Endobronchial ultrasound in the management of lung cancer: Integration of a new technology into clinical care

Daniel Paul Steinfort

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Department of Medicine (RMH/WH)
Faculty of Medicine, Dentistry & Health Sciences

The University of Melbourne
Abstract

Previous studies have described technical aspects of endobronchial ultrasound (both radial & linear). These included performance of the techniques and diagnostic accuracy, though notably early experience was confined to several centres with extensive & experienced interventional bronchoscopy services. Integration of new technology can evolve rapidly, preceding a more complete understanding of potential limitations and complications.

The body of work presented in this thesis was commenced at a time where endobronchial ultrasound was being used more frequently in an increasing number of centres worldwide. There remained a number of outstanding questions regarding the optimal performance of the techniques and their safety profile. This thesis attempts to address several such issues to more clearly define how endobronchial ultrasound (EBUS) is best performed and best incorporated into routine clinical care.

Radial EBUS has been demonstrated to have utility in assessment of peripheral lung lesions, though no comparison with alternate diagnostic procedures had previously been undertaken. I performed a prospective randomized pragmatic trial to determine the comparative effectiveness of endobronchial ultrasound-guided transbronchial lung biopsy (EBUS-TBLB) and CT-guided percutaneous needle biopsy (CT-PNB) for the investigation of PPL. Overall complication rates were higher in those undergoing CT-PNB (27% v 3%, p=0.03), while diagnostic accuracy of EBUS-TBLB was shown to be non-inferior to that of CT-PNB. Expected diagnostic accuracy and complication rates are likely to differ for individual patients on the basis of specific complex clinicoradiologic factors, which will influence the comparative effectiveness and cost-utility between EBUS-TBLB and CT-PNB for individual patients. Decision tree analysis is suited to applying clinical research findings to broader patient populations however more accurate understanding of diagnostic performance of EBUS-TBLB was required. A systematic review of published literature evaluating radial probe EBUS accuracy was performed to determine point sensitivity and specificity, and to construct a summary receiver-operating characteristic curve. Sub-group analysis and linear regression was used to identify possible sources of study heterogeneity. Meta-
analysis demonstrated that EBUS is a safe and relatively accurate (point sensitivity of 0.73, 95%CI 0.70–0.76) tool in investigation of PPLs. Diagnostic sensitivity of EBUS-TBLB may be influenced by the prevalence of malignancy in the patient cohort being examined and lesion size. Decision-tree analysis was applied to compare downstream costs of endobronchial ultrasound-guided transbronchial lung biopsy (EBUS-TBLB) with CT-guided percutaneous needle biopsy (CT-PNB). The costs of EBUS-TBLB and CT-PNB to evaluate PPL appear to be equivalent. Specific factors known to influence procedural outcomes will influence cost-benefit outcomes. Consideration of disutility did not significantly alter cost outcomes.

Issues regarding safety and tolerability of EBUS-guided transbronchial needle aspiration were undertaken. Incidence of bacteraemia following EBUS-TBNA is comparable to that following routine flexible bronchoscopy. Performance of TBNA does not appear to measurably increase the risk of bacteraemia over that associated with insertion of the bronchoscope into the airway. EBUS-TBNA may safely be performed under conscious intravenous sedation. Such practice is associated with very high levels of patient satisfaction.

Both malignancy and granulomatous disease may be diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). Demonstration of granulomas by lymph node EBUS-TBNA in the staging of NSCLC is of uncertain significance. Studies demonstrated that sarcoidal reactions are seen in 4.3% of all patients with NSCLC. Metastatic involvement by NSCLC is not seen in lymph nodes exhibiting sarcoidal granulomatous reactions. No NSCLC patients with sarcoidal granulomas in regional lymph nodes experienced disease recurrence. Case control matching was performed indicating a significantly higher rate of disease recurrence in control subjects (0% v. 44%, p=0.044, $\chi^2$=4.051). Sarcoidal reactions within regional lymph nodes of NSCLC patients predicts a lower rate of disease recurrence following definitive surgical resection. Sarcoidal reactions may represent an effective anti-tumour immunity.

Decision-tree analysis was applied to compare downstream costs of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), conventional
TBNA and surgical mediastinoscopy. Findings indicated that EBUS-TBNA was the most cost-beneficial approach (in comparison to traditional surgical techniques) for mediastinal staging of NSCLC patients across all studied parameters. Diagnostic accuracy of EBUS-TBNA in the evaluation of suspected lymphoma remained uncertain. A retrospective review of a prospectively recorded database of consecutive patients with suspected lymphoma who underwent EBUS-TBNA was examined. Findings indicated that diagnostic accuracy of EBUS-TBNA for lymphoma is lower than that for lung cancer staging. Small volume biopsies may be subject to significant interobserver variability in subtype determination. Interobserver agreement in interpretation of EBUS-TBNA specimens is moderate for determination of NSCLC subtype. Agreement is highest following examination of IHC specimens.
Declaration

This is to certify that

i) the thesis comprises only my original work towards the PhD.

ii) Due acknowledgement has been made in the text to all other material used

iii) The thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Signed

Daniel Paul Steinfort
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The randomized pragmatic clinical trial was conducted with contributions from several colleagues and co-investigators. Medical and surgical colleagues in the RMH lung multidisciplinary clinic assisted in identification of subjects for recruitment. A/Prof Lou Irving contributed to development of the study protocol, in particular, the refining of inclusion criteria and the formalization of the “pragmatic” nature of the study. Support for the project was readily given by Mr Phillip Antippa, director of lung cancer services. Dr Janette Vincent & Dr Stefan Heinze performed CT-guided percutaneous biopsy of patients randomized to this arm of the study.

The systematic review and meta-analysis of radial probe endobronchial ultrasound was undertaken with the assistance of my primary supervisor A/Prof Lou Irving. Daniel Steinfort initiated and wrote the protocol, with advice from Dr Renee Manser (Department of Haematology & Oncology, Peter MacCallum Cancer Institute). Review of abstracts and fulltext articles was performed independently by Daniel Steinfort & Renee Manser. Data extraction was performed by Daniel Steinfort & Dr Yet Hong Khor. Yet Khor also undertook assessment of the methodologic quality of included studies. Lou Irving also provided feedback on the write-up of the review.

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Analysis of interobserver agreement in assessment of NSCLC specimens acquired by EBUS-TBNA was undertaken with input from a number of colleagues. A/Prof Gavin Wright (Dept Surgery, St Vincent’s Hospital) was involved in concept development. Drs Prudence Russell (Dept. Pathology, St Vincent’s Hospital), Alpha Tsui (Dept. Pathology, RMH) and Gordon White (Dept. Pathology, RMH) provided review of the specimens and I am grateful for both their expertise and also their time in undertaking this work. I am particularly grateful to Prue Russell who contributed significantly to development of a final manuscript and provided expert pathology commentary to this end.

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TABLE OF CONTENTS

ABSTRACT .............................................................................................................................. ii
DECLARATION .......................................................................................................................... v
ACKNOWLEDGEMENTS .......................................................................................................... vi
LIST OF TABLES ....................................................................................................................... xviii
LIST OF FIGURES .................................................................................................................... xx

CHAPTER 1: Introduction and Literature Review ......................... 1

1.1 INTRODUCTION .............................................................................................................. 1

1.2 LUNG CANCER ............................................................................................................... 4

1.2.1 Significance ................................................................................................................ 4

1.2.2 Classification of lung cancer ....................................................................................... 5

1.2.3 Aetiology and risk factors ........................................................................................... 8

1.2.3.1 Cigarette smoking .................................................................................................. 8

1.2.3.2 Passive smoking ..................................................................................................... 9

1.2.3.3 Radon ..................................................................................................................... 9

1.2.3.4 Radiation ................................................................................................................ 9

1.2.3.5 Asbestos ................................................................................................................ 10

1.2.3.6 Non-malignant lung disease .................................................................................. 11

1.2.3.7 Cannabis ............................................................................................................... 11

1.2.3.8 Other exposures .................................................................................................... 12

1.2.3.9 Exercise & diet ...................................................................................................... 12

1.2.3.10 Genetic factors ..................................................................................................... 14

1.2.3.11 Acquired gene mutations ..................................................................................... 15

1.2.4 Epidemiology .............................................................................................................. 16

1.2.4.1 Age & socioeconomic status ................................................................................. 16

1.2.4.2 histologic subtypes ............................................................................................... 17

1.2.4.3 Lung cancer in never-smokers ............................................................................. 19

1.2.4.4 Gender .................................................................................................................. 20

1.3 PATHOLOGY AND PATHOGENESIS OF LUNG CANCER .................. 22
1.4 PERIPHERAL PULMONARY LESIONS ........................................... 27
  1.4.1 Definitions ........................................................................ 27
  1.4.2 Solitary Pulmonary Nodule ................................................ 27
  1.4.3 Management of indeterminate pulmonary nodules ............. 31

1.5 LUNG CANCER SCREENING ...................................................... 33
  1.5.1 Identification of high risk patients .................................... 33
  1.5.2 Radiologic screening .......................................................... 34
  1.5.3 Bronchoscopic screening ...................................................... 43
  1.5.4 Screening/Surveillance following curative therapy of lung cancer
        (secondary screening) .......................................................... 45

1.6 CLINICAL PRESENTATION OF LUNG CANCER ................... 46

1.7 DIAGNOSIS OF SUSPECTED LUNG CANCER ....................... 48
  1.7.1 Non-invasive investigation of PPL ...................................... 48
    1.7.1.1 Chest x-ray ............................................................. 48
    1.7.1.2 CT chest .................................................................. 48
    1.7.1.3 Positron Emission Tomography .................................... 49
    1.7.1.4 Non-invasive diagnosis ............................................... 50
  1.7.2 Invasive diagnosis of PPL .................................................. 51
    1.7.2.1 bronchoscopy .......................................................... 51
    1.7.2.2 CT-guided percutaneous sampling ............................... 53
    1.7.2.3 Video-assisted thoracoscopic surgery .......................... 54

1.8 STAGING OF LUNG CANCER .................................................. 55
  1.8.1 Non-invasive staging of Non-small cell lung cancer ............ 57
    1.8.1.1 CT chest ............................................................... 57
    1.8.1.2 FDG-PET ............................................................. 58
    1.8.1.3 Other imaging modalities .......................................... 59
  1.8.2 Invasive staging of NSCLC ................................................. 60
    1.8.2.1 Surgical Mediastinoscopy .......................................... 61
    1.8.2.2 Intra-operative mediastinal staging .............................. 63
    1.8.2.3 Minimally invasive staging techniques ......................... 64
    1.8.2.4 Lymph node micrometastases and isolated tumour cells ....... 66
CHAPTER 2: Research hypotheses, aims and methodology ........ 87

2.1 HYPOTHESES AND AIMS ................................................................. 87
  2.1.1 Background to study aims.......................................................... 90
    2.1.1.1 Aim 1 .............................................................................. 90
    2.1.1.2 Aim 2 .............................................................................. 91
    2.1.1.3 Aim 3 .............................................................................. 93
    2.1.1.4 Aim 4 .............................................................................. 95

2.2 RESEARCH METHODOLOGY .......................................................... 97
  2.2.1 Comparative Effectiveness Research........................................... 97
  2.2.2 Decision Tree Analysis.............................................................. 100

CHAPTER 3: Determining optimal performance of radial probe endobronchial ultrasound ................................................................. 101

3.1 BACKGROUND ................................................................................. 101
3.2 RADIATION DOSE TO PATIENTS AND STAFF DURING FLUOROSCOPICALLY GUIDED ENDOBRONCHIAL ULTRASOUND-GUIDED BIOPSY OF PERIPHERAL PULMONARY LESIONS .......... 102

3.2.1 Introduction ........................................................................................................ 102

3.2.2 Methods ............................................................................................................ 103
  3.2.2.1 Measurement of patient dose ................................................................. 103
  3.2.2.2 Measurement of staff dose ..................................................................... 104
  3.2.2.3 EBUS procedure .................................................................................. 104

3.2.3 RESULTS ......................................................................................................... 105
  3.2.3.1 Radiation exposure to patients ................................................................. 106
  3.2.3.2 Radiation exposure to clinicians .............................................................. 106

3.2.4 DISCUSSION ..................................................................................................... 108
  3.2.4.1 Study limitations .................................................................................... 111

3.2.5 CONCLUSIONS ............................................................................................... 112

CHAPTER 4: Determining the optimal procedure for minimally invasive assessment of peripheral pulmonary lesions ...................... 113

4.1 BACKGROUND .................................................................................................... 113

4.2 COMPARATIVE EFFECTIVENESS OF RADIAL PROBE ENDOBRONCHIAL ULTRASOUND VERSUS CT-GUIDED NEEDLE BIOPSY FOR EVALUATION OF PERIPHERAL PULMONARY LESIONS: A RANDOMIZED PRAGMATIC TRIAL ................................................. 115

4.2.1 INTRODUCTION ............................................................................................. 115

4.2.2 METHODS ....................................................................................................... 116
  4.2.2.1 Trial design ............................................................................................ 116
  4.2.2.2 Participants ............................................................................................ 117
  4.2.2.3 Performance of EBUS-TBLB ................................................................. 118
  4.2.2.4 Performance of CT-PNB ........................................................................ 118
  4.2.2.5 Statistical analysis ................................................................................ 119

4.2.3 RESULTS ......................................................................................................... 120
  4.2.3.1 Diagnostic performance ........................................................................ 122
4.4.2.4 Health care costs.................................................................151
4.4.2.5 Other input parameters.........................................................152
4.4.2.6 Sensitivity analysis...............................................................154
4.4.2.7 Cost-effectiveness...............................................................154
4.4.2.8 Assumptions ..................................................................157

4.4.3 RESULTS ...........................................................................157
4.4.3.1 Base-case analysis ...........................................................157
4.4.3.2 Sensitivity analysis.............................................................157
4.4.3.3 Probabilistic sensitivity analyses.........................................159
4.4.3.4 Cost-effectiveness analysis...............................................159

4.4.4 DISCUSSION .......................................................................163
4.4.4.1 Strengths and Limitations ................................................164

4.4.5 CONCLUSIONS ...................................................................165

CHAPTER 5: Assessment of the tolerability and safety of EBUS-TBNA ................................................................. 166

5.1 BACKGROUND ......................................................................166

5.2 INCIDENCE OF BACTERAEMIA FOLLOWING ENDOBRONCHIAL ULTRASOUND-GUIDED TRANSPTRONCHIAL NEEDLE ASPIRATION .................................................................168
5.2.1 INTRODUCTION .................................................................168
5.2.2 MATERIALS AND METHODS ..............................................169
5.2.2.1 Statistics .......................................................................170
5.2.3 RESULTS .............................................................................170
5.2.4 DISCUSSION .......................................................................173
5.2.5 CONCLUSION .....................................................................176

5.3 PATIENT SATISFACTION DURING EBUS-TBNA PERFORMED UNDER CONSCIOUS SEDATION .........................................................177
5.3.1 INTRODUCTION .................................................................177
5.3.2 METHODS .........................................................................177
5.3.2.1 Performance of EBUS-TBNA ...........................................178
5.3.2.2 Patient questionnaire ................................................................. 178
5.3.2.3 Procedural and demographic data ............................................... 179
5.3.2.4 Statistical analysis ..................................................................... 179
5.3.3 RESULTS ..................................................................................... 179
5.3.4 DISCUSSION ............................................................................... 182
5.3.5 CONCLUSION ............................................................................. 184

CHAPTER 6: Issues in the integration of EBUS-TBNA into routine care – comparison with current standards of care .......... 185

6.1 BACKGROUND .................................................................................. 185
6.2 COST-BENEFIT OF MINIMALLY INVASIVE STAGING OF NON-SMALL CELL LUNG CANCER: A DECISION TREE SENSITIVITY ANALYSIS ................................................................. 187

6.2.1 INTRODUCTION ........................................................................... 187
6.2.2 METHODS .................................................................................... 188

6.2.2.1 Modelling approach ................................................................. 188
6.2.2.2 Model population ..................................................................... 188
6.2.2.3 Health care costs ..................................................................... 189
6.2.2.4 Other input parameters ............................................................. 191
6.2.2.5 Sensitivity analysis ................................................................. 191
6.2.2.6 Assumptions ........................................................................... 192

6.2.3 RESULTS ..................................................................................... 195

6.2.3.1 Base-case analysis ................................................................. 195
6.2.3.2 Sensitivity analysis ................................................................. 195
6.2.4 DISCUSSION ............................................................................... 198

6.2.4.1 Strengths and Limitations ....................................................... 200

6.2.5 CONCLUSION ............................................................................. 202

6.3 INTEROBSERVER AGREEMENT IN DETERMINATION OF NON-SMALL CELL LUNG CARCINOMA SUBTYPE IN SPECIMENS ACQUIRED BY EBUS-TBNA ................................................................. 203

6.3.1 INTRODUCTION ........................................................................... 203
6.3.2 MATERIALS AND METHODS .................................................204
6.3.2.1 Patients ........................................................................204
6.3.2.2 Performance of EBUS-TBNA .......................................204
6.3.2.3 Specimen processing .....................................................204
6.3.2.4 Pathology review ..........................................................205
6.3.2.5 Statistical methods .......................................................206

6.3.3 RESULTS ........................................................................206
6.3.3.1 Cytology smears ...........................................................206
6.3.3.2 Haematoxylin & Eosin specimens ..............................207
6.3.3.3 Immunohistochemistry ...............................................207

6.3.4 DISCUSSION .................................................................211
6.3.4.1 Limitations ..................................................................214

6.3.5 CONCLUSIONS .............................................................215

CHAPTER 7: Diagnostic and prognostic significance of sarcoidal reactions demonstrated by EBUS-TBNA in regional lymph nodes of patients with non-small cell lung cancer ............216

7.1 BACKGROUND .....................................................................216

7.2 SARCOIDAL REACTIONS IN REGIONAL LYMPH NODES OF PATIENTS WITH NON-SMALL CELL LUNG CANCER: INCIDENCE AND IMPLICATIONS FOR MINIMALLY INVASIVE STAGING WITH ENDOBRONCHIAL ULTRASOUND ...............................................................217
7.2.1 INTRODUCTION ..............................................................217
7.2.2 METHODS ......................................................................218
7.2.2.1 Statistics .....................................................................219
7.2.3 RESULTS .........................................................................219
7.2.4 DISCUSSION .................................................................222
7.2.4.1 Limitations .................................................................225
7.2.5 CONCLUSIONS .............................................................226

7.3 SARCOIDAL REACTIONS IN REGIONAL LYMPH NODES OF EARLY STAGE NON-SMALL CELL LUNG CARCINOMA PATIENTS
List of Tables

Table 3.1: Diagnoses made by EBUS-GS bronchoscopy ........................................105
Table 3.2: Patient exposure data during EBUS-GS bronchoscopy ..........................107
Table 3.3: Effective radiation doses for common sources of ionizing radiation .......107
Table 3.4: Recorded staff effective radiation doses .............................................107
Table 4.1: Demographic and clinicoradiologic data for randomized patients ..........123
Table 4.2: Final diagnoses in all patients undergoing minimally invasive biopsy ....124
Table 4.3: Diagnostic performance for detection of lung cancer, and complication rates for the two study groups ...............................................................125
Table 4.4: Comparison of radiologic features of PPLs between patients with lung cancer in whom EBUS-TBLB was diagnostic, versus those in whom EBUS was non-diagnostic. The only factor predictive for a diagnostic procedure was the ability to locate the lesion with the radial EBUS probe ....125
Table 4.5: Evidence-based summary of clinicoradiologic features affecting diagnostic yield & complication rates following invasive biopsy of peripheral pulmonary lesions ........................................................................128
Table 4.6: Bibliographic search strategy ................................................................136
Table 4.7: Main characteristics of selected studies ...............................................140
Table 4.8: Results of pooled analysis, and heterogeneity .....................................152
Table 4.9: Hospital costs associated with uncomplicated procedures ...............152
Table 4.10: Hospital costs associated with complicated procedures .................153
Table 4.11: Parameter values used for variables in performance of decision tree analysis ........................................................................................................153
Table 4.12: Calculated base-case costs of the two diagnostic approaches ..........158
Table 4.13: Cost calculations for specific hypothetical patient scenarios ..........161
Table 4.14: Values used in Monte Carlo simulation ............................................161
Table 4.15: Results of Monte Carlo simulation .....................................................162
Table 5.1: Indication for performance of EBUS-TBNA, and final diagnoses........171
Table 5.2: Lymph node stations sampled. ..............................................................172
Table 5.3: Clinical features of patients with confirmed bacteraemia following
    TBNA .............................................................................................................172
Table 5.4: Demographic data of patients completing satisfaction questionnaire .....180
Table 5.5: Doses and combinations of agents used to achieve sedation during
    EBUS-TBNA performed under conscious intravenous sedation .....................180
Table 5.6: Frequency & severity of reported symptoms during performance of
    EBUS-TBNA. .................................................................................................181
Table 6.1: Hospital costs associated with each procedure ..................................194
Table 6.2: Parameter values used for variables in performance of decision tree
    analysis .......................................................................................................194
Table 6.3: Calculated costs of the four modelled diagnostic approaches ..........194
Table 6.4: Interobserver agreement for each specimen type. Overall agreement
    is recorded, as well as agreement according to the degree of confidence
    expressed by the pathologists in their diagnosis ...........................................208
Table 6.5: Final diagnoses in 56 of 60 NSCLC specimens examined in this
    study. In four cases of NSCLC each pathologist reported a different
    histologic subtype as their final diagnosis .................................................208
Table 7.1: Histologic and staging information for non-small cell lung cancer
    patients undergoing surgical biopsy of mediastinal lymph nodes .................221
Table 7.2: Demographic and clinical characteristics of study subjects ..............230
List of Figures

