adequacy of sampling was compared against samples taken by respiratory physicians.

Table 1. Baseline characteristics and final diagnosis of 106 patients that underwent neck lymph node sampling by respiratory physicians

Characteristic	Value
Mean age (SD), years	65.2 (16.1)
Males, *n* (%)	55 (51.9)
Mean short lymph node diameter (SD), mm	13.2 (6)
Diagnosis on lymph node sample, *n* (%)	
Lung cancer	69 (65.1)
Cancer other than lung	8 (7.5)
Lymphoma	4 (3.8)
Sarcoidosis	6 (5.7)
Tuberculosis	2 (1.9)
Other benign[1]	8 (7.5)
Inadequate sampling	9 (8.5)

SD, standard deviation. [1] Other benign: normal lymphoid material or evidence of reactive lymphadenopathy.

Procedures

All patients included underwent standardised NUS. Procedures were performed using a linear US probe with a frequency of 5–12 MHz using one of two machines (Zonare Z one ultra machine [Zonare®, California, USA] and Hitachi EUB-7500A machine [Hitachi, Ltd., Tokyo, Japan]). Patients were positioned in a semi-supine position. Initially, the thyroid isthmus was identified and once visualised the probe was moved laterally to identify the carotid artery and internal jugular vein. The probe, oriented horizontally and later vertically, was then moved cranially to assess the lower, middle, and upper cervical chain to the level of the submandibular gland. The probe was then moved caudally along the posterior cervical chain until the supraclavicular fossa was identified and assessed. The procedure was then repeated to fully assess the contralateral neck.

After this initial screening assessment, any visualised lymph nodes were further assessed in detail. Features including size, shape, presence of hilum, necrosis, and blood flow were recorded. The largest accessible suspicious lymph nodes, based on US features [7], were sampled under direct visualisation following informed written consent. The area was cleaned using chlorhexidine wash and 1 or 2% lidocaine was applied intradermally and subcutaneously to provide local anaesthesia. A sterile sheath was applied to the US probe. After sonographic identification of the node, direct sampling using a 22-G needle was performed with real-time US guidance. The first pass was used to make slides and the rest of the material was sent for analysis in formalin pots. If well tolerated and technically feasible, 2–3 core needle biopsies (CNBs) were obtained from lymph nodes using an 18-G SuperCore™ needle (Aragon Medical Devices, Texas, USA).

Outcomes

Diagnostic yield and sampling adequacy are reported for neck lymph node sampling performed by respiratory physicians and radiologists. The pathological diagnosis on lymph node sampling is also reported including the suitability of samples for special tests for molecular and immunotherapy targets in the case of lung cancer.

Statistical Analysis

Minitab-18 (Minitab® Statistical Software, Pennsylvania, USA) was used to conduct the statistical analysis. Categorical variables are reported as frequencies and percentages and associated 95% CI, while continuous variables are reported as mean and standard deviations or median and interquartile range. χ^2 or Fisher exact tests were conducted for categorical variables, as appropriate. A p value of <0.05 was considered significant.

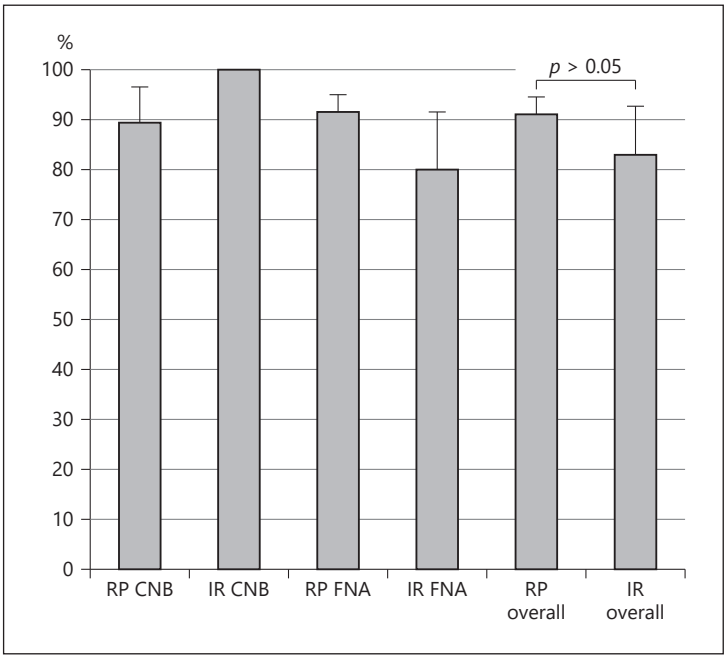

Fig. 1. Bar chart with associated 95% upper CI of adequacy of neck lymph node sampling performed by interventional radiologists (IR) and respiratory physicians (RP). CNB, core needle biopsy; FNA, fine needle aspiration. "Overall" means all procedures combined.

Results

Over a 5-year period, respiratory physicians performed cervical lymph node sampling in 106 consecutive patients compared to 35 consecutive patients by radiology. Respiratory physicians performed NUS in 306 patients and sampled 106 (34%) of those (mean age 65 ± 16 years, 51.9% males, suspected lung cancer in 72.3%) (Table 1). Neck lymph node fine needle aspiration (FNA) and CNB were performed in 38 patients (35.8%) and FNA only in 68 patients (64.2%). A diagnosis was achieved on lymph node sampling in 89/106 cases (84%). The most common diagnosis was lung cancer.