Figure 1.1: The 1999 World Health Organization/International Association for the Study of Lung Cancer Histological Classification of Lung and Pleural Tumours .................................................................7

Figure 1.2: Diagrammatic summary of WHO criteria for bronchial squamous dysplasia/CIS, and the associated morphologic changes ........................................23

Figure 1.3: Axial CT chest demonstrating spiculated lesion in the apical segment of Right Lower Lobe .................................................................29

Figure 1.4: descriptors from the 7th edition of the TNM staging system for lung cancer ......................................................................................56

Figure 1.5: Performance of radial probe endobronchial ultrasound, as described by Kurimoto et al...............................................................80

Figure 1.6: Linear probe endobronchial ultrasound bronchoscope and performance of real-time transbronchial needle aspiration ..................84

Figure 1.7: Domains illustrating the extremes of explanatory and pragmatic trial design ....................................................................................99

Figure 4.1: Flow diagram illustrating progression of all patients referred for evaluation of PPL to our multidisciplinary service during the study period ...........121

Figure 4.2: images demonstrating lesions declined by interventional radiologists from CT-PNB on the basis of a high risk of complications suggested by radiologic appearances ................................................................121
Figure 4.3: Radial probe endobronchial ultrasound image indicating presence of peri-bronchial mass lesion .........................................................134

Figure 4.4: Forest plot of sensitivity of EBUS-TBLB ...........................................141

Figure 4.5: Summary receiver-operator characteristic curve .................................141

Figure 4.6: Results of linear regression examination of relationship between prevalence of malignancy and reported sensitivity of individual studies ...........141

Figure 4.7: Decision tree illustrating possible clinical pathways following selection of a diagnostic approach .........................................................156

Figure 4.8: Graphical representation of effect on expected cost of each procedure ..........................................................160

Figure 4.9: Results of two-way sensitivity analysis (ie. alteration of two input parameters). The most cost-beneficial diagnostic pathway for the combination of the two varied parameters is indicated by the pattern present on the graph .....160

Figure 4.10: Results of two-way sensitivity analysis, with cost-effectiveness measured according to disutility arising from procedural complications ...............162

Figure 6.1: Decision tree illustrating possible clinical pathways following selection of one of the four diagnostic approaches being evaluated ..................190

Figure 6.2: Graphical representation of effect on expected value of each diagnostic pathway during one-way sensitivity analysis with variation in prevalence of lymph node metastases among the modeled population ..........197

Figure 6.3: Graphical representation of effect on expected value of each diagnostic pathway during one-way sensitivity analysis with variation in sensitivity of EBUS-TBNA ..........................................................197
Figure 6.4: Two-way sensitivity analysis with variation in prevalence of lymph node metastases, and sensitivity of EBUS-TBNA ........................................197

Figure 6.5: Demonstrates a smear specimen where each pathologist identified a different NSCLC subtype ..................................................................................................................210

Figure 6.6: Cytology smear specimens stained by Papanicolaou staining .........210

Figure 7.1: Staging FDG-PET from NSCLC patient demonstrating high uptake in large peripheral right tumour and high uptake in the subcarinal region ........................................................................................................................................221

Figure 7.2: Histopathology images (original magnification x200) demonstrating the appearance of; A) sarcoild granulomas, B) sinus histiocytosis ........................................................................................................................................232

Figure 7.3: Kaplan-Meier curve illustrating disease-free recurrence (DFR) of patients with pN0 NSCLC .................................................................................................................................232
CHAPTER 1: Introduction and Literature Review

1.1 INTRODUCTION

Lung cancer is a common malignancy occurring predominantly in people over 50 years of age. It is the fourth most commonly diagnosed malignancy in Australia,[1] and is the commonest cause of cancer death in Australia,[1] and in the Western world generally.[2] As such it is also the cancer with the highest burden of years of life lost due to premature mortality.[1] The age-standardized death rates from lung cancer in Australia have fallen marginally in the twenty years to 2005, however the numbers of deaths due to lung cancer each year continues to rise – 7,400 in the year 2005.

The vast majority of lung cancer is due to cigarette smoking.[3] This has been recognised since the 1950’s,[4, 5] and more importantly, this is recognized as the major target of primary prevention of lung cancer. Smoking cessation is associated with a significant reduction in long-term mortality from lung cancer compared to continuing smokers,[6] as well as other smoking-related illnesses such as cardiovascular disease.[7, 8] Significant success in reduction in smoking rates have been seen, however the risk of lung cancer in ex-smokers never returns to that of non-smokers and more recently the number of ex-smokers diagnosed with lung cancer has exceeded the number of current smokers. Unfortunately there is no effective form of primary or secondary prevention.

Lung cancer may result in one or several symptoms leading to medical assessment, or may be noted incidentally on imaging performed for other reasons.[9] The proportion of lung cancers detected incidentally appears to be increasing slightly,[10] possibly due to the increase in use of CT imaging of the thorax for other reasons, such as suspected PE,[11] cardiac CT,[12, 13] or even abdominal CT.[14] However symptomatic presentation remains the rule in all published studies, with over 90% of patients presenting with symptoms relating to the primary tumour, sites of metastatic involvement or due to paraneoplastic systemic effects of malignancy.[9, 15]
Following detection of radiographic chest abnormalities, either as a result of investigation of symptoms, or as an incidental finding, further evaluation is required as the differential diagnosis for peripheral lung lesions is very wide. Clinical and radiographic factors may aid in determining the probability that a pulmonary lesion is malignant, though such models are not more accurate than assessment by experienced clinicians.[16] The possibility that such lesions may be benign emphasizes the need to obtain pathologic diagnosis via as minimally invasive means as possible.

Non-invasive evaluation of pulmonary lesions may be enhanced with fluorodeoxyglucose positron emission tomography (FDG-PET). FDG-PET has a proven high sensitivity for the detection of malignant nodules in the lung, however its specificity is lower, and highly variable.[17] The consequence of a false positive diagnosis of malignancy is that patients will be subject to surgical lobectomy, with the associated morbidity and mortality. CT-screening studies have shown that 18% – 34% of such operations are performed in patients with benign nodules.[18-20] Consequently, attempts at minimally invasive pathologic diagnosis are strongly favoured.

Non-invasive diagnosis may be achieved via sputum cytology however the diagnostic accuracy, and diagnostic yield is very low for peripheral lesions.[21, 22] Minimally invasive diagnosis is frequently achieved using either CT-guided percutaneous sampling or bronchoscopic techniques. Diagnostic yield of routine bronchoscopy is poor when evaluating peripheral lung lesions,[23, 24] but is improved considerably when guidance techniques are utilized.[25] Diagnostic yield of CT-guided lung biopsy approximately 90%,[17] however complications occur frequently, with 20 to 40% of procedures complicated by pneumothorax.[17, 26, 27] The optimal technique by which to evaluate patients with peripheral pulmonary lesions remains unclear.

For all histological subtypes of lung cancer, the most important factor for survival is the stage of disease at diagnosis.[28] Staging of lung cancer is also essential in determining optimal treatment approaches for individual patients. A majority of patients with lung cancer will have locoregional or distant metastases at the time of diagnosis,[29] excluding the option of treatment with primary surgical resection of their malignancy. Presence of metastatic disease may be suspected based on
symptoms or radiographic abnormalities. PET/CT is more accurate than CT alone in staging lung cancer.[30] The negative predictive value of PET-CT in evaluating the mediastinum is over 90%, allowing procession to surgical resection.[30] However the specificity of PET-CT is approximately 85%.[30] therefore pathologic confirmation of radiologically suspected mediastinal disease is imperative.

Mediastinal lymph node evaluation was traditionally achieved by surgical mediastinoscopy, and many consider this to still be the gold standard. More recently, minimally invasive evaluation has become possible. Transbronchial needle aspiration of mediastinal lymph nodes was first described in 1983,[31] allowing a significant proportion of patients with locally advanced lung cancer to avoid a surgical procedure. Image-guided needle aspiration of mediastinal lymph nodes became possible following the introduction of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA).[32] and later endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was introduced,[33, 34] allowing “real-time” bronchoscopic mediastinal staging.

In the present thesis, several aspects of the clinical application of endobronchial ultrasound in the diagnosis and staging of lung cancer have been evaluated. The diagnostic accuracy of both radial and linear probe endobronchial ultrasound had been established prior to commencement of work described in this thesis. However, several issues surrounding the clinical utility of EBUS remained to be delineated. These included issues of safety and tolerability of the techniques, the performance characteristics of the tests when compared to alternative methods of tussie biopsy, and the cost-effectiveness of the techniques. Finally, the role of molecular signals, either as prognostic or predictive markers in the management of lung cancer continues to expand. The ability of low-volume specimens to provide such information is yet to be established. I have examined the potential role of regional lymph nodes to provide information regarding prognosis of non-small cell lung carcinoma, based on immunologic behaviour of the tumour. I have also examined the feasibility of molecular evaluation of mediastinal lymph node tissue acquired by EBUS-TBNA.
1.2 LUNG CANCER

1.2.1 Significance
A century ago lung cancer was a rare disease.[35] Since this time, the incidence of lung cancer has increased steadily in all industrialized nations.[36] It is now the fourth most common cancer by incidence in Australia, and the commonest cause of cancer death.[1] Such observations are consistent in all developed countries.[2, 37, 38]

A reduction in smoking rates has seen a recent decline in lung cancer mortality in Australia among males, however due to increased rates of smoking among women, lung cancer mortality among Australian females continues to rise.[36] Given the known lag between tobacco smoke exposure and development of lung cancer, mortality among Australian females is not expected to peak until at least the next decade.[36] The expected mortality burden from smoking due to lung cancer is likely to be much larger in many developing countries where smoking rates continue to rise.[39] Of the worlds one billion cigarette smokers, one third live in China,[40] where a major epidemic of lung cancer is expected.[41]

Recently published records reveal 7,400 people died from lung cancer in Australia in 2005,[42] and approximately 11,000 diagnoses of lung cancer are expected in Australia this year. Only marginal improvements in overall 5-year survival have been seen over the previous 20 years,[42] and the survival rate remains the lowest of the 12 most common malignancies – 10.7% for men, and 14.0% for women. Unlike other common cancers this figure has not changed over multiple decades. It is therefore unsurprising that lung cancer is responsible for the highest proportion of years of life lost due to cancer.[43]

The poor 5-years survival rates reflect the fact that more than 75% of patients with non-small cell lung cancer (NSCLC) have advanced stage disease, rendering them ineligible for surgical resection of their malignancy. Surgery is recognized as the most effective therapy for lung cancer but is appropriate only for the minority of patients with early stage disease. Even among such patients, the 5-year survival rate is just 36
– 73%. [28] The 5-year survival rate for NSCLC patients with extrathoracic metastases is just 2%. [28, 44]

1.2.2 Classification of lung cancer
Several histological subtypes of primary epithelial lung carcinoma are recognized in the World Health Organization classification of lung tumours (Figure 1.1). [45] Traditionally these have been broadly separated into two categories, based on patterns of biologic behaviour and response to therapy. Small cell lung cancer (SCLC) is a biologically aggressive form of lung cancer and is most strongly associated with cigarette smoking. [46] It is notable for its rapid doubling time, and the early development of systemic metastases. Consequently, survival is poorest for lung cancer patients with this subtype. The World Health Organization recognizes several other histologic forms of lung cancer. [47] However, biologic behaviour is much more consistent among these, and these are grouped together as non-small cell lung carcinoma (NSCLC).

The three commonest forms of NSCLC comprise approximately 82% of cases. [48] Adenocarcinoma is the predominant form of NSCLC, comprising almost 40% of cases. Several morphologic forms of adenocarcinoma exist, and adenocarcinomas may be heterogeneous, frequently consisting of two or more of the histologic subtypes. [49] Adenocarcinoma also includes the morphologic variant formerly known as Bronchioalveolar cell carcinoma (BAC) subtype. This is an uncommon form of adenocarcinoma distinguished by growth in a purely lepidic fashion along alveolar walls with preservation of the underlying septal architecture. [49] The mucinous form of BAC may exhibit intrapulmonary spread, and is frequently multifocal. While such a pattern of disease is associated with a poorer prognosis, solitary non-invasive BAC is generally associated with an excellent prognosis. [50] Recognition of the differing clinical behaviour of different histomorphologic subtypes of adenocarcinoma has resulted in a new classification system for lung adenocarcinoma, with the term BAC no longer used, and variants formerly classified as BAC now reclassified as either adenocarcinoma in-situ, lepidic predominant, or invasive mucinous adenocarcinoma. [51]
Squamous cell carcinoma (SCC) constitutes approximately 20% of NSCLC cases.[48] These tumours develop through a spectrum of morphologically recognizable changes in the bronchial epithelium, that appear to represent the intermediate steps in a process in which the cells evolve from a normal (non-squamous) phenotype into a malignant phenotype.[52] Specific oncogenetic alterations in epithelial cells are associated with these morphologic changes.[53] They are most frequently seen endobronchially and are therefore more associated with symptoms and complications of central tumours, such as haemoptysis or airway obstruction than other NSCLC. Spread of SCC, or recurrence of surgically resected disease, is more likely to be locoregional than non-squamous forms of SCC.[54, 55] Conversely, distant metastases are less frequent for SCC.

Large cell carcinoma constitutes approximately 10% of NSCLC. They do not morphologically demonstrate squamous or glandular differentiation, though may have electron microscopic features of SCC or adenocarcinoma.[49] Large cell carcinoma may demonstrate neuroendocrine features either morphologically or immunohistochemically, though prognosis remains significantly poorer than for carcinoid tumours.[49]

Several other morphologic variants of NSCLC are recognized. These are individually rare and frequently have unique clinical and biologic features as compared to the more common forms of NSCLC described above. In some tissue specimens it is not possible to determine a histologic subtype of NSCLC. Lung cancers are classified according to the best-differentiated element,[49] however in some tissue specimens it is not possible to determine the histologic subtype. Use of the category ‘NSCLC not otherwise specified’ is suggested for such specimens, and has been shown to improve accuracy in reporting of NSCLC.[56] This category may apply to over 20% of patients with NSCLC though patient and biopsy factors are known to influence the likelihood of such a diagnosis.[57] There is renewed interest in accurately subtyping NSCLC as treatment preferences may alter based on underlying histology.[58-60]
Figure 1.1: The 1999 World Health Organization/International Association for the Study of Lung Cancer Histological Classification of Lung and Pleural Tumours (from [45]), with amendments following new classification of lung adenocarcinoma (from [51]).

<table>
<thead>
<tr>
<th>Epithelial Tumours</th>
<th>1.3.6. Carcinomas with pleomorphic, sarcomatoid or sarcomatous elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Benign</td>
<td>1.3.6.1. Carcinomas with spindle and/or giant cells</td>
</tr>
<tr>
<td></td>
<td>1.3.6.1.1. Pleomorphic carcinoma</td>
</tr>
<tr>
<td></td>
<td>1.3.6.1.2. Spindle cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>1.3.6.1.3. Giant cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>1.3.6.2. Carcinosarcoma</td>
</tr>
<tr>
<td></td>
<td>1.3.6.3. Pulmonary blastoma</td>
</tr>
<tr>
<td></td>
<td>1.3.7. Carcinoid tumour</td>
</tr>
<tr>
<td></td>
<td>1.3.7.1. Typical carcinoid</td>
</tr>
<tr>
<td></td>
<td>1.3.7.2. Atypical carcinoid</td>
</tr>
<tr>
<td>1.2. Preinvasive lesions</td>
<td>1.3.8. Carcinomas of salivary-gland type</td>
</tr>
<tr>
<td></td>
<td>1.3.8.1. Mucoepidermoid carcinoma</td>
</tr>
<tr>
<td></td>
<td>1.3.8.2. Adenoid cystic carcinoma</td>
</tr>
<tr>
<td></td>
<td>1.3.8.3. Others</td>
</tr>
<tr>
<td>1.3. Malignant</td>
<td>1.3.9. Unclassified carcioma</td>
</tr>
<tr>
<td></td>
<td>2 Soft Tissue Tumours</td>
</tr>
<tr>
<td></td>
<td>2.1 Localized fibrous tumour</td>
</tr>
<tr>
<td></td>
<td>2.2 Epithelioid haemangiendothelioma</td>
</tr>
<tr>
<td></td>
<td>2.3 Pleopulmonary blastoma</td>
</tr>
<tr>
<td></td>
<td>2.4 Chondroma</td>
</tr>
<tr>
<td></td>
<td>2.5 Calcifying fibrous pseudotumour of the pleura</td>
</tr>
<tr>
<td></td>
<td>2.6 Congenital peribronchial myofibroblastic tumour</td>
</tr>
<tr>
<td></td>
<td>2.7 Diffuse pulmonary lymphangiomatosis</td>
</tr>
<tr>
<td></td>
<td>2.8 Dermoïd small round cell tumour</td>
</tr>
<tr>
<td>3 Mesothelial Tumours</td>
<td>2.9 Other</td>
</tr>
<tr>
<td>3.1 Benign</td>
<td>3.2 Malignant</td>
</tr>
<tr>
<td></td>
<td>3.2.1 Epithelioid mesothelioma</td>
</tr>
<tr>
<td></td>
<td>3.2.2 Sarcomatoid mesothelioma</td>
</tr>
<tr>
<td></td>
<td>3.2.2.1 Dermoïd mesothelioma</td>
</tr>
<tr>
<td></td>
<td>3.2.3 Other</td>
</tr>
<tr>
<td>4 Miscellaneous Tumours</td>
<td>5 Lymphoproliferative Disease</td>
</tr>
<tr>
<td></td>
<td>5.1 Lymphoid interstitial pneumonia</td>
</tr>
<tr>
<td>5.2 Nodular lymphoid hyperplasia</td>
<td></td>
</tr>
<tr>
<td>5.3 Low-grade marginal zone B-cell lymphoma of the</td>
<td>5.4 Lymphomatoid granulomatosis</td>
</tr>
<tr>
<td>mucosa-associated lymphoid tissue</td>
<td></td>
</tr>
<tr>
<td>6 Secondary Tumours</td>
<td>7 Unclassified Tumours</td>
</tr>
<tr>
<td>7 Tumours-like Lesions</td>
<td>8 Other</td>
</tr>
<tr>
<td>8.1 Tumourlet</td>
<td></td>
</tr>
<tr>
<td>8.2 Multiple meningothelioid nodules</td>
<td></td>
</tr>
<tr>
<td>8.3 Langerhans cell histiocytosis</td>
<td></td>
</tr>
<tr>
<td>8.4 Inflammatory pseudotumour (Inflammatory myofibroblastic tumour)</td>
<td></td>
</tr>
<tr>
<td>8.5 Organizing pneumonia</td>
<td></td>
</tr>
<tr>
<td>8.6 Amyloid tumour</td>
<td></td>
</tr>
<tr>
<td>8.7 Hyalinizing granuloma</td>
<td></td>
</tr>
<tr>
<td>8.8 Lymphangioleomyomatosis</td>
<td></td>
</tr>
<tr>
<td>8.9 Multifocal micronodular pneumocyte hyperplasia</td>
<td></td>
</tr>
<tr>
<td>8.10 Endometriosis</td>
<td></td>
</tr>
<tr>
<td>8.11 Bronchial inflammatory polyp</td>
<td></td>
</tr>
<tr>
<td>8.12 Others</td>
<td></td>
</tr>
</tbody>
</table>

1 Epithelial Tumours

1. Benign

1.1. Papillomas

1.1.1. Squamous cell papilloma

Exophytic

Inverted

1.1.1.2. Glandular papilloma

1.1.1.3. Mixed squamous cell and glandular papilloma

1.1.2. Adenomas

1.1.2.1. Adenocarcinoma

1.1.2.2. Papillary adenoma

1.1.2.3. Adenomas of salivary-gland type

1.1.2.4. Basaloid

1.1.3. Small cell carcinoma

1.1.2.1. Combined small cell carcinoma

1.3. Malignant

1.3.1. Squamous cell carcinoma

1.3.1.1. Papillary

1.3.1.2. Clear cell

1.3.1.3. Small cell

1.3.2. Adenocarcinoma

1.3.2.1. Combined small cell carcinoma

1.3.3. Adenosquamous carcinoma

1.3.4. Large cell carcinoma

1.3.4.1. Large cell neuroendocrine carcinoma

1.3.4.1.1. Combined large cell neuroendocrine carcinoma

1.3.4.2. Basaloid carcinoma

1.3.4.3. Lymphoepithelioma-like carcinoma

1.3.4.4. Clear cell carcinoma

1.3.4.5. Large cell carcinoma with rhabdoid phenotype

1.3.5. Adenosquamous carcinoma

Pre-invasive lesions

Atypical adenomatous hyperplasia

Adenocarcinoma in situ (<3 cm formerly solitary BAC)

Nonmucinous

Mucinous

Mixed mucinous/nonmucinous

Minimal invasive adenocarcinoma (<3 cm lepidic predominant tumour with <5 mm invasion)

Nonmucinous

Mucinous

Mixed mucinous/nonmucinous

Invasive adenocarcinoma

Lepidic predominant (formerly nonmucinous BAC pattern with >5 mm invasion)

Acinar predominant

Papillary predominant

Micropapillary predominant

Solid predominant

Variants of invasive adenocarcinoma

Invasive mucinous adenocarcinoma (including formerly mucinous BAC)

Goblet (low and high grade)
1.2.3 Aetiology and risk factors

1.2.3.1 Cigarette smoking

Cigarette smoking is primarily responsible for approximately 90% of cases of lung cancer. The unequivocal role of cigarette smoking in causing lung cancer is one of the most thoroughly documented causal relationships in biomedical research.[3] The association between cigarette smoking and the development of lung cancer has been recognized since 1950,[61, 62] and accumulated evidence allowed the relationship to be officially recognized by the Royal College of Physicians in 1962,[63] and the US Surgeon General in 1964.[64] Smoking confers a 20-fold risk of development of lung cancer compared to those who have never smoked. While smoking cessation is known to reduce the long-term risk of lung cancer,[65] exposure to cigarette smoke causes potentially irreversible genetic changes in epithelial cells, so the risk never returns to that of non-smokers.[6, 7]

A dose-response effect between smoking exposure and risk of lung cancer exists.[3] Studies have indicated a stronger effect of duration of smoking compared to number of cigarettes smoked. Tripling the number of cigarettes smoked per day is suggested to triple the risk of lung cancer, whereas tripling the duration of cigarette exposure is suggested to increase the risk 100-fold.[3]

Conversely, the risk of lung cancer may be significantly reduced through cessation of exposure to cigarette smoke. Measurable effects on lung cancer incidence are not seen until at least 5 years after cessation.[66] Exposure to cigarette smoke causes potentially irreversible genetic changes in epithelial cells, therefore lung cancer incidence and mortality trends closely reflect patterns in smoking prevalence from 20 to 30 years earlier.[67, 68] The risk of lung cancer never returns to that of non-smokers,[7] however long-term incidence of lung cancer in sustained quitters is reduced by greater than 50% compared to those who continue to smoke.[7] Stopping smoking before middle age avoids more than 90% of the risk attributable to tobacco.[69]
1.2.3.2 Passive smoking

Exposure to environmental cigarette smoke exhaled by smokers (passive smoking) was first suggested as a risk for lung cancer following the observation that non-smoking wives of heavy smokers have a higher risk of lung cancer than those marries to non-smokers.[70] Accumulated evidence resulted in recognition by the US Surgeon General, and the US Environmental Protection Agency of the lung cancer risk posed by passive smoking.[71, 72]

Non-smokers environmentally exposed have elevated levels of tobacco smoke byproducts in biological samples.[73] The relative risk increase is modest, and may not be sustained following removal from exposure,[74] with the lower incidence of lung cancer in passive smokers being reflective of the lower dosage of carcinogens received, but suggest there is no safe dose for tobacco smoke exposure. Despite the reduced risk, passive smoking is still estimated to be responsible for 25% of lung cancer cases among never-smokers,[75] and to be responsible for approximately 3,000 deaths per year in the USA.[72] The excess risk of lung cancer in non-smokers who lived with a smoker is estimated to be 24%, with risk increased by both increased ‘dose’ of passive smoking and increasing duration of exposure.[76]

1.2.3.3 Radon

Radon in indoor environments is now considered the second-leading cause of lung cancer,[77, 78] and a potentially modifiable risk factor for lung cancer.[79] It is estimated to be responsible for 2 – 3% of lung cancer cases.[69, 79] Radon is an inert gas resulting from decay of Uranium and is a recognized respiratory carcinogen.[80] Outdoor radon concentrations are usually low, but indoors they are higher, especially in houses and other small buildings, and in most countries radon is the largest source of exposure to natural ionising radiation.[77] The carcinogenic effect of exposure to both tobacco and radon appears synergistic.[81, 82]

1.2.3.4 Radiation

Two forms of ionizing radiation are recognized, determined by the rate of energy transfer to tissue. low linear energy transfer (LET) radiation (eg, x-rays, gamma rays)
and high-LET radiation (eg, neutrons, radon, alpha particles). High-LET radiation produces ionization of relatively higher density in tissues than low-LET radiation, so in equivalent doses, more biological damage is produced by high-LET than low-LET radiation.[83]

Ionizing radiation is present in the environment, and this ‘cosmic’ constitutes over 80% of lifetime radiation exposure, with dosages estimated at 2.4 milliSieverts (mSv) per year.[84] The biologic effects of radiation are non-linear and, while low doses and dose rates of sparsely ionizing forms of radiation (e.g., x rays, gamma rays, beta particles) may in fact stimulate natural cancer preventative processes,[85] exposure to higher doses of ionizing radiation is recognized to increase the risk of numerous malignancies, as well as benign disease.[86] Radiologic imaging for medical purposes is one of the major sources of increased radiation exposure.[87, 88]

Knowledge of cancer risk associated with exposure to ionising radiation in excess of background radiation is largely based on studies of Japanese atomic bomb survivors. These groups had very high exposures and were observed to experience higher rates of both solid organ and haematological malignancies.[89, 90] However, linear extrapolation of data from populations exposed to high doses overestimates the cancer risks of low-dose exposures.[91] The biologic effects of low-dose and high-dose ionising radiation are not linearly distributed[92] and recovery from radiation-induced injury is much more effective following low-dose exposures.[93] and following low dose rates.[94]

While high dose radiation therapy to the thorax is associated with increased risk of cancer,[95] recurrent exposure to low-dose radiation has not been associated with increased cancer risks in either medical[96, 97] or occupational cohorts.[97-99]

1.2.3.5 Asbestos

The relationship between asbestos exposure and lung cancer has been recognized for several decades.[100, 101] Increased incidence of lung cancer is seen in both smokers and non-smokers,[102] and the effect of smoking on lung cancer risk is synergistic with asbestos exposure,[102, 103] possibly due in part to augmentation of asbestos
fibre retention within the lung.[104] Radiographic asbestosis (i.e. interstitial lung disease) predicts a higher likelihood of lung cancer, though this is in part confounded by the dose-response relationship between asbestos exposure and development of asbestosis.[105] That lung cancer risk is increased in asbestos-exposed individuals without radiographic evidence of asbestosis is generally, though not universally accepted.[105-107] While the relative risk of mesothelioma following asbestos exposure is much greater than that for lung cancer, the mortality from lung cancer exceeds that for mesothelioma by two to one.[108]

1.2.3.6 Non-malignant lung disease

Pulmonary fibrosis has been associated with an increased risk of lung cancer, with population-based studies suggesting a relative risk exceeding 8, independent of the risk of smoking.[109, 110] However not all studies have demonstrated such a relationship.[111] Shared pathogenic factors between lung cancer, such as smoking,[112] metal dust exposure,[113, 114] or genetic mutations,[115-117] may underlie the relationship. Alternatively, the diffuse inflammatory process of IPF may increase lung cancer risk.[118]

Lung cancer risk in patients with chronic obstructive pulmonary disease (COPD) is significantly increased even following adjustment for age, gender, and smoking status.[119, 120] COPD is also more strongly associated with the SCC histological subtype of NSCLC.[121] COPD is even associated with increased risk of lung cancer in never-smokers.[122] Recurrent or persistent inflammation and chronic immune stimulation, as well as shared genetic determinants are thought to underlie this relationship. Lung cancer is the most common cause of death in patients with mild to moderate COPD,[123] though is second to respiratory failure in those with severe COPD.[124]

1.2.3.7 Cannabis

Cannabis use is associated with an increase in lung cancer even following adjustment for tobacco exposure in multiple studies.[125, 126] While cannabis is frequently smoked mixed with tobacco, the topography of cannabis smoking (i.e. number of
puffs, puff volume, duration, and velocity) differs from cigarette smoking – cannabis is usually smoked without filters, inhaled more deeply and held for longer.[125] The carcinogens, present in higher concentrations than in tobacco,[127] are therefore delivered much more effectively to the lung periphery.

### 1.2.3.8 Other exposures

Numerous other occupational and environmental exposures are recognized to increase the risk of lung cancer. Urban air contains markedly higher concentrations of inhalable carcinogens.[128] Many studies have observed an epidemiologic association between high pollution, as measured by concentration in air of particulate matter, and incidence of lung cancer.[128] Long-term exposure to traffic-related air pollution has been associated with an increased risk of lung cancer in non-smokers, though such a relationship has not been confirmed in cigarette smokers.[129] Vehicle emissions are thought to be particularly important in this association.[130]

Environmental exposure to Diesel motor emissions has been suggested to increase risk of lung cancer,[131] Evidence regarding such an association is stronger in the occupational setting,[132] though remains inconsistent.[133] Indoor pollution associated with use of some cooking and heating fuels has been linked to lung cancer in some regions of the developing world.[134, 135]

Exposure to numerous occupational pollutants may increase the risk of lung cancer, with an estimated 9% of lung cancers in men being attributable to occupational exposures, though this number includes asbestos-related disease. For example, exposure to silica dust is estimated to roughly double the risk of lung cancer.[136] Other occupational exposures associated with increased risk of lung cancer include beryllium,[137] vinyl chloride,[138] nickel,[139] cadmium,[140] arsenic,[141] and chromium.[142]

### 1.2.3.9 Exercise & diet

Limited, though consistent, data indicates that physical activity reduces the risk of lung cancer. Moderate leisure-time physical activity may reduce lung cancer risk by
13% while high activity is observed to achieve an even greater reduction in risk of 30%. The effect is seen in both men and women though the magnitude of effect is greater in women.[143]

Alcohol consumption is associated with a modest increase in lung cancer risk (RR 1.2 for consumption >30g/day versus 0g/day). The effect is clearer in non-smokers and in males.[144, 145] Consumption <30g/day appears not to increase the risk of lung cancer.[145]

Fruits and vegetables are rich sources of free-radical-scavenging antioxidant nutrients, including carotenoids and vitamin C, and may therefore protect against oxidative insults associated with cigarette smoking. Meta-analyses suggest that elevated fruit intake is predominantly responsible for the modest reduction in lung cancer risk observed with increased fruit/vegetable consumption.[146, 147] It is difficult to separate the observed effect from confounding by socioeconomic or smoking status.[148] though a modest protective effect is suggested by most authors. Disappointingly, supplementation of diet with carotenoids has been associated with a weak increase in the risk of lung cancer,[149, 150] and is not recommended for chemoprevention of lung cancer.[151]

Large population-based studies suggest Dietary mineral consumption may influence lung cancer risk, but the associations differ by type of mineral and population subgroups.[152] For example, dietary iron intake is protective in women, and magnesium consumption increased lung cancer risk in men and in female current smokers. Mineral intake from supplements does not affect lung cancer risk.[152]

No association with fat intake has been observed,[153] however red meat and cured/processed meats,[154] deep-fried cooking, and chilli have been associated with an increased lung cancer risk in specific populations.[155] Not all studies have reported an increased risk associated with red meat consumption, with some reporting no effect,[156] or even a protective effect.[157] Similarly inconsistent findings have been reported for fish consumption.[157, 158]
1.2.3.10 Genetic factors

While tobacco smoking is unequivocally the strongest identified risk factor for lung cancer, only 10 – 15% of smokers develop lung cancer.[159] This suggests that individuals may differ in their susceptibility to tobacco carcinogens. Several studies have examined the effect of a family history on individual lung cancer risk. A recent meta-analysis of 52 such studies observed a two-fold increase associated with family history, with evidence of risk being related to early age of diagnosis and number of relatives affected.[160] This risk applied equally to smokers and never-smokers.

Other observations also indicate a genetic predisposition to lung cancer. Risk of lung cancer in increased in individuals with COPD/emphysema,[120, 161-163] or chronic bronchitis,[163-165] even after adjustment for smoking. Conversely, a prior history of multiple pneumonia diagnoses is associated with a lower risk of lung cancer.[165, 166]

It is unclear whether these associations reflect shared causal pathways or whether the inflammatory or immune environment resulting from the respiratory disease is responsible for the observed relative risks. Allelic variability has been shown to influence the risk of lung cancer.[167, 168] Certain genetic polymorphisms in genes involved in the metabolism of carcinogens,[169-171] and in DNA repair,[172-174] have also been associated with an increased risk of lung cancer in smokers and never-smokers.

Genetic studies have also illustrated a role in smoking behaviour, with allelic variation in genes encoding nicotinic acetylcholine receptor proteins influencing the probability of nicotine addiction.[175, 176] The resultant increase in tobacco exposure, and nicotinic stimulation has obvious implications for cancer risk. Nicotinic acetylcholine receptors (nAChR) are over-expressed in many lung cancers,[177, 178] Nicotine and its metabolites may also act to promote carcinogenesis and cancer progression through multiple mechanisms including autocrine stimulation,[179] inhibition of apoptosis,[180] upregulation of growth factor expression and receptor expression,[181] and stimulation of cellular pathways promoting cell survival.[182] Such behaviour is recognized to be influenced by allelic variation in protein subunits.
comprising the nAChR.[176] Further studies have suggested that specific single nucleotide polymorphisms of the nicotinic receptor protein are associated with an increased lung cancer risk, independent of tobacco exposure.[183, 184]

1.2.3.11 Acquired gene mutations

The epidermal growth factor receptor (EGFR) (also known as HER-1 or ErbB-1) is a transmembrane glycoprotein that modulates many normal cellular processes, including cellular proliferation, and angiogenesis, and survival.[185] The majority of acquired EGFR mutations identified are heterozygous, implying that they are dominant. They are present only in the tumour and, to date, no germline mutations have been described. EGFR-mutant lung adenocarcinoma is thought to be a distinct clinical entity by many authors. The presence of EGFR mutations is closely correlated to clinical and pathologic factors clinically observed to be associated with response to EGFR TKIs: female gender, Asian ethnicity, adenocarcinoma histology, never-smoking history.[186] The proportion of NSCLC patients with activating mutations ranges from 10% to 40%.[187]

Presence of activating EGFR mutations (especially exon 19 deletions or the L858R mutation) strongly predict a response to tyrosine kinase inhibitors (TKIs – see Novel biologic agents, below).[188, 189] Germ-line polymorphisms in EGFR have also been suggested to be both prognostic and predictive in NSCLC.[190]

An inversion in the short-arm chromosome of chromosome 2 may cause the fusion of part of the Echinoderm Microtubule-associated protein Like protein 4 (EML4) gene with the intracellular signalling portion of the anaplastic lymphoma kinase gene (ALK), resulting in the fusion gene EML4-ALK.[191] The resultant protein appears to promote and maintain malignant behavior. Although ALK gene rearrangements affect only approximately 4% of all lung cancers they are more frequent in younger patients, never or light smokers, and those with adenocarcinoma and appear to be mutually exclusive with EGFR and KRAS mutations.[192] It is more common in light- or never-smokers and in males.[193]
1.2.4 Epidemiology

1.2.4.1 Age & socioeconomic status

Approximately 11,000 new cases of lung cancer diagnosed in Australia annually,[1] and in 2002 an estimated 1.35 million people were diagnosed with lung cancer worldwide.[194] Approximately 70% of cases occur in males, with age-standardized new-case rates of 40 and 13 per 100,000 population for males and females respectively.[195] The median age at diagnosis is similar for both genders, being just under 70 years.[195] Worldwide during 2002, 5% of lung cancer cases were diagnosed among people aged 0 to 44 years, 14% in the 45 to 54 age group.[195] The age-specific mortality from lung cancer increases with increasing age and is greatest in those over 80 years old.[36]

The long latency between smoking exposure and development of lung cancer means that epidemiology of lung cancer generally reflects smoking prevalence thirty years prior.[196] Education and tobacco control measures have seen smoking rates fall in most Western countries.[197, 198] Australia for example, has seen the prevalence of tobacco smoking drop from 27.1% of men and 23.2% of women in 1985 to 16.6% overall in 2007.[199, 200] Conversely, smoking rates have increased significantly in developing nations recently. Early age of smoking initiation is an important risk for lung cancer,[201] making the recently observed increased prevalence of smoking among young people a significant global issue.[202, 203]

These changes in the prevalence of smoking have seen incidence of lung cancer among males in Westernized countries peak during the 1980’s,[204] however smoking prevalence did not peak in Western women until after 1960,[205] so lung cancer incidence continues to rise among females in developed countries, as well as in both genders in Southern & Eastern European, and Asian populations.[204] Due to observed increasing smoking rates, the incidence of lung cancer in Asia and Africa is expected to increase considerably in the future.[206] While developed nations currently have a similar incidence of lung cancer to developing nations, their younger populations mean age-standardized incidence of lung cancer in developing nations is estimated to be approximately double that of developed countries.[195]
Lung cancer disproportionately affects lower socioeconomic populations. An inverse association with education level, income and social class has been observed in multiple populations.[207] While smoking rates in lower socioeconomic status groups is invariably higher than higher SES groups,[208] the effect seems to persist even after adjustment for smoking.[207] Lower SES has also been associated with later stage at diagnosis.[29]

Rates of non-cancer mortality are significantly increased in those with lung cancer, compared to the general population.[209] However over 94% of patients with lung cancer will die from their disease.[209] This varies considerably depending on the extent of disease at diagnosis (see ‘Staging of lung cancer’ below), with 20 to 40% of early stage lung cancer patients dying of other (usually smoking related) causes.[210] Overall mortality rates in males in Australia have fallen by over 3% per year from 1991 to 2003, but have risen slightly in females during this period.[211]

Despite this, prognosis for lung cancer remains poor. 5-year survival among all lung cancer patients in Australia is just 11% for males, and 14% for females,[212] with similar outcomes seen in most industrialized nations.[204] Only 16% of patients have localized disease at the time of diagnosis,[44] and even these patients experience 5 year survival rates of under 60%.[213] However, a majority of patients have distant metastatic disease at the time of diagnosis,[29] and 5 year survival among these patients is just 2%.[44]

1.2.4.2 histologic subtypes
The relative prevalence of histologic subtypes of lung cancer has been observed to change over the past 50 years.[214] Initial studies of lung cancer noted a predominance of SCC,[215] however incidence of histologic type of lung cancer has progressively altered, such that adenocarcinoma now is the most common subtype in developed nations.[49, 204, 216] Three factors appear to be responsible for this phenomenon.