During the study period, the radiology department performed 35 NUS-guided lymph node sampling procedures with a final diagnosis of malignancy in 10/35 cases (28.6%). CNB was performed in 5 patients (14.3%) and FNA in 30 patients (85.7%). There was no difference in the mean short diameter of lymph nodes sampled by radiologists and respiratory physicians (11.75 ± 5.7 vs. 13.2 ± 6 mm [$p = 0.203$]). There was also no significant difference in the adequacy of sampling in the two groups. The overall adequacy rate for respiratory physicians was 91.5% (95% CI 84.5–96%) compared to 82.9% (95% CI 66.4–93.4%) for radiologists ($p = 0.2$). Results are displayed in Figure 1. No significant complications were reported in either group.

Other Procedures and Further Pathological Testing

Among patients assessed by respiratory physicians, neck lymph node sampling was the only procedure performed to obtain tissue in 48 cases (45.3%). The most commonly performed other procedure was EBUS in 26 patients (24.5%). Excisional lymph node biopsy was performed in 8 cases (Table 2).

Among 76 patients with suspected malignancy on cytological examination there was sufficient material for immunohistochemistry staining in 73 patients (96.1%). Further testing for molecular analysis or programmed death ligand 1 (PDL 1) was requested in 18 samples and was possible in 17 (94.4%). In 1 case the percentage of tumour cells in the sample was <10% and therefore a polymerase chain reaction test for mutations was not possible. PDL 1 was requested in 3 cases and samples were adequate for testing in all of those.

Table 2. Breakdown of results of excisional lymph node biopsy performed in 8 cases

Diagnosis on needle sampling	Excisional biopsy result
Inadequate	NHL
SCLC and granulomatous inflammation	NHL
Adenocarcinoma	Adenocarcinoma
Reactive lymphadenopathy	Low-grade B-cell lymphoma
NHL	NHL
Reactive lymphadenopathy	Castleman lymphadenopathy
NHL	NHL
NHL	NHL

SCLC, small cell lung cancer; NHL, non-Hodgkin's lymphoma.

Discussion

In this paper we report our results of NUS-guided sampling of adenopathy led by respiratory physicians. Our results demonstrate that this can be performed with a high level of adequacy and safety by respiratory physicians trained in this procedure. Our sampling inadequacy rate (8.5%) was comparable to results from a previous systematic review of US-guided sampling of neck lesions, where the inadequacy rate was 9.6% for radiologists and 11% for clinicians without rapid on-site evaluation (ROSE) [8]. Importantly, in 14/15 (93.3%) cases confirmed as a primary lung adenocarcinoma, further mutational analysis was possible in 93.3% of samples. This demonstrates that adequate material is available in these cases for additional testing which is becoming increasingly important in the modern oncological management of this patient population consistent with a previous study where molecular analysis was possible in 85% of the cases [9].

Incorporating NUS done by respiratory physicians as a point-of-care diagnostic test in the suspected lung cancer clinic and respiratory procedural environment has a significant impact on the patient pathway. This safe, quick procedure provides early confirmation of cancer type and stage, whilst potentially preventing more invasive and expensive diagnostic and staging investigations. Such an impact, explored in diagnostic algorithms, may also have a positive effect on not only individual patient pathway time, but the wider patient cohort flow undergoing investigation by freeing interventional radiology and EBUS lists with likely cost benefits. We believe that this hypothesis is worth further assessment in a prospective study in lung cancer patients.

US as performed by non-radiologists has become increasingly common over the last decade. Adequate training guidance in NUS for the use in this setting has historically been an area of uncertainty. However, the Royal College of Radiologists (RCR) in the UK now have published guidelines for procedures performed by non-radiologists [10]. The guidelines recommend experience in NUS for level 2 training in pleural US, acknowledging the potential benefits of such a skill for respiratory physicians. An inadequate sampling rate of <15% was recommended for level 2 training in head and neck US – a metric achieved in our practice. However, for further advancement of NUS as a skill for respiratory physicians, we propose that separate tailored guidelines and training recommendations should be developed.

This study has a few inherent limitations. Firstly, this is a retrospective cohort and most cases were identified with adenopathy either by careful clinical examination or radiological assessment of the neck; however, the indications for neck imaging in the first place were heterogeneous, introducing an element of selection bias which might be associated with a higher diagnostic yield. In addition, all procedures were performed by 1 of 4 chest physicians with varying degrees of experience in NUS and sampling including core biopsy of neck nodes.

It is unclear how much experience is required to achieve a high level of sampling adequacy. Further prospective studies should be undertaken to elucidate the role of training respiratory physicians in NUS-guided lymph node sampling.

Conclusion

This study demonstrates that NUS can be performed by respiratory physicians with accuracy in patients with identified adenopathy by clinical examination or imaging of the neck. Subsequent sampling of nodes under direct sonographic guidance was associated with a high level of accuracy and diagnostic yield. Guidelines need to be developed to allow training of respiratory physicians, particularly those with a special interest in lung cancer diagnosis and management.

Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Galway University Hospital Research Ethics Committee – approval: C.A. 2024.

Disclosure Statement

The authors declare no competing interests.

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