Following recognition of the cancer risk posed by cigarettes, multiple measures were taken in an attempt to reduce this risk. Measures were generally designed to reduce
the dose of inhaled ‘tar’. Tar is a complex mixture of many thousand chemicals, over 60 of which are recognized carcinogens.[217] Cigarette filters were introduced in the 1960s in an attempt to minimize inhalation of cigarette carcinogen-containing ‘tar’, and overall tar content of cigarettes has declined substantially over the last 40 years.[218]

However the reduced nicotine delivery resulting from these two strategies results in altered smoking topography to maintain delivery of nicotine.[219] Increased puff volume and duration seen to result from reduced tar content and use of filters results in enhanced delivery of tobacco smoke to the peripheral airways and alveoli. Indeed, in a study that compared tumor location in lung cancer patients, lower-tar cigarettes were associated with a higher likelihood of peripheral than central tumors.[220]

Finally, nitrate levels in tobacco smoke have steadily increased. Tobacco-specific nitrosamines have been observed to induce adenocarcinoma exclusively in mice,[221] and are well recognized to induce genetic mutations frequently present in adenocarcinomas. Genetic polymorphisms in CYP2E1, which metabolises nitrosamine compounds, has been shown to alter the risk of adenocarcinoma.[222]

Initial evidence suggested both reduction of tar content and use of filters on cigarettes may reduce the risk of lung cancer. Consequently, the majority of cigarettes sold in the developed world are filtered “low-tar” varieties.[223] Such changes to cigarette design have preferentially decreased the incidence of centrally occurring cancers, such as SCC and SCLC, but due to the above factors, the overall rate of adenocarcinoma appears to have increased.

However, the association between lung cancer risk and tar content is not linear. While smoking very high content tar unfiltered cigarettes may be associated with a greater risk of lung cancer, no difference exists between those smoking medium tar (15-21 mg), low tar (8-14 mg), or very low tar cigarettes (≤ 7 mg).[224] Lung carcinogen and nicotine uptake is the same in smokers of regular, light, and ultralight cigarettes. This is consistent with epidemiologic studies that show no difference in lung cancer risk in smokers of these cigarettes,[225] and comprehensive reviews have concluded that
lower tar yield cigarettes are not associated with a reduced risk of lung cancer.[226, 227]

1.2.4.3 *Lung cancer in never-smokers*

Lung cancer in never smokers is estimated to account for up to 25% of all lung cancer cases, and is the seventh most common cause of cancer death worldwide.[194] The histologic profile of lung cancer in never-smokers is different to that in smokers, with cases overwhelmingly being of the adenocarcinoma type. The incidence of lung cancer in never-smokers does not appear to have changed over the last 50 years.[228] Although some environmental, genetic, hormonal and viral factors associated with lung cancer risk have been identified (including those mentioned above), no predominant factor has emerged, and the major cause(s) of lung cancers arising in never smokers have yet to be identified.[229]

Some epidemiologic associations have been identified to predict the risk of lung cancer in never-smokers. These include occupational exposure to solvents or paints, and welding equipment.[230] Family history of lung cancer has also been associated with increased relative risk of lung cancer in never-smokers. In support of this, numerous genetic determinants of susceptibility in never-smokers have been reported.[231, 232]

There appears to be distinct differences in biologic behaviour of lung cancers between never-smokers and smokers. Survival in never-smokers is improved, independent of stage and histologic subtype.[233] There is a higher proportion of women, and a preponderance of adenocarcinoma (particularly bronchoalveolar cell carcinoma) histology.[233]

It remains controversial whether oestrogen is causally associated with lung cancer. This possibility may explain the preponderance of lung cancer in never-smoking women, in comparison to men. Oestrogen receptor expression is more frequent in lung cancers from never-smokers (compared to smokers),[234] and in vitro and in vivo studies have indicated responses to oestrogen receptor stimulation (including hormone replacement therapy) and inhibition resulting from anti-oestrogen
therapies,[235-238] Oestrogen may have the potential for carcinogenesis,[239] or progression of established malignancy.[240, 241]

1.2.4.4 Gender

The temporal incidence of lung cancer has differed between men and women for over a century. This has largely reflected the differing smoking habits between the two genders.[242] Whereas a reduction in smoking rates over the past 30 years has seen the incidence on lung cancer in men begin to fall in developed countries, the concomittant rise in smoking rates among women have resulted in a four-fold increase in lung cancer in women over a 30-year period.[243] While smoking behaviour is responsible for much of the changing epidemiology there appears to be independent factors resulting in differing epidemiology of lung cancer based on gender.[244]

Evidence regarding a differing risk between men and women of development lung cancer from smoking is inconsistent,[245] however smoking status, or duration of abstinence, does confer a worse survival in women diagnosed with lung cancer, unlike in men.[246] There are other epidemiologic differences between lung cancer in women compared to men. Survival in all disease stages is better in women,[247, 248] and response to therapies appear to be better.[249, 250] The proportion of lung cancer patients who are never-smokers is higher among women,[251] and there is a preponderance of adenocarcinoma subtype.[250, 251] At diagnosis, women are more likely to be younger and have an earlier stage of disease.[250]

Numerous plausible hypotheses to explain the observed epidemiologic differences based on gender have been suggested - for example, and female smokers have higher incidences than males of p53[252] and K-ras mutations.[253] Phenotypic variation in expression of genes involved in metabolism of tobacco carcinogens is recognized to contribute to an increased risk of lung cancer in women compared to men.[254] Expression of growth factors involved in tumour development and progression is also frequently higher in women than in men.[255, 256] DNA repair capacity, linked to risk of lung cancer,[172] may be reduced in women.[257] Human papilloma infection has been associated with lung cancer in women,[258] though this finding is inconsistent across studies.[259]
In addition, the role of oestrogen (as outlined above) may also be significant. It is unknown if these factors also explain the observed improved survival experienced by women, however factors such as reduced DNA repair capacity have been suggested to predict prolonged survival after chemotherapy administration.[260]
1.3 PATHOLOGY AND PATHOGENESIS OF LUNG CANCER

There appears to be a sequential accumulation of molecular genetic changes occurring within the normal bronchial epithelium. The accumulation sequence of these abnormalities can be clearly seen in examination of varying degrees of histologic atypia in bronchial epithelial cells. The WHO classification of lung cancers recognises a progressive path of cellular atypia in the progression of epithelial cells from normal epithelium to hyperplasia, squamous metaplasia, mild, moderate, and severe dysplasia, then towards carcinoma *in situ* (CIS), and finally, microinvasive SCC (Figure 1.2).[261]

The sequence of histologic and molecular changes in bronchial epithelium leading to invasive lung cancer is well described for squamous cell carcinomas, owing to the ready access of central airway epithelium to bronchial biopsy and, more recently, improved methods of detection of central airway lesions, such as autofluorescence bronchoscopy.[262] Much less is understood regarding development and progression of precursor lesions for SCLC or adenocarcinoma.

Squamous cell carcinoma arises from bronchial epithelial cells. Precursor lesions may demonstrate increasingly aberrant light microscopic appearance with greater number of mitotic figures seen.[263] The prevalence of pre-invasive lesions has fallen recently, commensurate with the reduced incidence of SCC overall, but may still be seen in 5 – 10% of current smokers.[263, 264] There has been only limited study of the natural history of pre-invasive bronchial lesions, with sometimes conflicting results. Higher grade lesions appear more likely to progress to invasive cancer – progression may be seen in 1 – 9% of patients with mild dysplasia versus 32% of patients with severe dysplasia.[265, 266] One study examined a cohort of patients with preinvasive lesions and noted a cumulative risk of developing lung cancer in patients with a high-grade lesion was 33% and 54% at 1 and 2 years, respectively. In contrast, none of 17 low-grade lesions progressed to invasive carcinoma.[267]

Spontaneous regression of lesions is also seen, with 59% of lesions with severe dysplasia observed to regress in one pooled review study.[263] The time period
between original observation of dysplasia and development of malignancy may be as little as a few months,[265] or up to several years.[268] In contrast, regression of CIS is uncommon, and progression to invasive carcinoma may occur in a majority of patients.[269, 270] Development of invasion in such malignancies may no longer be amenable to endobronchial therapy, therefore guidelines advise local therapy for such lesions be strongly considered.[269]
Interestingly, Smoking cessation at this relatively late stage of carcinogenesis does not seem to influence the outcome of potentially malignant preneoplastic lesions,[265] and the prevalence of preinvasive lesions did not change substantially for more than 10 years after smoking cessation.[271, 272]

Lesions are very commonly multifocal.[270, 273] While the grade of such lesions cannot be used to estimate the future risk of lung cancer, increasing number of lesions does predict a higher likelihood of progression to lung cancer.[274] Previous studies have also noted that more cancers developed from a separate site in the same individual than from the initially biopsied site. Therefore the presence of dysplasia/CIS is a risk marker for lung cancer developing elsewhere in the lung.[267, 275]

“Field cancerization” was first described in patients with oral cancer,[276] and has subsequently been demonstrated to occur in lung cancer also. Due to the widespread carcinogen exposure (secondary to tobacco smoking) throughout the respiratory tract, both genetic and epigenetic changes may be seen in non-neoplastic bronchial epithelium adjacent to established bronchial cancers.[277] It is considered to be universal in smoking patients, and explains the rate of second primaries (2% per year) [278] in patients treated for a first primary tumour.

Atypical adenomatous hyperplasia (AAH) is thought to be a potential precursor lesion of invasive adenocarcinoma of the lung. There is good morphological evidence that AAH may progress from low to high grade to adenocarcinoma in situ bronchioloalveolar carcinoma (BAC; a non-invasive lesion by definition). Invasion then develops from in situ lesions, either with lepidic progression or frank tissue invasion, and peripheral lung adenocarcinoma evolves.[279] Neither the incidence of AAH in either smoking or never-smoking subjects, nor is the likelihood of progression of AAH to invasive carcinoma known.

Atypical adenomatous hyperplasia (AAH) was first described in the 1980’s and postulated to be the precursor lesion to adenocarcinoma of the lung. The natural history of these lesions is unknown and conclusive proof that these lesions are preneoplastic is yet to arise.[279] However, AAH lesions have been observed to
contain both genetic [280] and epigenetic [281] changes typical of advanced lung adenocarcinoma, and AAH is currently regarded as a form of glandular CIS.[280]

AAH may frequently be difficult to distinguish from bronchioalveolar carcinoma in situ.[279] Lesions are usually microscopic,[279] multiple,[282] and are mostly identified incidentally in lung resected for other reasons (usually invasive lung cancer). Incidence is higher in patients with lung cancer,[279] and higher in patients with adenocarcinoma compared to squamous cell carcinoma.[283] However even in lungs resected for benign disease, up to 9% of specimens may demonstrate AAH.[279]

Hyperplasia of the airway neuroendocrine cells of the airway may be seen in association with chronic inflammation or lung fibrosis. Such findings are not regarded as preinvasive. Lesions with invasion of basement membrane by such cells are characterized as carcinoid tumourlets, or carcinoid tumour if greater than 5mm in diameter.[279] Diffuse idiopathic pulmonary neuroendocrine hyperplasia (DIPNECH) is an exceptionally rare lesion associated with the development of multiple carcinoid tumourlets, frequently accompanied by carcinoid tumours. Almost nothing is known of its biology. DIPNECH may be asymptomatic or may present with cough and dyspnoea due to airway obstruction, which may result from airway narrowing or through humoral bronchoconstriction.[284] It is typically an indolent and non-progressive disorder.[284] The relation of DIPNECH to isolated carcinoid tumours remains unknown, though some authors have postulated that DIPNECH may be a precursor to invasive neuroendocrine lung tumours.[279]

The precursor lesions for SCLC are almost completely unknown. Molecular analysis of preneoplastic epithelium in patients with SCLC reveals more extensive DNA changes than in patients with squamous cell or adenocarcinoma, suggesting that the developmental pathways for these different cell types may differ.[285]

White early preneoplastic histologic changes (hyperplasia, metaplasia) may occur as a response to acute/chronic inflammation/irritation, the development of accumulating genetic changes may be seen to accompany progressively higher degrees of cellular atypia. Genetic changes commonly seen in invasive squamous malignancies (eg.
DNA ploidy, loss of heterozygosity, altered oncogene expression) may be seen in dysplasia/CIS, with increased numbers of changes correlating with degree of histologic atypia.[279] Many of these changes may also be seen in morphologically normal bronchial epithelium, so the exact contribution to carcinogenesis is unclear.

The progressive acquisition of genetic and epigenetic abnormalities occurring as a result of tobacco exposure most commonly occurs due to DNA adduct formation.[286] Failure of adduct excision may result in critical mutations to proteins involved in either stimulatory signalling pathways or tumour suppressor gene pathways.[287] These include the epidermal growth factor receptor pathway, p53 pathway or the retinoblastoma gene pathway. Further mutations allow evasion of apoptotic signals.

Epigenetic changes (alteration of gene expression without changing the DNA sequence) may also contribute to tumourigenesis. For example, DNA methylation is a physiological function used to down-regulate gene expression. It is used to control expression of oncofetal genes or tissue-specific gene expression. Hypermethylation of the promoter regions of tumour suppressor genes results in under-expression of gene function. Many genes, from many signal pathway groups, have been found to be silenced by promoter methylation.[288] Micro-RNA molecules (miRNAs) are a class of small (~22 nucleotides) nonprotein-encoding RNA molecules that regulate gene expression by modulating the activity of specific messenger RNA targets via direct base-pairing interactions.[289] miRNA expression is commonly disregulated in a variety of cancers, including lung cancer,[290] and may function either as oncogenes or tumour suppressor genes.

Genetic and epigenetic alterations appear to occur in a relatively predictable sequence.[263] Furthermore, genetic lesions such as gene methylation,[291] loss of heterozygosity,[292] and chromosomal aneuploidy [293] are more frequently seen in high grade dysplastic lesions than lower grade dysplasia/hyperplasia. Presence of such lesions also predicts the likelihood of regression or progression of dysplastic epithelium.[293, 294]
1.4 PERIPHERAL PULMONARY LESIONS

1.4.1 Definitions
Radiographic abnormalities of the lung may be detected using multiple imaging modalities, such as chest x-ray (CXR) or computed tomography of the chest (CT chest). Observation of such abnormalities may be in the setting of symptom-directed investigation of the respiratory system, or findings may incidentally be noted on imaging performed for other indications. Specific patterns of radiographic abnormalities are associated with specific disease processes. The most common radiographic presentation of lung cancer is as a peripheral pulmonary lesion.[295]

Peripheral pulmonary lesions (PPLs) are further subdivided into solitary pulmonary nodules (SPN) and pulmonary masses. The distinction is made on the basis of size alone, with lesions <3cm characterized as an SPN and those >3cm being pulmonary masses. The probability of malignancy in pulmonary masses is very high and such lesions are presumed to represent bronchogenic carcinoma until proven otherwise.[296]

1.4.2 Solitary Pulmonary Nodule
By definition, the solitary pulmonary nodule (SPN) is a single, well-circumscribed, radiographic opacity surrounded completely by aerated lung. There is no associated atelectasis, hilar enlargement, or pleural effusion.[297] Indeterminate nodules are SPN that are not calcified in a benign pattern, and that have not been shown to be stable after >2 years of radiographic follow-up.[296] SPN lesions are common and may be seen on up to 0.2% of all CXRs,[16] though are usually not evident until at least 9mm in size.[298] Lung cancer screening studies of patients at increased risk for lung cancer have shown SPN may be identified in as many as 7% of baseline CXR studies,[299, 300] and approximately half of all smokers >50 years have at least one SPN.[300] Only a minority of such incidentally detected SPN are malignant, therefore non-invasive and minimally invasive methods are very important in the evaluation of
such lesions in order to avoid costly and invasive procedures in patients without malignant disease.

The differential diagnosis in patients with an SPN is very wide and equally, the likelihood that an SPN represents lung cancer varies widely among studies, from 1 to 12%.[17] The differential diagnosis of multiple pulmonary nodules is very different to that for SPN. Metastatic (to lung) solid organ malignancy is the most likely cause with lesions >1cm, or >0.5cm in patients with known malignancy.[301] More numerous and more rounded lesions also predict for metastases.[302] Colorectal and lung cancer, as well as lymphoma, are the most common malignancies causing multiple pulmonary nodules.[302] Calcification of nodules is more associated with benign causes. A large number of non-malignant inflammatory or infective conditions may present with multiple pulmonary nodules.

Lung cancer presenting as an SPN is significant in that they represent early stage disease which is associated with the highest chance of long-term cure from disease. Thus there is some imperative to establish a diagnosis to allow definitive surgical resection of lung cancer in a timely manner. However, CT-screening studies have demonstrated that proceeding directly to surgical resection of SPNs is not appropriate as up to 34% of thoracotomies performed for SPN reveal benign causes for the radiographic abnormalities.[18-20] Eighty per-cent of benign SPNs represent post-infectious granulomas, with a further 10% being hamartomas,[297] making surgical intervention for such lesions inappropriate. Determination of the likelihood that an SPN represents early lung cancer may be assisted by clinical and non-invasive imaging modalities,[296, 303] though only tissue biopsy can definitively diagnose the cause of an SPN.[297]

Both and clinical features and radiographic appearances may assist in estimation of the probability that an SPN represents a lung cancer. Clinical factors predicting malignant nature of SPNs include patient age, cigarette-smoking status, and a prior history of cancer.[303] Of these, a positive smoking history is the strongest predictor,[297] Increasing age also strongly predicts an increased likelihood of malignancy,[296, 297, 303, 304] with each 10-year rise in age associated with an
odds ratio of malignancy of 2.2.[296] Multiple studies have suggested that over 50% of SPN in patients older than 60 years are malignant.[304]

Three radiographic features of SPN, as determined by CT-chest, have also been shown to have predictive value in determining the likelihood of malignancy of SPNs.[303] Multiple studies have identified both a spiculated margin (see Figure 1.3),[303, 305, 306] and an upper lobe location of SPN as being associated with a higher risk of lung cancer.[303, 307] However, SPN size is by far the strongest determinant of the probability of malignancy. The risk of SPN being malignant is <1% in lesions <8mm diameter,[308] though exceeds 60% in lesions >2cm.[17] Consequently, serial CT surveillance imaging only is recommended for lesions <8mm.[308]
Features suggesting a benign cause for SPN have been widely described. Stability or regression as demonstrated by serial CT chest indicates a high probability of benignity. International guidelines for management of small pulmonary nodules detected on CT chest suggest that resolution of SPNs, or stability in size observed over a period exceeding 2 years need not be further imaged as such behaviour excludes the possibility of malignancy.[306, 308] This concept has recently been challenged by the observation in CT screening studies of very long tumour doubling times.[309, 310] Tumours with volume doubling times (VDT) exceeding 730 days will appear stable during a 2-year observation period. To illustrate the significance of this, the median VDT for adenocarcinoma with ground-glass opacity was reported as exceeding 800 days.[310]

Calcification of pulmonary nodules may occur over half of all benign nodules.[311] Certain patterns (nidus, laminated, popcorn, or diffuse) are associated with a near 100% likelihood of benignity.[311, 312] CXR is neither sensitive nor sufficiently specific for detection of calcification of SPN,[313] and therefore assessment should only be performed on CT imaging. Calcification of lung cancers may occur, though occurs in <2% of lung cancers <3cm,[314] and tends to occur in a typical pattern (eccentric, amorphous, stippled, or diffuse).[315] Calcification of SPNs alone does not preclude them from surveillance imaging, if warranted on the basis of other clinicoradiologic factors.[307]

More novel CT features of SPN may be used to predict likelihood of malignancy in SPNs, though remain to be incorporated into widespread clinical use. CT densitometry involves the measurement of attenuation values, expressed in Hounsfield units. Attenuation values are usually higher for benign nodules than they are for malignant nodules,[311] though this feature has no discriminative power.[316, 317] Increasing density observed on serial surveillance CT of SPN may be suggestive for malignancy.[316]
The degree of enhancement on spiral CT after the injection of intravenous contrast material may also assist differentiation between benign and malignant SPN,[318] though there is considerable overlap between behaviour of benign and malignant nodules,[319, 320] and other non-invasive imaging modalities have superior diagnostic accuracy in evaluation of SPN.[321]

MRI is rarely used in the imaging of the lungs, as it achieves poor resolution of proton-sparse inflated lung tissue, and suffers from susceptibility artifact due to the many air–tissue interfaces, and motion artifact intrinsic from respiratory movement and cardiac pulsation.[322] Dynamic contrast-enhanced MRI has demonstrated some ability to differentiate between benign and malignant SPN.[323, 324] However, contrast enhancement, and washout of contrast agent appear to be functions of SPN vascularity,[325] and consequently, MRI appears poor at differentiating between lung cancer and benign inflammatory lesions.[323] Area under the Receiver operating characteristic curve in differentiating lung cancer from focal organizing pneumonias varied from 0.72 to just 0.54 for different lesion enhancement characteristics (sensitivity of 63% and a specificity of 74%).[323] The absence of significant enhancement on dynamic MRI appears a strong predictor that an SPN is benign,[323, 326] though discriminatory performance is not yet sufficiently high enough to warrant inclusion in routine clinical evaluation of SPN.

### 1.4.3 Management of indeterminate pulmonary nodules

Due to the incidence of new nodules observed on follow-up scanning,[300] and the further radiation exposure that mandated CT imaging would result in, low-risk patients (e.g. never smokers, patients <40 years old) with lesions 4mm diameter or less are recommended to undergo no further chest imaging.[308] SPN with suspicious morphology or occurring in high-risk subjects, are recommended to undergo a single follow-up scan in 12 months.[308] Surveillance imaging using non-contrast low-dose CT chest is recommended for lesions 5-8mm in diameter, with interval period influenced by size of SPN and clinical risk factors.[308] Nonsolid (ground-glass) or
partly solid nodules may require longer follow-up to exclude indolent adenocarcinoma.[310]

Further evaluation of patients with SPN >8mm is recommended [308] due to the increased probability of malignancy in these lesions (18% for lesions 8-20mm, 50% for lesions >20mm). This may be performed with non-invasive metabolic imaging tools (eg. Fluoro-deoxyglucose positron emission tomography) though a majority of lesions require minimally invasive or even surgical biopsy to optimally direct subsequent management.
1.5 LUNG CANCER SCREENING

Cancer screening describes performance of non-invasive or minimally invasive tests with the intent of detection of asymptomatic cancers. The aim of screening is to detect cancer prior to the onset of symptoms as symptomatic cancers are generally at a more advanced stage than asymptomatic ones. Detection at an earlier stage will hopefully therefore be associated with improved survival from that cancer.

Improved awareness of symptoms may result in earlier presentation to medical care and subsequent earlier diagnosis. However the delay between onset of symptoms and presentation to medical care in patients with lung cancer is frequently less than a few months,[327] indicating major ‘stage-shift’ is unlikely to be achieved through improved public awareness of concerning symptoms. Screening for breast cancer using mammography, and colorectal cancer using faecal occult blood testing may achieve reductions in cancer-specific mortality.[328] Given the incidence of and mortality from lung cancer, and the fact that at diagnosis over 40% of patients have distant metastatic disease, and a further 35% have regional metastases,[329] there is much potential for improvement in survival through use of a effective screening tool for lung cancer.

The Criteria for appraising the viability, effectiveness and appropriateness of a screening programme have been considered by many groups. The United Kingdom National Screening Committee have determined criteria that should be met before screening of a condition is undertaken.[330] These pertain to the condition itself, the screening test to be implemented, the presence of an effective disease-modifying treatment, and the need for high quality evidence demonstrating that the screening programme is effective in reducing mortality or morbidity.

1.5.1 Identification of high risk patients

Determination of patients in whom targeting is warranted is based on the clinical risk of lung cancer. The frequency of benign lesions in recent CT-screening studies is ≥50
times higher than the lung cancer detection rate (<1% per yr).[331] In unselected there is therefore a high chance of false-positive results, elevated costs and potential morbidity for the screened population. The consequences of this are highlighted by CT-screening studies which noted up to one third of surgical biopsies were performed in patients ultimately demonstrated to have benign lesions.[20] Identification of patients at high risk of lung cancer who may benefit from screening studies is therefore very important.

The strongest risk factors for lung cancer is smoking status.[3] Advancing age, family history of lung cancer, and presence of COPD have also been associated with odds ratios for lung cancer exceeding 1.35.[332] Formal predictino tools have been developed to more accurately quantify the clinical risk for individual patients. The Liverpool Lung Project was conceived in order to develop a model predicting the probability than an individual would develop lung cancer within 5 years, based on clinical risk factors.[333] This model has been validated multiple times and has been used to select high-risk subjects for inclusion in CT-screening trials.[334]

1.5.2 Radiologic screening
Screening with CXR was undertaken in numerous non-randomized trials through the 1960s & 70s and all failed to demonstrate a mortality benefit. More recent randomized studies examining the benefit of routine CXR alone or in combination with sputum cytology also failed to demonstrate a definitive benefit. A Cochrane review of CXR & sputum cytology for lung cancer screening not only observed no benefit but suggested a slightly higher mortality may be associated with frequent CXR screening.[335] It has been noted that patients in the control arms of these studies frequently also underwent CXR.[336] In addition, some of these studies were powered to detect only large mortality reductions (50%) therefore smaller but still clinically significant improvements in mortality may have been missed.[337] It is worth noting that more than one randomized study reported detection of a larger number of cancers in the screened groups than control groups,[338, 339] and that case-control studies have suggested that there might still be a benefit from CXR
Therefore concerns remained that a small but clinically important benefit from screening may have gone undetected.

Subsequently the PLCO study was initiated. This study randomized participants to undergo screening with CXR (baseline, and annually thereafter for 3 years) versus usual care. Interestingly, 54% of women and 36% of men enrolled were never-smokers. Compliance with screening was excellent, at greater than 92% for each yearly review. The screening test was positive in 8.9% of all participants at baseline and steadily decreased to 7.0% at the 3-year scan. Overall, 18.5% of screened participants had at least one positive screening test. Overall, approximately 20% of participants underwent CT scan to evaluate “positive” screening CXR, and 3% underwent diagnostic biopsy. Just 1.7% of participants with “positive” screening CXRs were diagnosed with cancer (positive predictive value 0.017). Percentages were higher at the baseline scan, and higher in current smokers.

Given the low PPV of CXR-detected abnormalities, the investigators have published clinical predictors that indicate a higher likelihood a CXR-detected abnormality represents a true-positive finding (i.e. cancer). Both clinical (age, low socioeconomic status, smoking history, family history of lung cancer, low body mass index) and radiographic (presence of mass or nodule or infiltrate, unilateral hilar/mediastinal lymphadenopathy, upper/middle lobe location of abnormality) characteristics were identified that predicted an increased likelihood of CXR findings representing a true-positive finding for lung cancer.

Perhaps most promisingly, in 77,464 participants, a total of 564 lung cancers were diagnosed, of which 306 (54%) were screen-detected cancers and 87% were non–small cell lung cancers. Among non–small cell lung cancers, 59.6% of screen-detected cancers and 33.3% of interval cancers were early (I–II) stage. The study is due to report on mortality in 2015.

Detection of nodules on routine CXR require that lesion be in excess of 1cm, and one prospective study observed that lesions were not detected until they reached an average size of 2.4cm, and as large as 9cm. From 20% to as many as 65% of lung cancers may be missed on standard CXR. Multiple studies...
examining the characteristics of malignancy missed by CXR indicate that missed lesions are significantly smaller than those detected by CXR, and have a median diameter of 13 – 16 mm.[344, 345, 347] Human error is contributory,[348] as a proportion of missed lesions may be visible in retrospect.[347] A review on this subject noted “the majority of limitations are either inherent to the human visual system or decision-making process, are related to the limitations of the plain film method itself, are related to the complexity of the image of the lungs, or are due to the location and edge characteristics of the tumour itself.”.[348]

Of over 17,000 CXR abnormalities detected during performance of the PLCO, approximately 20% underwent CT chest to further characterize abnormalities. CT-chest is used as it provides much better anatomic resolution in evaluation of chest abnormalities. Early CT scanners were associated with significant radiation dosage, limiting their use as screening tools. Development of low-radiation-dose spiral CT (LDCT) scanning in the 1990s[349] allowed marked reduction in radiation and increased interest in use of CT chest as a screening tool for lung cancer as dose reduction at CT does not substantially decrease sensitivity for small pulmonary nodules.[350, 351] The first seminal paper describing the efficacy of screening for lung cancer by CT chest was published in 1999 by the Early Lung Cancer Action Project (ELCAP) Investigators.[299]

The ELCAP project performed screening with low-dose CT in 1,000 individuals aged 60 years or more with >10 pack-years history of smoking, who were fit to undergo surgery. All individuals underwent an annual spiral CT and chest X-ray. Baseline findings emphasize the value of CT over CXR for lung cancer screening. Of 233 individuals with nodules identified on CT chest, CXR demonstrated these findings in just 33 individuals. Furthermore, CXR detected ‘nodules’ in another 35 individuals in whom CT confirmed the absence of any lesions. Twelve percent of CT-detected lesions proved to be malignant, but just 26% of these were detected by CXR. Twenty-three of 27 lung cancers were Stage I. CXR detected just one sixth of these lesions.[299] Overall, therefore, the study demonstrated a prevalence of lung cancer of 2.7%, with markedly higher detection rates via CT than CXR.[299] Similar prevalence data was reported by numerous other authors examining LDCT for lung cancer screening.[300, 352, 353]
CT screening studies have noted a particularly high prevalence of non-calcified nodules requiring further investigation. Varying rates are reported, from 23%,[299] to 43%,[353] to as high as 66%.[300] To limit the number of biopsies performed in patients with nodules detected by CT chest, study designs have specified clear \textit{a priori} recommendations for management of nodules. These include the size and attenuation of pulmonary nodules, with biopsy recommended for soft-tissue-attenuating nodules larger than 10 mm or of smaller lesions with documented growth, unless low-dose CT features strongly suggested a benign nodule.[299, 353] Just 30 of 233 with nodules detected underwent biopsy recommended by the study protocol. Twenty-eight of these had biopsy performed and malignancy was demonstrated in 27.

Most nodules will require further evaluation over time which also raises concerns regarding repeated exposure to radiation. Algorithms determining surveillance protocols of screen-detected nodules are therefore just as important as those regarding biopsy of these lesions. Such algorithms are continually under revision, and some authors suggest improvements in CT technology and technique mean that as little as a single further study may be sufficient to evaluate screen-detected lesions.[354]

The ELCAP group then undertook a much larger international (I-ELCAP) study where 31,567 asymptomatic persons at risk for lung cancer underwent annual CT chest. Lung cancer was detected in 484 individuals, with 85% of these being Stage I. Although median follow-up was 40 months, the authors estimated an 88% 10-year survival.[355] However, there was no control (CXR) arm, and follow-up was limited and did not include mortality. Consequently, the study was widely criticized. While the I-ELCAP authors felt their findings vindicated the use of LDCT for screening of lung cancer, this was a widely held view. In addition, the only other large observational study reached a very different conclusion.[331]

CXR screening studies had demonstrated that screening may detect more cancers but still have no influence on mortality. Although this may be the result of inadequate sample sizes, numerous biases particularly relevant to screening studies may explain the observation. Without a control group, it is difficult if not impossible to distinguish between these effects, or even to be sure that screening has any true effect at all.[356]
By design, screening detects cancers earlier. However, if the cancers detected by screening ultimately prove fatal anyway and death occurs at the same time as it would have without screening, all screening has done is advance the time of diagnosis without moving back the time of death. Such ‘lead-time bias’ produces an apparent improvement in survival comparisons.[357] It may also result in an increased number of detected cases among screened populations. Lead-time bias is a significant confounder in lung cancer screening studies, particularly for adenocarcinomas.[358]

Periodic screening will detect a large proportion of slower growing cancers because they persist longer in an asymptomatic state. Screen-detected indolent tumours will result in apparent improvements in detection of early-stage disease and survival rates in a screened population. This phenomenon is known as Length Bias and may be determined by comparing survival rates for patients with screening-detected cases with survival in patients whose cancers were diagnosed following clinical presentation (“interval cases”). Studies have suggested that while interval-detected cancers may grow more rapidly than screening-detected cancers, length bias is not a major issue in LDCT screening for lung cancer.[358]

Screening may also detect slow growing cancers that do not need treating, as they will not cause symptoms or impact on patient survival. Overdiagnosis bias is in fact an extreme of lead-time bias, where detection of clinically unimportant (as compared to clinically indolent) tumours results in a higher than expected number of lung cancer diagnoses. This will result in improvements in proportion of early stage tumours, resectable tumours, and apparent survival.[357] Autopsy studies examining the rates of post-mortem lung cancer diagnoses illustrate there are some lung cancers that remain undetected during life and do not contribute to death.[359]

Criteria for determination of individual lung cancers that may be ‘overdiagnosed’ have been proposed on the basis of tumour growth, or ‘volume doubling time’ (VDT). A much used equation may be used to calculate VDT on the basis of increased diameter of a lesion over a fixed period of time.[360] A VDT in excess of 400 days has been proposed to identify tumours which would be ‘overdiagnosed’. [361] The influence of overdiagnosis bias in screening studies may be determined by comparing
the number of expected lung cancer diagnoses for a patient group with the number actually detected on screening. The study by Bach *et al* suggested overdiagnosis to be a major issue in lung cancer screening.[331]

Bach *et al* reported a multi-centre trial examining the effect of LDCT screening in 3246 current or ex-smokers. This was an observational study however they used validated models to predict the expected number of cases overall, and of each stage.[362, 363] Numbers of detected cancers were 2.3 times higher than the predicted number, with number of operations over 7 times higher than predicted, and there was a high proportion of early stage lung cancers, and those with stage I and II NSCLC demonstrated 2-year survival rates of 90%; significantly higher than survival rates in clinical studies. Importantly, there was no meaningful reduction in the risk of advanced lung cancer diagnosis or death due to lung cancer.[331]

The authors suggested that overdiagnosis of lung cancers was responsible for their findings, and noted that most of the lung cancers that were ultimately fatal were not detected until an advanced stage, and symptomatic, or until they caused death (ie. interval cancers).[331] The authors acknowledged the limitations of their findings, including absence of a control arm, small study size and short follow-up time but emphasized that their data, and that of the I-ELCAP study did not yet support the institution of LDCT lung cancer screening programs until the robustly-powered studies with designs accounting for well-recognized biases were completed.

Importantly, it is recognized that while stage distribution, resectability, and survival are subject to the above-described biases, mortality is not subject to these confounding biases.[357] The definitive end-point for screening studies must be mortality. The PLCO study of lung cancer screening with CXR will report on mortality in 2015 and multiple current studies of LDCT have been designed with the lessons of previous screening studies in mind (eg. adequate power, randomized studies without contamination of control group, mortality end-points).

The largest of these was NLST study, which recently published its results. This study randomized 53,000 participants between 55 and 74 years of age who had a history of cigarette smoking of at least 30 pack-years, and, if former smokers, had quit within
the previous 15 years, to undergo yearly review with either CXR or low-dose CT chest.[364] Three screening examinations in total were performed. The rate of adherence to screening was more than 90%. The rate of positive screening tests was 24.2% with low-dose CT and 6.9% with radiography over all three rounds. A total of 96.4% of the positive screening results in the low-dose CT group and 94.5% in the radiography group were false positive results. The incidence of lung cancer was higher in the CT arm (RR 1.13; 95%CI, 1.03 to 1.23). A statistically significant reduction in relative risk of lung cancer-specific mortality was seen in the CT group (RRR 20.0% (95% CI, 6.8 to 26.7; P=0.004) though the absolute benefit was small, and the number needed to screen to prevent one lung cancer death was 320. A 6.7% (95% CI, 1.2 to 13.6) RRR in all-cause mortality was seen in the CT group, though the comparison was not significant when lung cancer deaths were excluded.[364]

A number of limitations of this study have been noted both by the authors and others. Lung cancer mortality was lower in the CXR arm than observed in previous population studies, suggesting a likely ‘health volunteer bias’. Assessment and care was undertaken in large tertiary institutions renowned for their expertise. The operative mortality reported (1%) is lower than in previous studies and may be difficult for other centres to replicate. Overdiagnosis remains an issue, with minimal difference in rates of advanced disease but a significantly higher number of early stage lung cancers seen in the CT group. However, the value of screening may be illustrated by the low rate of interval lung cancer diagnoses in the CT arm (6.3% v 33%). The rate of resection of benign disease was not reported in the study, and the harm resulting from radiation-induced cancer risk is also yet to be established. Given the high number needed to screen, cost-effectiveness studies are also required prior to implementation in clinical practice.

11.4% of CT-arm participants with positive screening results in the NLST underwent at least one invasive medical procedure. Bronchoscopy was the commonest minimally invasive procedure (3.8% of all patients with positive results), however a significant proportion of patients underwent surgical resection without tissue diagnosis. This highlights the importance of strict protocols to guide management of screen-detected nodules. Meta-analysis has determined that surgically excised lesions in patient populations experience a rate of resection for benign disease of 18%.[365] To
succeed, screening studies must minimize rates of resection of benign disease. Each study has described clear management protocols to achieve this.

A single-centre study from Milan experienced a 14% rate of benign diagnosis following surgical resection.[366] Their reported nodule assessment protocol was based on lesion diameter, determined on CT slice thickness of 2.5mm.[367] Such settings are inadequate to reliably detect a 50% increase in volume of a 7mm nodule,[368] highlighting the importance of technical accuracy. Intra-observer error in nodule size assessment has been estimated at 1.32mm,[369] emphasizing the potential value of automated assessment, though such tools are not without their problems. Intra-observer agreement is modest (kappa = 0.64) for assessment of 2-dimensional measurements,[370] and is optimized with use of 3-dimensional (volume) analysis.[371]

Multiple European collaborations examining the value of CT screening for lung cancer are proceeding. Only one has published their final results.[372] The remainder have published baseline study results [373-376] however final results, including mortality outcomes, are not yet known. The size of each trial is approximately one tenth of the NLST trial, therefore meta-analysis may address the inadequate statistical power these results individually possess. Meta-analysis of baseline findings of a number of these studies indicated a higher number of stage I cancers in CT arm, and a rate of 4 thoracotomies for benign disease for every 1000 patients screened.[377] Rate of thoracotomy for benign disease ranged from 4.5% [374] to 27%.[376]

The sole European study to report beyond baseline results highlights the issue of overdiagnosis, as well as other issues that may limit the efficacy of screening.[372] 2,472 patients were randomized to either screening with low-dose CT (LDCT) or to the control arm. At three years (median follow up 33 months), 4.7% and 2.8% of LDCT patients and control patients, respectively, had been diagnosed with lung cancer (rates consistent with those seen in the NLST). While Stage I disease was detected at three times the rate in the LDCT arm (compared to the control arm), surgical resectability rates were unchanged. In addition, numbers of advanced lung cancer diagnoses were similar in the two groups and the lung cancer mortality was no
different. Death due to lung cancer constituted under 50% of all deaths observed during the study in both groups.[372]

In addition to issues with overdiagnosis, tumours at the other end of the biologic spectrum also may limit the efficacy of lung cancer screening. Some lung cancers are highly aggressive with rapid growth and propensity to metastasize early. This is emphasized by findings from the Bach et al study, described above.[331] The period in which asymptomatic cancer can be detected by CXR is estimated to be less than six months.[378] The ‘window’ for detection in an asymptomatic state may be longer for CT chest,[378] nevertheless, in the 12-month interval between screening CTs a proportion of tumours may progress to the point of being clinically apparent, and may metastasize beyond the lung. Although these ‘interval’ cancers have generally been around 5% of all malignancies diagnosed,[18] in one LDCT screening study, one third of all cancers diagnosed were locally advanced lung cancers which presented symptomatically in the interval between screening scans.[379]

It is plain therefore that numerous other measures also need to be undertaken to curb the high incidence and mortality from lung cancer. Smoking cessation is the most important of these and interestingly, there is considerable evidence that lung cancer screening programs may positively influence quit rates.[380, 381]

A majority of participants in the ELCAP study indicated their involvement increased their motivation to quit,[382] with increased success seen in those who perceived a benefit of quitting,[382] felt ‘cancer anxiety’, [382] were younger, [382] reduced FEV1,[383, 384] and had abnormal CT findings. [380, 382-386] Both younger [382, 386] and older [383, 384] age have been reported to predict higher abstinence rates in screening participants.

Long-term abstinence in screening participants may be improved by provision of resources to aid/encourage cessation.[387] A negative screening CT does not appear to promote continued smoking.[383, 384, 388] Self-reported smoking status among participants in a lung cancer screening trial was highly consistent with biochemical assessment of smoking behaviour,[389] and therefore is sufficient to identify those who may benefit from interventions encouraging abstinence from smoking.
One other concern dampening enthusiasm for lung cancer screening with CT is the risk resulting from radiation doses associated with CT. Great effort has been made to minimize the doses associated with screening and the average effective dose of CT in NLST trial was 1.5mSv.[364] This compares well to standard CT chest, which is associated with a dose of 8mSv. However some risk remains though the magnitude of this remains uncertain. Elaborate modelling suggests that significant reductions in lung cancer mortality may be required to offset the expected increase in lung (and other, particularly breast) cancer resulting from radiation exposure.[390] The risk of cancer due to radiation exposure may exceed the estimated mortality benefit in young subjects,[390] or those with modest smoking histories.[391]

1.5.3 Bronchoscopic screening

Centrally arising squamous cell carcinoma of the airway, especially in heavy smokers, is thought to develop through multiple stages from squamous metaplasia to dysplasia, followed by carcinoma in situ (CIS), progressing to invasive cancer. Identification of these lesions under normal ‘white-light’ bronchoscopy is poor, with as few as 30% accurately identified.[392] In addition, the yield of standard white-light bronchoscopy (WLB) for primary screening of even high-risk patients is essentially 0% [264] and routine bronchoscopic screening is therefore not recommended.[269]

When the bronchial surface is illuminated by light, light may be reflected, back-scattered, absorbed, or may induce tissue fluorescence. Tissue autofluorescence is not visible to the unaided eye because its intensity is very low and overwhelmed by the reflected and back-scattered light. It may be visualized with suitable augmentation technologies. Early studies trialed use of intravenous porphyrin to enhance autofluorescence, but were limited by photosensitivity reactions and prohibitive costs.[393, 394] During these studies it was noted that ‘autofluorescence’ (the natural emission of light by biological tissue in response to incident light, without the aid of fluorophore chemicals) of normal and premalignant/malignant tissue occurred at different wavelengths. Autofluorescence bronchoscopy (AFB) utilizes a sensitive image-intensified camera to amplify and capture fluorescence images at characteristic wavelengths.
spectral bands (wavelengths). These spectral differences can be exploited to enhance our ability to localize areas of intraepithelial neoplasia in the tracheobronchial tree without fluorescent drugs.[395]

Sensitivity of detection of preinvasive lesions is improved by use of AFB + WLB over WLB alone (relative sensitivity 2.0), however relative specificity of AFB+WLB versus WLB alone is just 65%.[262] In addition, detection of invasive cancer is only minimally improved with AFB, with relative sensitivity of AFB+WLB versus WLB alone just 1.15. Sensitivity also appears to vary according to the endoscopy device used with many devices demonstrating no improved ability to detect invasive lesions.[262] Given the low yield,[264] poor specificity,[262] and high cost of AFB, its use is limited to evaluation of patients with atypia/carcinoma on sputum cytology, and normal chest CT.[269]

Angiogenesis is a relatively early event in lung cancer development, and increased vessel density may be observed in the submucosa in bronchial squamous dysplasia.[396] Narrow-band imaging (NBI) is a new, alternative light-wavelength capture system that takes advantage of altered blood vessel morphology of bronchial dysplasia. Bronchoscopic illumination of the airway is performed within two narrow ‘bands’ of light. Wavelengths in the blue (390 – 445 nm) and green (530 – 550 nm) spectrum coincide with the peak absorption spectrum of oxyhemoglobin, and observation of bronchial mucosa using only these ‘bands’ allows much clearer observations of blood vessels.[397]

Bronchoscopic assessment using NBI increases the sensitivity for detection of pre-malignant and malignant central airway lesions.[398] Sensitivity of NBI is similar to that of AFB+WLB, but with the advantage of significantly improved specificity.[399] The authors hypothesized that angiogenesis is a more specific event than changes in extracellular matrix proteins and thickening of superficial mucosa in identifying intraepithelial neoplasia. AFI and NBI does not appear to increase diagnostic yield significantly.[399]
1.5.4 Screening/Surveillance following curative therapy of lung cancer (secondary screening)

Despite staging utilizing FDG-PET, from 20% to 30% of patients with stage I NSCLC develop recurrence following surgical resection.[400] Recurrent disease is considered to be incurable, but needs to be distinguished from a second primary (metachronous) cancer which should still be approached with curative intent, as survival for metachronous primary lung cancer is not different to that of patients diagnosed with a first lung cancer.[401, 402] Metachronous second primary lung cancers occur at a rate of approximately 2% per patient per year following successful resection of NSCLC.[278] Rates as high as 6% per year are seen following successful treatment of SCLC.[403]

Rates of metachronous primary lung cancer are even higher following diagnosis of head/neck squamous cell cancers, and survival is not different to patients without a history of head/neck cancer.[404] In this setting use of surveillance bronchoscopy with AFB is suggested to aid early diagnosis,[405, 406] However no trials have examined the effect on treatment outcome, and use of AFB in this setting remains investigational.
1.6 CLINICAL PRESENTATION OF LUNG CANCER

Lung cancer may result in a number of symptoms, however it may be present for very long period of time before manifesting symptomatically. Cancer may grow to a considerable size, and may metastasize outside the chest before symptoms occur. This means that up to 80% of patients have surgically incurable disease at the time of diagnosis.[9] While increased use of CT imaging for investigation of symptoms (eg. heart, abdomen) has resulted in detection of larger numbers of patients with asymptomatic indeterminate pulmonary nodules, the overall proportion of patients with symptoms of their cancer at the time of diagnosis remains largely unchanged. Over 85% of patients have symptoms at the time of diagnosis.[9]

Symptoms may have been present for long period of time before a definitive diagnosis of lung cancer is made. The delay may be due to delayed presentation of patients to medical care,[327, 407] or delayed investigation of patients following initial presentation.[407, 408] The delay in presentation could explain why asymptomatic patients may be more frequently diagnosed at an early stage.[408] Numerous authors have noted a poorer prognosis for patients with symptoms at diagnosis.[10, 408]

Symptoms may arise either due to the primary tumour (eg. cough, breathlessness, chest pain), due to metastatic disease (eg. bony pain, neurologic deficits) or may be non-specific constitutional symptoms (eg. loss of weight, fatigue). Cough is the commonest symptom,[9] though most will have multiple symptoms of their cancer.[10, 327] The non-specific nature of many of these symptoms (particularly the respiratory or constitutional symptoms) in part explains delayed presentation and diagnosis. Haemoptysis is the one ‘alarm symptom’ which may provoke early evaluation and investigation.[10]

Paraneoplastic syndromes are a group of clinical disorders that are associated with malignant diseases that are not directly related to the physical effects of primary or metastatic tumors. The extent of paraneoplastic symptoms is unrelated to the size of the primary tumor, and in some cases can precede the diagnosis of malignant disease. The most frequent mechanism of paraneoplastic syndromes is humoral, with
production of biologically active substances by the tumour itself. The commonest manifestation of these is hypercalcemia (occurring in 2 – 12% of patients),[9] thought to be mediated by a parathyroid hormone related protein (PTH-rP).[9] PTH-rP has been associated with shorter survival times and a higher likelihood of bony metastases, suggesting it may have a role in facilitating bone metastases.[409]

Elevated antidiuretic hormone (ADH) levels and impaired water handling are found in a substantial proportion of patients with lung cancer, though only a small minority develop the syndrome of inappropriate ADH production (SiADH).[410] Other humorally mediated syndromes include Cushings syndrome and finger clubbing or Hypertrophic Pulmonary Osteoarthropathy (HPOA).[9]

Neurologic paraneoplastic syndromes appear to be auto-immune – mediated.[9] They are rare, and occur almost exclusively in small cell lung cancer patients. The commonest, the Lambert-Eaton myasthenic syndrome, occurs in less that 2% of SCLC cases.[411]
1.7 DIAGNOSIS OF SUSPECTED LUNG CANCER

1.7.1 Non-invasive investigation of PPL

1.7.1.1 Chest x-ray

CXR is generally the first procedure performed in evaluation of respiratory symptoms. It may demonstrate parenchymal opacities produced by peripheral tumours, though up to 40% of the radiographic findings associated with lung cancer have been estimated to be the result of obstruction of central airways, with resultant distal collapse of infection.[412] A significant proportion of pulmonary nodules are radiographically occult.[413] In addition, information regarding suspicious lesions that is essential to optimally guide further management (eg. Lobar location, proximity to central airways, lymph node enlargement) are not reliably determined by CXR. Therefore more accurate anatomic imaging is required to fully evaluate suspicious lesions, or suspicious symptoms in patients with normal appearing CXR.

1.7.1.2 CT chest

CT imaging is almost universally the first imaging study performed to evaluate patients with suspected lung cancer following a suspicious CXR finding. Characterization of a lesion detected by CXR allows a more accurate evaluation of anatomic features of peripheral pulmonary lesions, including size, margin, relationship to other intrathoracic structures, and lobar position (as described above). All of these features may be used by clinicians to determine the likelihood of cancer (and therefore the need for more invasive investigation), and to determine the optimal approach to invasive biopsy. Valuable information regarding clinical staging of a suspected malignancy may also be determined from CT chest (see ‘non-invasive staging’, below).

A peripheral pulmonary lesion is the commonest radiologic presentation of lung cancer. Conversely the prevalence of malignancy in SPN varies very widely between studies,[17, 414] with clinical patient cohorts demonstrating a significantly higher
prevalence than SPN identified in screening studies.[414] Lung cancer may also produce other CT appearances. CT-screening studies have demonstrated early stage lung cancers may frequently appear as ground-glass opacities (GGOs). Such lesions are almost exclusively adenocarcinomas, and predominantly of the bronchioalveolar type. Semi-solid lesions may also be seen. CT appearances appear to correlate with biologic behaviour, with VDT of GGOs frequently exceeding 400 days,[310] the threshold above which lung cancers may be overdiagnosed.[361] Bronchioalveolar cell (BAC) carcinomas may also present with a consolidative radiographic pattern,[415] and may be multifocal in over a quarter of cases.[416]

As well as evaluation of the peripheral pulmonary lesion (if present), CT also permits evaluation of other areas frequently complicated by lung cancer metastases. Mediastinal lymphadenopathy may be evident (see ‘Non-invasive staging of lung cancer’, below), and pleural effusion may be visualized. Bony lesions may also been seen on CT chest. Expert guidelines suggest initial tissue sampling be performed from suspected metastatic lesions, if accessible.[417] Radiologic features of a peripheral lesion may guide clinicians in selection of the optimal investigation to evaluate peripheral lesions (see ‘Invasive diagnosis of suspected lung cancer’, below).

1.7.1.3  **Positron Emission Tomography**

Positron Emission Tomography (PET) with fluorine 18 fluorodeoxyglucose (\(^{18}\)F-FDG or FDG) is used to evaluate glucose metabolism in tumours. FDG is taken up selectively by malignant tumor cells, which overexpress the glucose transporter protein. FDG subsequently accumulates within the cell because the radiolabeled glucose analog is phosphorylated once but not metabolized further. Malignant tissues typically demonstrate higher FDG uptake than benign lesions and normal tissue, though FDG uptake may be seen in inflammatory or infective conditions. The false positive findings seen in such conditions contribute to reduced specificity, previously calculated in meta-analysis at 78%.[418]

Significant gains in diagnostic accuracy and observer confidence can be achieved with the co-registration of data provided by both CT and FDG-PET imaging modalities. Combined PET/CT allows correlation of anatomic findings with metabolic findings.
Overall diagnostic accuracy of integrated PET/CT exceeds 90%.[419, 420] and is more sensitive and accurate in the detection of malignancy in SPN that dynamic CT imaging.[419]

1.7.1.4 Non-invasive diagnosis

Given the significant proportion of patients in whom PPL represents a benign process, there is considerable importance placed on the ability to definitively diagnose such peripheral lesions in order to plan appropriate therapy. Whereas a diagnosis of cancer may warrant expeditious surgical removal of the lesion, benign lesions frequently require no specific therapy at all. Referral for definitive surgical treatment of lesions with a very high pre-test probability of malignancy (see ‘Treatments and outcomes of lung cancer’, below), based on clinical, CT, and PET information, is suggested by some expert guidelines.[296]

Thoracosopic surgery allows definitive determination of PPL, with up to 100% accuracy.[421] though it entails significant risks, which are completely unjustified for benign lesions. In addition, 15 – 20% of operations may require conversion to open thoracotomy in order to resect the lesion.[421-424] In clinical studies reporting use of VATS for evaluation of SPN, the proportion of patients with primary lung cancer varied from 14 – 55%.[301, 421, 423-425] Therefore considerable emphasis is placed on determination of a histologic diagnosis to allow planning of appropriate therapy in patients with SPN.

Non-invasive diagnosis may be achieved via sputum cytology in a small proportion of patients. Sensitivity for central airway lesions may be maximized by examination of multiple specimens and has been reported to be as high as 0.66.[417] However, sensitivity varies greatly between published studies and, in addition, there is some concern regarding the possibility of false positive results.[417] Specificity for the diagnosis of lung cancer may be as low as 90%.[426] Sensitivity is very poor for peripheral malignancies. In addition, inability to expectorate is common, and is the most common reason for non-diagnostic sputum cytology.[427] Induced sputum, using either hypertonic saline [428] or cholinergic medications [429] may improve diagnostic success in such patients.
1.7.2 Invasive diagnosis of PPL

1.7.2.1 bronchoscopy

Endoluminal examination of the bronchial tree was first performed in 1897 by Professor Gustav Killian in order to remove an inhaled foreign body (pork bone). The procedure was performed using a rigid esophagoscope, with vision provided by a head light, and with only topical cocaine as an anaesthetic agent.[430] Dedicated bronchoscopic instruments were developed over the next few decades.[431] Use of a rigid bronchoscope allowed endobronchial examination and biopsy of endobronchial tumour.[432] However, it was able to examine only a small portion of the bronchial tree, and diagnostic sensitivity was poor for the detection of even central lung cancer.[433] Evaluation of peripheral lung lesions using rigid bronchoscopy was not feasible.

Flexible bronchoscopy (FB) was first performed in 1966,[434] affording a much more extensive view of the tracheobronchial tree.[435] Procedures were originally performed to evaluate for possible central airway lung malignancy.[436] Use in examination of peripheral lesions indicated a lower sensitivity of flexible bronchoscopy, as compared to central lesions, however use of fluoroscopic guidance during performance of peripheral sampling did improve diagnostic performance.[25, 437] Conventional sampling included use of biopsy forceps, as well as cytology brush and bronchial washings, both of which yielded specimens suitable for cytologic analysis.

Performance characteristics of FB in the diagnosis of lung cancer vary considerably according to the position of the lesion within the thorax. Sensitivity in evaluation of central lesions (those visible at FB) is excellent, at approximately 88%.[417] Bronchial biopsy is the most valuable single technique in yielding a diagnosis, though the other methods may contribute to increased yield.[417] Needle aspiration may also contribute to increased diagnostic yield in central lesions, with the value being highest.
for lesions with submucosal spread without overt exophytic endobronchial tumour.[438]

Sensitivity of FB is reduced in investigation of peripheral lesions, and is also affected by lesion size under investigation. Bronchoscopic investigation of peripheral lesions should always be performed with fluoroscopic guidance as it reduces the incidence of pneumothorax.[439] Even with such guidance, sensitivity for lesions >2cm is reduced to 63%, and falls to just 34% when lesions are <2cm diameter.[417] The false negative rate for bronchoscopy has not been defined in published studies, and expert guidelines strongly recommend further investigation in patients suspected of having lung cancer in whom bronchoscopy is non-diagnostic.[417]

As an invasive procedure, complications may be noted following bronchoscopy. Routine bronchoscopy is extremely safe, with a mortality rate of 0–0.04%.[440-443] Most complications are minor (eg. haemoptysis, nausea/vomiting, transient hypoxemia, laryngeal spasm, fever) and transient.[440, 444] and hospital admission for management of complications is required in less than 0.7%.[440, 441] Pneumothorax rates following routine bronchoscopy are less than 0.05%.[441, 442] Complications of FB for investigation of suspected lung cancer are generally a result of transbronchial lung biopsy (TBLB).

The two major complications of TBLB are haemorrhage and pneumothorax.[444] Significant airway bleeding requiring endobronchial therapy (eg. adrenaline) is seen in under 0.3% of patients not on anticoagulant medication.[445, 446] Use of aspirin does not increase bleeding rates,[447] though clopidogrel is associated with a significantly elevated risk of severe bleeding – one study suggested 89% of patients may experience some bleeding, and 27% may experience bleeding requiring endobronchial therapy when TBLB is performed on clopidogrel therapy.[445] Increased rates of bleeding may be seen in uraemic or thrombocytopaenic patients. Pulmonary hypertension has not been associated with increased bleeding rates following TBLB.[448] No reports of haemorrhage complicating TBLB requiring therapy beyond endobronchial (bronchoscopic) management are reported in international literature.
Incidence of pneumothorax complicating TBLB for investigation of PPL varies between reports, from 0 – 6%. Use of fluoroscopy has been suggested to reduce the need for intercostal catheter insertion, though not the overall rate of pneumothorax. Systematic studies have not determined specific clinicoradiologic factors that predict an increased risk of complications specific to TBLB. A majority of pneumothoraces complicating TBLB may be managed conservatively, though 0.1 – 2% of patients will require intercostal catheter drainage.

1.7.2.2 CT-guided percutaneous sampling

Transthoracic sampling of pulmonary parenchymal lesions may be performed via a percutaneous route. Sampling may be performed using either a fine needle (aspirate only), or a co-axial core biopsy needle. Diagnostic accuracy is higher than fluoroscopically-guided TBLB, with overall accuracy exceeding 90%. However, diagnostic accuracy may be reduced in evaluation of very small nodules, with a reduced diagnostic accuracy for detection of malignancy in nodules <2cm reported by multiple authors. Other studies have noted no effect of lesion size on diagnostic accuracy.

The risk of complications is significantly higher than seen following TBLB, almost certainly as the biopsy instrument must breach visceral pleura to access the PPL. Pneumothorax rates as low as 12 – 15% are reported however a majority of studies experience pneumothorax rates exceeding 24%. with rates over 60% reported. Rate of detection of pneumothorax may be higher when post-biopsy CT is used rather than CXR. 0.5–5% of patients undergoing CT-biopsy will require intercostal catheter drainage, though ICC insertion rate may exceed 14%

Pneumothorax rates are higher with use of larger gauge needles, and multiple clinicoradiologic factors may influence pneumothorax rates. Pulmonary haemorrhage is less frequent than pneumothorax, though still complicates 1 – 10% of CT-PNB. Haemorrhage requiring intervention is extremely rare.
More serious complications are rare and overall mortality from the procedure is estimated at between 0.02 – 0.15%.[470, 471] Air embolism occurs in 0.2 – 0.4%.[472, 473] Malignant seeding of the needle tract or pleural space in patients with lung cancer biopsied by percutaneous approach appears rare,[474] though was reported to occur in over 0.5% of patients in one retrospective study.[472]

### 1.7.2.3 Video-assisted thoracoscopic surgery

Video-assisted thoracoscopic resection may be performed for evaluation of PPL. Definitive therapy of peripheral early stage lung malignancies is surgical resection and, if frozen section examination of the resected lesion confirms a diagnosis of lung cancer, completion lobectomy and lymph node dissection (see ‘treatment of NSCLC’, below) can be performed at the same operation. Such an approach should be reserved for highly selected patients – non-invasive evaluation using FDG-PET (see Non-invasive staging of lung cancer’, below) must be indicative of early stage lung cancer, and physiologic evaluation should indicate a low probability of morbidity/mortality. Even optimally selected patients experience morbidity and mortality of 0–9.6% and 0–0.5%, respectively.[421, 424, 425, 475, 476] A majority of patients require post-operative admission for a median 2 days.[475]

Localization of pulmonary lesions may be required prior to performance of VATS. In studies where localization was not utilized, 15 – 20% of operations required conversion to open thoracotomy in order to resect the lesion.[421-423] Smaller lesion size, and increasing distance from pleural surface predict a higher rate of inability to localize a lesion at VATS. If the distance between a pulmonary nodule <10mm diameter and the pleural surface was > 5 mm, the probability of failure to detect a nodule was 63% in one retrospective analysis.[477] Use of localization techniques reduces the rate of conversion to open thoracotomy.[478] This may be performed using CT-guided hookwire insertion just prior to surgery, or methylene blue staining of pleural surface.[479]
1.8 STAGING OF LUNG CANCER

Following a diagnosis of lung cancer, it is essential that the extent of disease be accurately determined. ‘Staging’ describes the process by which the extent of the primary tumour and the extent of tumour spread within the body are established. That survival of patients with non-small cell lung cancer (NSCLC) is influenced by the extent of disease at diagnosis has long been recognised.[480] Accurate staging of lung cancer is essential to allow optimal selection of treatment approach for individual patients. It also has been shown to be the most accurate predictor of prognosis for patients diagnosed with lung cancer. In support of this, recent studies have noted that the value of accurate staging of NSCLC in influencing prognosis may exceed that of recent novel and highly expensive targeted therapies.[481, 482]

Staging systems differ for NSCLC and small cell lung cancer. Small cell lung cancer is staged according to a two-stage system. Limited-stage disease is defined as that which is limited to one hemithorax, with hilar and mediastinal lymph nodes that can be encompassed within one tolerable radiotherapy field. Extensive-stage disease is any disease beyond those boundaries. Following a diagnosis of small cell lung cancer, subsequent investigation is intended to identify any site of disease that would render patients ‘extensive’ stage. Initial investigation is guided by clinical history and examination findings. Routine staging investigations are performed to evaluate organs frequently involved by (asymptomatic) metastases, and include CT chest/abdomen, CT brain, and bone scan.[46] PET has been suggested to be useful in upstaging a small proportion of patients determined to have limited stage disease by conventional staging studies,[483] though this is not a universal finding, and FDG-PET is not currently recommended as a routine staging investigation for patients with small cell lung cancer.[46]

Staging of NSCLC is performed according to the TNM system used for many solid organ malignancies and, as such, is based solely on the anatomic extent of disease. The T-stage (1 – 4) describes features of the primary tumour, N-stage (0 – 3) determines the extent of hilar/mediastinal lymph node involvement, and the M-stage (0 – 1) describes the presence or absence of distant (extrapulmonary) disease (see
Staging is based on these TNM scores, and is used to determine the optimal treatment approach. Survival also differs between stage groupings, and this information may be used to provide some prognostic advice to patients.[484]

Staging may be based on clinical and radiologic findings. Estimates of disease stage based on clinical and radiologic findings are termed ‘clinical’ stage and are denoted as cT1-4,N0-3,M0-1. Clinical staging therefore may be achieved by non-invasive modalities. Definitive treatment decisions are generally made following pathologic confirmation of clinical findings, with such ‘pathologic’ staging being denoted by pT1-4,N0-3,M0-1. Pathologic staging is based only on tissue samples obtained by invasive means.

Post-operative staging may also describe the adequacy of surgical resection. No residual tumour is denoted as R0, with microscopically positive margins without visible tumour R1, and visible or palpable tumour remaining at completion of surgery staged as R2.[485]
1.8.1 Non-invasive staging of Non-small cell lung cancer

1.8.1.1 CT chest

Radiologic imaging with computerized tomography (CT) scanning of the chest is standard in patients with suspected lung cancer, following identification of abnormalities on CXR, or on the basis of concerning symptoms despite a normal CXR. CT chest is recommended in all patients with lung cancer as it provides significant information on the primary lesion, and the hilar and mediastinal regions allowing assessment of the cT and cN stage of a tumour.[30] Limited imaging of the bony skeleton as well as upper abdominal organs may also permit some conclusions regarding the M-stage status.

T-stage is determined by CT chest based on features of the primary tumour, including diameter, proximity to/involvement of mediastinal structures or chest wall, and presence of satellite nodules or even ipsilateral or contralateral metastatic lesions. The only method by which clinicians may more accurately assess T-stage is following surgical exploration/resection. T-stage may be altered post-operatively in approximately 30% of NSCLC patients.[486]

Accurate assessment of N-stage is critical given the influence this tumour feature has on selection of treatment strategy (see below). Initial evaluation is performed on the basis of CT chest, ideally with contrast enhancement. Involvement of hilar (N1) or mediastinal (N2 or N3) lymph nodes by NSCLC is assessed on CT by size criteria alone. The most widely used criterion is a short-axis lymph node diameter of ≥ 1 cm on axial CT imaging.[30] However this is cut-off is somewhat arbitrary, chosen as it demonstrates the best trade-off between sensitivity and specificity.[30]

While median size of metastatic LN is larger than non-involved nodes,[487] it is not possible to reliably differentiate malignant mediastinal nodes from benign nodes by size alone. Indeed, in over one sixth of pN2/3 patients, the largest resected lymph node may not contain metastatic tumour.[487] In up to 75% of mediastinal lymph nodes pathologically confirmed as metastatic, LN size is <1cm.[488, 489] The median size of mediastinal LN metastases has been reported at 8mm,[487] while Prenzel et al
suggested that over 10% of LN sized 5-10mm will be positive for malignant disease at pathologic analysis.[490] Consequently, diagnostic accuracy of CT for evaluation of N-status is limited.

A recent systematic review of literature relating to the accuracy of CT scanning for noninvasive staging of the mediastinum in patients with lung cancer demonstrated pooled sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis were 51% (95% confidence interval [CI], 47 to 54%) and 86% (95% CI, 84 to 88%), respectively,[30] confirming that CT scanning has a limited ability either to rule in or exclude mediastinal metastasis.

1.8.1.2  **FDG-PET**

More accurate non-invasive staging of NSCLC may be achieved by FDG-PET than by CT chest. Its use is routine in pre-treatment evaluation of patients with NSCLC and may alter planned therapy in a majority of patients.[491] Meta-analysis has demonstrated that FDG-PET is more accurate than CT chest in mediastinal staging of NSCLC.[492] Integrated PET/CT is significantly more accurate than FDG-PET alone in assessment of cN-status in NSCLC,[493] with accuracy of mediastinal lymph node metastases at almost all hilar and mediastinal lymph node stations higher with PET/CT versus PET alone.

The specificity of PET/CT is higher with decreasing lymph node size. Meta-analysis of 14 studies examining performance of FDG-PET at different lymph node sizes suggested that the NPV of PET in LN 10-15mm is 5%.[494] In contrast, LN >16mm identified as non-involved by FDG-PET were determined pathologically to be metastatic in 21%.[494] Median specificity of FDG-PET in the assessment of mediastinal LN is 78%.[492]

In contrast to the limitations of size criteria applied to staging via CT chest, outlined above, due to the functional nature of PET it is able to detect metastatic LN deposits significantly smaller than 1cm. Sensitivity may be slightly reduced in detection of metastatic LN <1cm, though overall diagnostic accuracy is comparable to that for evaluation of larger LN lesions.[495] Metastatic foci as small as 4mm may be
detected.[496] Sensitivity of PET in evaluation of LN > 1cm exceeds 90% [492] and Gupta et al have suggested it may approach 100%. [495]

Detection of distant metastases (cM1) may also be achieved via FDG-PET and PET/CT is significantly better than either modality alone in detection of extra-thoracic disease.[497] In up to 18% of patients staged cN0/1 by CT chest, (and 24% of patients staged cN2/3) PET may detect occult extrathoracic metastatic disease.[498]

The sensitivity of FDG-PET may be reduced in detection of residual disease after induction therapy.[499] Meta-analysis indicates both sensitivity and specificity of PET is reduced when restaging patients with Stage III NSCLC who have undergone neoadjuvant therapy.[500]

Use of PET/CT to non-invasively stage patients has been demonstrated in multiple settings to be cost-effective.[501-503] This is predicated upon the ability to identify with greater accuracy than CT-chest patients for whom surgical thoracotomy is not beneficial. Those with mediastinal or extrathoracic metastatic NSCLC detected by PET avoid undergoing ‘futile’ thoracotomy. PET is more cost-effective than CT alone.[504] Due to the imperfect specificity of PET/CT, some patients may be incorrectly upstaged by non-invasive means. Such patients would incorrectly be denied surgery and for this reason published guidelines recommend pathologic confirmation of all PET-detected mediastinal metastatic disease.[30]

1.8.1.3 Other imaging modalities

While FDG-PET has proven value in detection of extrathoracic disease, alternate modalities may be used in the absence of PET technology to detect ‘M1’ disease in NSCLC. In addition, FDG-PET is not currently recommended, or reimbursed, for use in staging SCLC. Extensive imaging is not required in patients who exhibit clinically obvious metastatic disease eg. supraclavicular/cervical lymphadenopathy, or skin metastases.

CT Brain is required in patients with clinical suspicion of cerebral metastases. In patients in whom no clinical evidence of brain metastases exists, CT brain may
demonstrate cerebral metastases is approximately 3% of patients.[30] Specificity of findings is less than 11% so a number of patients will require invasive biopsy to confirm radiologic suspicion of M1 disease. MRI brain is more sensitive in the detection of brain metastases, though studies have suggested this does not alter survival. Increased prevalence of cerebral metastases are associated with advanced stage of NSCLC and adenocarcinoma.[30] Patients undergoing radical therapy for Stage III NSCLC are generally evaluated with CT or MRI brain.

Bone scan was previously advocated due to the high prevalence of occult bone metastases at time of diagnosis of NSCLC. Approximately 16% of may have occult disease demonstrated by bone scan.[30] The ability of FDG-PET to demonstrate bony disease has resulted in bone scan being used very rarely. It may still be clinically useful in investigation of clinically suspicious bony disease though the specificity of findings due to co-existence of degenerative/traumatic skeletal disease may be compromised.

1.8.2 Invasive staging of NSCLC

Invasive mediastinal staging is essential in directing management of NSCLC given the different treatment approaches recommended for Stage I/II NSCLC as compared to Stage III/IV (see below). As outlined above, the non-invasive staging modalities have insufficient diagnostic accuracy to alone determine management and instead serve to direct invasive pre-operative staging of NSCLC. Discrepancies between non-invasive and invasive staging may be seen in approximately one third of NSCLC patients.[505] In those staged cN0 by CT chest, upstaging following surgical LN evaluation occurs in up to 20%.[489] Prior to widespread use of FDG-PET for non-invasive staging, many centres practiced routine mediastinoscopy to allow pre-operative staging.

The increased sensitivity of FDG-PET for detection of N2/3 NSCLC, in comparison to CT chest, has reduced the need for pre-operative invasive staging. The negative predictive value of FDG-PET in mediastinal staging of NSCLC is sufficiently high to
obviate invasive staging in such patients (>85% [506]) Multiple authors have demonstrated that high sensitivity of FDG-PET for detection of N2/3 NSCLC means routine mediastinoscopy is not cost-effective.[501, 507] Therefore, due to the low yield of invasive staging in patients, international guidelines recommend these patients proceed directly to curative resection of NSCLC.[30]

Although there are no clinical trials comparing surgical resection to other forms of therapy for treating stage I and II lung cancer (pN0 & pN1, respectively), extensive clinical experience indicates that the best chance of cure for these tumors comes with surgical resection.[508] In contrast initial therapy in patients with pre-operatively confirmed N2/3 NSCLC consists of combination chemoradiotherapy.[509] Patients falsely up-staged by FDG-PET would be offered inferior therapy for the true stage of their disease. Specificity of FDG-PET for mediastinal staging in NSCLC is 90%.[492] Therefore cytologic/histologic confirmation of clinically suspected N2/3 disease is mandated by published international guidelines.[30]

Multiple clinical factors predicting a higher likelihood of post-operative up-staging in patients in whom FDG-PET suggests the absence of mediastinal metastases have been identified. These include patients staged cN1 by CT [510] or PET,[511-513] centrally located tumours,[511, 512, 514] high SUVmax,[513, 514] adenocarcinoma histology,[513, 514] age,[512, 515] and upper lobe tumours.[512, 513] Such patients may be considered for pre-operative staging procedures, though widespread variation in clinical practice exists with respect to this.

1.8.2.1 Surgical Mediastinoscopy
Surgical examination of the mediastinum was first described in 1954,[516] with its intent being to spare patients a surgical thoracotomy should mediastinal disease be demonstrated as, even at this time, involvement of the mediastinum was recognized to preclude surgical resection of lung cancer.[517] Cervical mediastinoscopy involves introduction of a rigid scope through a suprasternal incision and blunt dissection inferiorly along the pretracheal fascia to access both right and left paratracheal lymph nodes.[518] Lymph node stations 1, 2, 4, 7, and possibly 10R may be accessed in this manner. Extended cervical mediastinoscopy may potentially allow sampling of
stations 5 and 6,[519] though diagnostic accuracy is uncertain and this procedure is performed in very few centres worldwide.

Clinical guidelines differentiate between procedures on the basis of thoroughness of mediastinal LN evaluation.[520, 521] Performance of mediastinoscopy may be ‘selective’ (targeting a single – or multiple – enlarged lymph node station, to investigate radiologically detected lymphadenopathy), ‘systematic’ (minimum sampling requirement of 5 LN stations – 2R 4R 2L 4L & 7, and stations 5 & 6 if tumour is in LUL), or complete (all of stations 1, 2, 3, 4, 7, 8, and 5 & 6 if LUL tumour).

Until the introduction of minimally invasive methods for mediastinal lymph node sampling, cervical mediastinoscopy was the sole method of pre-operative staging of the mediastinum. Strikingly, for a procedure considered gold standard, there is considerable room for improvement in diagnostic performance. A recent systematic review calculated a pooled sensitivity of mediastinoscopy of just 80%.[520] Sensitivity may be significantly lower in patients clinically staged cN0.[522] There also appears to be a very large variation in the quality of mediastinoscopy performed. For example, when mediastinoscopy was performed, not even a single lymph node was biopsied in more than half of the patients in a 2001 US patterns-of-care study.[523]

In addition, there is a small but significant complication rate. Complications include mediastinitis, cardiac arrhythmia, neurovascular damage, haemothorax, pneumothorax, pneumomediastinum. Post-operative pain requiring opioids is frequent.[524] The overall morbidity and mortality rates for mediastinoscopy are 2 – 5%, and 0.2%, respectively.[525-527]

Repeat mediastinoscopy (eg. after induction therapy, or to investigate clinical suspicion of disease recurrence) is associated with a reduced diagnostic sensitivity due to fibrosis and adhesions resulting from the original procedure.[528-530] Complications of repeat mediastinoscopy also appear to be higher.[531] Consequently, minimally invasive evaluation is strongly favoured against invasive
surgical mediastinoscopy in those who have already undergone cervical mediastinoscopy.

1.8.2.2  **Intra-operative mediastinal staging**

Intraoperative mediastinal staging refers to LN biopsies performed at the time of resection of a primary NSCLC tumour, and can consist of a mediastinal lymph node dissection (MLND), a systematic sampling, or a selective sampling. International clinical practice guidelines suggest that performance of selective LN intra-operative sampling is inappropriate,[532] as accuracy of staging is inferior to systematic sampling.[533, 534] A systematic nodal dissection requires at least three mediastinal LN stations be sampled.[532] Some authors advocate a lobe-specific systematic node dissection, which consists of dissection directed by the work of Naruke et al [535] and Asamura et al [536] who described LN drainage for each lobe of the lung. Published data suggest this is similar in diagnostic accuracy (for staging) to complete MLND.[532]

At least 27 to 36% of patients with metastatic disease to the mediastinal N2 nodes will not have involvement of the hilar or lobar lymph nodes, emphasizing the importance of systemic mediastinal lymph node sampling.[537, 538]

Complete MLND does not appear to significantly adversely affect operative times or post-operative morbidity,[539] and meta-analysis has suggested that disease recurrence may be significantly reduced following performance of complete MLND.[540] Current clinical practice guidelines recognize this issue remains contentious,[508] and a recently published landmark study which randomized over 1,000 patients to lobectomy with complete MLND versus lobectomy with LN sampling demonstrated no survival benefit.[541]

A histologic finding not included in current staging systems for NSCLC, that may be detected LN acquired by surgical biopsy is detection of very low volumes of malignant tissue. Micrometastases are lesions ≤2mm,[542] and may be distinguished from isolated tumour cells which are single tumor cells or small cell clusters ≤0.2mm, showing no stromal reaction and no proliferative potential. The incidence
of isolated tumour cells may exceed 20%,[543, 544] though the significance of such findings is unclear – while multiple studies suggest reduced survival in patients in whom ITC’s are detected,[543-546] this is not a universal finding.[547, 548] Such analysis has, to date, only been performed on surgically resected LN specimens.

1.8.2.3 Minimally invasive staging techniques

Wang needle biopsy was first described in 1978.[549] The procedure was initially performed via a rigid bronchoscope,[550] however development of a flexible needle allowed transbronchial needle aspiration (TBNA) of mediastinal lymph nodes to be performed via a standard flexible bronchoscope.[31] The procedure is more convenient, less risky, and cheaper than surgical staging and may even be used for diagnosis of suspected malignancy with mediastinal metastases.[551] While select institutions have reported excellent results with use of ‘conventional’ TBNA,[552, 553] published data regarding diagnostic accuracy of this method is highly variable.[520, 554]

Sensitivity of conventional TBNA is highly contingent on underlying prevalence of mediastinal metastases.[554] Diagnostic sensitivity also varies considerably according to lymph node position and size,[553, 555] and competency may take considerable time to achieve.[556, 557] Perhaps more importantly, the procedure remains significantly underutilized by bronchoscopists. Studies from Europe, the United States, and Australia all suggest only a small minority of pulmonologists perform TBNA.[451, 558, 559] Stated reasons include; problems with the technique; a belief that TBNA is not useful; and the lack of on-site cytopathology to assess the adequacy of the specimen.[558]

Certainly use of rapid on-site cytologic analysis of TBNA specimens may reduce the number of biopsies performed and the complication rate,[560, 561] but its absence is no barrier to its use. Furthermore, TBNA is clearly useful as it is able to obviate the need for surgical sampling of the mediastinum in up to 66% of patients with NSCLC and mediastinal lymphadenopathy on CT chest.[562] Likely underlying the issues stated as barriers to increasing use of TBNA is poor training and education in the technique. Haponik & Shure noted that very few North American centres offer TBNA
as part of their pulmonology training program,[558] and this is likely to be the case globally.

Concern regarding risk of inadvertent vascular puncture (given conventional TBNA is a “blind” procedure) is prominent among those without education, despite the published data indicating this is not a concern. In addition, the major complication rate of TBNA is 0.3% (comprising pneumothorax requiring tube drainage and major bleeding),[554] which is comparable to the rate of major complications following routine bronchoscopy, where major complications occur in less than 0.1% of procedures.[441, 442] Unfortunately use of TBNA remains confined to a few high-volume centres across the world.

Use of CT-fluoroscopy to direct TBNA has been reported,[563] and may improve accuracy of TBNA puncture.[564] However, logistical and cost issues have precluded further development of this approach.

Percutaneous mediastinal sampling, with CT-fluoroscopy has also been used to achieve minimally invasive staging of lung cancer. A number of issues preclude widespread use. Sensitivity and diagnostic accuracy vary are variable,[520] though frequently inferior to endoscopic/endobronchial methods of minimally invasive staging,[565] and pneumothorax may complicate in excess of 20% of procedures.[565] Biopsy is generally limited to significantly enlarged lymph nodes, where the prevalence of metastasis is very high, and only a single lymph node station may be evaluated at each procedure.[520] Therefore, particularly with recent more eloquent methods of minimally invasive staging, percutaneous evaluation of the mediastinum is rarely performed.

Endoscopic Ultrasound (EUS) was first described for evaluation of paraoesophageal structures in the mid-1980s.[566] Its utility was predicated on superior evaluation of lymph node anatomy compared to CT chest, in evaluation of gastrointestinal tumours. Sensitivity and specificity for staging of NSCLC was not markedly better than CT chest,[567] until EUS-guided fine needle aspiration (FNA) became available in the mid-1990s and allowed tissue diagnosis of mediastinal lymphadenopathy.[568]
The technique is excellent in evaluation of paraoesophageal lesions, including the left paratracheal lymph nodes (stations 2L, 4L) and subcarinal station (7) as well as the lower paraoesophageal (8) and pulmonary ligament (9) stations. Advantages of EUS-FNA include the ability to evaluate sub-diaphragmatic lesions, including coeliac lymph nodes and left adrenal gland.[569] Whether EUS is able to evaluate the para-aortic LN station (5) remains contentious. However interposition of the trachea between the oesophagus and the right paratracheal space results in poor sensitivity (<25%) in evaluation of stations 2R and 4R.[570] In addition, the overall false negative rate is still high at 19%.[520] meaning surgical confirmation of negative results is mandated.

1.8.2.4 Lymph node micrometastases and isolated tumour cells

Recurrence of Stage I NSCLC suggests the presence of occult disease at the time of curative surgery and demonstrates the shortcomings of the above-mentioned TNM staging system. Such occult disease is likely to be very low-volume and may be defined by its size as isolated tumour cells (small clusters of tumour cells of 0.2 mm or less) or micrometastases (tumour deposits 0.2 mm to 2 mm in diameter).[542] Due to their size such tumour deposits may frequently be missed on routine histologic examination. Several methods have been utilized, largely in research studies only, to improve their detection.

Improved accuracy of mediastinal LN staging may be achieved through serial sectioning of resected LN (as opposed to a single bisection of LN) – upstaging of N-status may occur in 8-30% of patients with breast cancer.[571] Very few studies examine this issue in NSCLC. Small cohort studies have reported that retrospective examination of LN by serial sectioning may result in up-staging of up to 37% of patients in whom resected Stage I NSCLC recurrence occurred, compared to 0% in a control group without disease recurrence.[572] However this method is time-consuming and expensive and is not routine practice.

Immunohistochemistry (IHC) allows very small volume metastases to be more readily identified. A molecule-specific antibody binds the protein target and is then highlighted through binding of a secondary antibody conjugated to a colour-producing
enzyme or fluorescent molecule. IHC detects metastatic disease in a higher proportion of patients when compared to routine histopathology using haematoxylin and eosin.[543, 573] While some authors have suggested the presence of micrometastatic disease predicts a poorer outcome,[543, 546, 574] numerous studies have reported no prognostic value to this finding.[575, 576]

Molecular studies have also been examined for detection of NSCLC lymph node metastases. Messenger ribonucleic acid (mRNA) may be detected using reverse transcriptase polymerase chain reaction (RT-PCR) techniques. Examination for epithelial cell-specific (eg. cytokeratin, or carcinoembryonic antigen),[577, 578] lung specific (eg. LunX, PLUNC)[579, 580] or epithelial cancer specific (eg. Muc-1, SCC antigen, surviving, c-met, BJ-TSA-9)[581] may be utilized. Molecular analysis appears more sensitive than IHC,[579] and may upstage up to 50% of Stage I patients.[582] While detection of LN micrometastases by RT-PCR is associated with reduced disease-free survival in most studies,[546, 579, 582] findings are yet to be confirmed and prospectively validated.

Imperfect specificity of some PCR targets remains a concern due to cross-reactivity with related mRNA molecules,[583] contamination with epithelial tissue,[ ref] or benign mesothelial cells.[548] Current guidelines for staging of NSCLC do not include discussion regarding use of IHC or PCR for LN staging.[520] Use of molecular tools to assist staging remains a research tool only at present, with further consistent evidence of its specificity and clinical implications required before widespread clinical use is recommended.

1.8.2.5  **Molecular staging of serum/plasma and bone marrow**

Aspiration of bone marrow and examination with IHC may demonstrate the presence of cytokeratin-positive cells in up to 27% of NSCLC patients staged M0 by conventional means.[546, 584] The presence of tumour cells within BM aspirates does not appear to influence long-term prognosis in a majority of studies,[546, 584] though multiple authors have reported reduced survival in Stage I patients in whom tumour cells are detected within bone marrow.[585, 586]
Circulating tumour cells (CTC) were first noted by clinicians in Melbourne in 1869.[587] Their presence may be inferred by detection of tumour-specific genetic material within serum or plasma, or cells may be visualized directly. Detection of epithelial cell-specific mRNA in either whole blood or serum may be observed in a significant proportion of lung cancer patients,[588] though occasional false positive results may be seen due to low expression of cytokeratins within peripheral blood mononuclear cells.[589] Lung-specific mRNA targets for detection of CTC have been reported,[590] though their clinical utility is not established.

Circulating free plasma DNA may be detected in patients with cancer, and is noted to be elevated in the plasma/serum in comparison to healthy controls. The detected DNA is presumed to have derived directly from the tumour.[591] Measurement of human telomerase reverse transcriptase (hTERT) in cell-free plasma is generally used as a surrogate of free circulating DNA.[592] Measurement of plasma hTERT has been used in research studies as a prognostic,[592] diagnostic,[593] as well as a screening tool[594] for lung cancer. Published results are conflicting,[595, 596] however, and standardization of sample processing and DNA detection are required before widespread clinical use is considered.

With recent developments in technology it has become possible to identify viable whole tumour cells rather than just genetic evidence of their presence. Whole blood is processed by multiple methods including filtering by ‘functionalized’ (EpCAM antibody-coated) posts,[597] flow cytometry,[598] or on the basis of size alone.[599] CTCs may be collected to allow non-invasive genetic testing of tumours, eg. cytogenetic abnormalities,[600] mutations of epidermal growth factor receptor status,[601] and recent studies suggest the concentration of CTC may be a novel prognostic factor in NSCLC.[602] Genetic differences between primary tumours and CTCs in individuals have been noted,[603, 604] and the significance of this remains to be determined.
1.9 TREATMENTS AND OUTCOMES OF LUNG CANCER

1.9.1 Small cell lung cancer

1.9.1.1 Extensive stage disease

Sixty to seventy percent of patients have extensive stage disease at diagnosis, and have a median survival of 7-12 months (with treatment) and 5-year survival of just 2%.[605] Untreated SCLC is aggressive, with a median survival of 2 to 4 months after diagnosis.[606] Where possible, patients are offered treatment with a maximum of six cycles of platinum-based combination chemotherapy. 20-30% of patients with extensive disease will achieve a complete response to combination chemotherapy however most patients will relapse, with a median progression-free survival of approximately 4 months. While overall survival is not improved with use of ‘maintenance’ chemotherapy for patients with SCLC,[607] those with relapsed disease should be considered for second-line therapy.[46]

In patients in whom chemotherapy results in a complete response in extra-thoracic disease and at least partial response of intrathoracic disease, a survival benefit has been reported with addition of thoracic radiotherapy to residual disease.[608]

1.9.1.2 Limited stage disease

Patients undergoing resection of SPN, suspected to be Stage I NSCLC but shown pathologically to be SCLC have improved survival in comparison to historical controls with limited stage SCLC treated with chemoradiotherapy.[609] Benefits from surgical therapy of SCLC are seen only in patients with TNM stage I disease. Such patients may be offered resection of their disease but should still undergo adjuvant postoperative combination chemotherapy.[605]

High rates of locoregional failure are seen following combination chemotherapy of limited stage SCLC.[605] Addition of thoracic radiotherapy is associated with improved long term survival.[610] Concurrent administration of radiotherapy and chemotherapy achieves superior results. The rapid growth rate of SCLC means
alternate dosing of radiation is warranted. Expert guidelines recommend the use of accelerated (dose exceeding 10 Grey per week) hyperfractionated (multiple treatments per day) radiation for optimal therapy of SCLC.[46]

Patients achieving a complete response to initial therapy of SCLC have a 50-60% risk of development of cerebral metastases.[611] Even more significantly, in 20-30% the brain will be the sole site of recurrence. Prophylactic cranial irradiation (PCI) is recommended for patients with limited stage SCLC in whom complete response is seen. Meta-analysis of PCI concluded that a relative risk reduction in incidence of cerebral metastases of 45%, and a 5% improvement in 3-year survival may be achieved.[612] Neurologic impairment may be seen in a significant minority of SCLC patients prior to PCI.[613] While high dose cranial irradiation may be associated with late neurotoxicity, PCI has not been associated with any cognitive or neurophysiologic impairment.[614, 615]

1.9.2 Non-small cell lung cancer

Treatment of NSCLC patients is selected on the basis of the disease stage, which in turn is determined on the basis of the TNM staging system, outlined above.

1.9.2.1 Early stage NSCLC

Stage I and Stage II disease are together defined as ‘early stage’ NSCLC. The practical ramification of ‘early stage’ disease is that it is surgically curable. There are no randomized clinical trials comparing surgery alone to radiation therapy alone or chemotherapy alone in the treatment of early stage (stage I and II) NSCLC. Based on large series of resected stage I and stage II NSCLC, the prognoses for stage IA, IB, IIA and IIB NSCLC, expressed in terms of 5-year survival rates, are commonly accepted to be 60 to 80% for stage I and 40 to 50% for stage II NSCLC. Perioperative mortality following lobectomy or pneumonectomy is significantly lower when performed by specialist thoracic surgeons rather than general surgeons.[616]
While limited ‘sublobar’ resections for early stage NSCLC may be considered for patients with insufficient cardiopulmonary reserve to tolerate lobectomy, this is inferior oncologic treatment. There is a three-fold increase in local recurrence of disease, compared to formal lobectomy, and cancer related deaths are also increased by 50%. In contrast, the mortality rate from surgery is unaltered.

A contentious issue in surgical resection of NSCLC is the extent of lymph node resection performed at the time of thoracotomy/thoracoscopy. Dissection of all mediastinal lymph nodes (lymphadenectomy) is associated with longer operative times and increased postoperative drainage volumes, however morbidity is otherwise not increased when compared to lymph node sampling.[539] Sampling of a minimum of 3 LN stations is recommended to optimize accuracy of nodal staging,[532] however some studies have suggested complete dissection of all mediastinal lymph nodes (lymphadenectomy) may improve overall survival.[540] Expert guidelines do not recommend one approach over the other.[508]

Adjuvant therapy has been associated with reduced survival in stage I NSCLC and neither chemotherapy nor radiotherapy are recommended following resection of Stage I NSCLC.[508] Radiotherapy may reduce the rate of local recurrence in Stage II patients undergoing complete resection of NSCLC but a survival benefit has not been demonstrated.[617] Therefore adjuvant radiotherapy is not recommended.[508]

Adjuvant chemotherapy may be of benefit in treatment of Stage II NSCLC. Significant improvement in survival is seen with multi-agent platinum-based chemotherapy and this is strongly recommended in expert guidelines.[508]

Data suggest that medically inoperable patients still mainly die from lung cancer despite their other medical problems, so treatment of the tumor is justified as opposed to supportive care. Patients with comorbidities precluding surgery may undergo radiotherapy with curative intent. Local recurrence is the predominant mode of disease recurrence following such patients,[618] (in contrast to those undergoing conventional lobectomy [619]) however median survival is significantly improved compared to historical controls.[618, 620] Survival may be improved further with use
of accelerated hyperfractionated radiation, with 4-year survival as high as 18% reported.[621]

Stereotactic body radiation therapy (SBRT) may allow higher doses of radiation to be delivered to smaller volumes of tissue, minimizing toxicity and maximizing anti-tumour effect. SBRT of great vessels and other mediastinal structures is associated with excess toxicity,[622] however treatment of peripheral Stage I NSCLC is associated with excellent local disease control [622, 623] and may be considered for patients with peripheral lesions who are unsuitable for surgery.

Other minimally invasive therapies exist for treatment of Stage I NSCLC in patients unable or unwilling to undergo surgery. Evidence supporting the use of these modalities remains limited. Photodynamic therapy (PDT) involves bronchososcopic irradiation of bronchial mucosal lesions with non-thermal visible light following systemic administration of a photosensitizer. Irradiation of the photosensitizer and subsequent energy transfer leads to photochemical reactions which generate cytotoxic species reactive oxygen species which induce apoptosis and/or necrosis of targeted lesion.[624]

PDT is most commonly used for superficial airway lesions not amenable to surgery due to their location, or in medically inoperable patients. In patients with T1 NSCLC, long-term cure may be achieved in a significant minority of patients,[625, 626] though efficacy may be significantly reduced in lesions exceeding 10mm.[627] It may also be used to “down-stage” patients to allow surgical therapy, or reduced extent of surgery.[628] Alternatively it may be used alone,[629] or combined with external beam radiation [630] or bronchoscopic brachytherapy [625] to achieve palliation of bulky endobronchial disease.

Radiofrequency ablation (RFA) of peripheral lung tumours is generally performed percutaneously under CT-fluoroscopic guidance. During RFA, a radiowave-emitting probe is inserted into the tumour under computed tomography (CT) guidance and is used to heat the tumour to 90–100°C, resulting in focal coagulation necrosis. Local control rates vary with lesion size, but may be as high as 64% at 2 years for tumours <3cm diameter.[631] RFA may also be utilized for management of metastatic lesions
in the lung.[632, 633] Due to the risk of mediastinal injury, use of RFA for centrally located tumours was not advocated though more recent experience suggests tumour location does not influence the rate of complications. RFA may be associated with a higher incidence of complications than other minimally invasive procedures, with pneumothorax occurring in >10% of patients and a procedure-related mortality rate of 2-3%. Due to the risk of mediastinal injury, use of RFA for centrally located tumours was not advocated though more recent experience suggests tumour location does not influence the rate of complications.[635]

### 1.9.2.2 Locally advanced NSCLC

Locally advanced NSCLC describes patients who have mediastinal metastatic disease at the time of their diagnosis. These patients may be Stage IIIA (ipsilateral mediastinal LN metastases, or T3 tumour with hilar LN metastases), or Stage IIIB (contralateral mediastinal LN metastases, or tumour staged T4). Comprehensive staging will generally detect most patients with mediastinal metastases, however in a small proportion of patients with mediastinal metastases thorough evaluation (including PET/CT) will fail to detect locoregional metastases (usually low volume mediastinal disease). Such patients are ‘up-staged’ following pathologic examination of surgically resected mediastinal lymph nodes and may be described as having “incidental” N2/3 disease.[509] Complete resection of lymph nodes in such patients is associated with the best 5-year survival rates.[509]

In patients with incidental N2/3 NSCLC, post-operative radiotherapy has been demonstrated to reduce rates of local disease recurrence, however the impact on overall survival remains unclear.[617] Some studies even suggest cardiopulmonary toxicity of mediastinal irradiation portends a poorer prognosis than patients not receiving radiation.[636] Currently, post-operative radiation is not routinely recommended, though may still be offered to individuals thought to be at high risk of local relapse (eg, positive resection margins, multiple or bulky node station involvement).[509] Adjuvant platinum-based chemotherapy has been associated in some randomized trials with improvements in disease-free and overall survival,[637] with one study suggesting improvement in 5-year survival from 26% to 42%. A survival benefit with adjuvant chemotherapy is not a uniform finding.[638] however
adjuvant chemotherapy is recommended by expert guidelines on the basis of an expected modest improvement in overall survival.[509] These guidelines recommend against the used of adjuvant combination chemoradiotherapy.

For most patients with Stage III disease, non-invasive and invasive staging investigations will determine the presence of mediastinal disease prior to consideration of surgery. Some centres may consider surgical resection of low volume N2 Stage III NSCLC patients, however there is limited evidence to suggest this is the optimal treatment approach for these patients. Use of neoadjuvant chemotherapy does not appear to increase long-term survival over surgery alone and neither neoadjuvant therapy nor surgery are recommended for patients with pathologically confirmed N2 disease. Multiple phase II studies of neoadjuvant chemoradiation in Stage IIIA and IIIB NSCLC have demonstrated the feasibility of this approach,[639-641] and suggested a possible survival benefit over combination chemoradiotherapy[642-644] though such tri-modality therapy remains experimental at present.

While survival for stage III is poor, conventional chemoradiation treatment may still be undertaken with curative intent. Patients with good performance status and minimal loss of weight may be recommended for platinum-based combination chemoradiotherapy. 5-year survival in excess of 20% is reported by multiple authors, though the absolute benefit in survival of chemoradiotherapy is 4% at 2 years and 2% at 5 years.[645] Patients with poor performance status or significant weight loss (>10%) may be treated with radiotherapy alone due to higher rates of toxicity from chemotherapy in this group.[646]

Significantly, many patients with Stage III disease have multiple co-morbidities which frequently limit the ability to give, or complete, radical treatment regimens. Multiple co-morbidities are more common in older patients.[647, 648] Multiple population-based studies indicate that over half of stage III NSCLC patients are ineligible for radical chemoradiation as a result of comorbidities or poor performance status.[647-649] Compounding this problem is the observation that comorbidities and poor performance status are independent predictors of outcome.[650]
However, for patients able to undertake concurrent chemoradiation, this treatment approach is associated with a significant survival benefit. 5-year survival may exceed 20%.[648] though median survival is poor at approximately 11 to 16 months.

1.9.2.3 Distant metastatic NSCLC

A majority of patients have extrathoracic metastatic disease at the time of diagnosis and are considered to have incurable disease. The median survival of patients with untreated metastatic non–small-cell lung cancer is only four to five months, with a survival rate at one year of just 10 percent.[651] Early studies examining the benefit of chemotherapy in these patients noted very minimal improvements, and substantial toxicity profiles.[652] With advent of more potent regimens, particularly those containing Platinum compounds, improved response rates and median survival were seen. A landmark study comparing four different Platinum-based dual agent regimens indicated median survival of 7.9 months, a 1-year survival rate of 33 percent, and a 2-year survival rate of 11 percent.[653] No single regimen was significantly better that the others examined in this trial.

Single agent chemotherapy may also be associated with modest improvements in median survival, though haematologic toxicity remains a concern even with this approach.[654] Single agent regimens are advocated for elderly patients, or those with reduced performance status.[655] In patients who have stage IV NSCLC and are ≥ 80 years old, the benefit of chemotherapy is unclear.[655] Triple agent chemotherapy regimens have not resulted in further improvements in survival, and are associated with significantly higher rates of toxicity than dual-agent regimens.[655]

As well as an absolute improvement in 12-month survival of 9%,[656] randomized studies comparing chemotherapy with the “best supportive care” have shown that chemotherapy reduces symptoms and improves the quality of life.[657] Meta-analysis of studies examining the addition of chemotherapy to “best supportive care” indicate that chemotherapy improves overall survival in all patients with advanced NSCLC.[658]
Palliative care is that which is primarily symptom-focused and has the potential to improve the quality of care and reduce the use of medical services. Referral to palliative care services may not occur until very late in the course of a patient’s illness,[659] and the potential for benefit is often negligible at this late time-point.[660] One recently published study examined the utility of early palliative care in the community and demonstrated not only improvements in quality of life, and mood scores but also a reduction in aggressive end-of-life treatments and an improvement in median survival of 2.7 months, in comparison to standard care.[661]

1.9.2.4 Novel biologic agents

Biologic agents used in the treatment of lung cancer generally are agents (usually small molecules or monoclonal antibodies) directed against abnormally activated molecules or physiological processes required for the maintenance or progression of tumours.[662] Agents targeting both the Epidermal Growth Factor Receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) pathways are in clinical use. As well a recently developed small molecule Tyrosine Kinase Inhibitor (TKI) has been found to be a potent inhibitor of the EML4-ALK fusion protein.

Two classes of EGFR inhibitors are used in clinical practice; small molecule TKIs (gefitinib and erlotinib) and monoclonal antibodies (e.g. cetuximab and panitumumab).[662] Erlotinib as second line therapy has been shown to improve median survival (6.9 months vs 4.7 months, \( P < 0.001 \)) [663] and Gefitinib when used in non-smokers and Asian patients may achieve the same result.[664] EGFR TKI therapy in combination with standard chemotherapy has failed to improve tumour response, time to progression, or overall survival in four large randomized trials.[662] Cetuximab has not produced any survival benefit.[665]

The strongest predictor of response to EGFR TKIs is the presence of specific somatic mutations in the tyrosine kinase domain of the EGFR gene. The two most common sensitising mutations are in-frame deletions of exon 19 and the L858R point mutation in exon 21. These account for ~ 90% of all mutations. Response rates of 60–90% in patients with sensitizing mutations are reported.[666] Acquired mutations of the EGFR gene may be seen in TKI-treated patients which may confer resistance.[667]
Bevacizumab is a recombinant humanized monoclonal antibody directed at VEGF. It does not appear to be particularly effective as monotherapy however in combination with standard chemotherapy it has been reported to achieve improved response rates (31.5% vs 18.8%) and time to progression (7.0 vs 5.9 months), though unacceptable rates of major haemorrhage were seen in patients with squamous cell subtype.[Johnson JCO 2004] Subsequent trials were performed in patients with non-squamous histology and limited benefit in survival was seen in patients receiving Bevacizumab (12.3 vs 10.3 months, $p = 0.003$).[668] There was significant treatment-related cost, with 15 treatment-related deaths (4.9%) occurred in the bevacizumab arm.

Crizotinib is a TKI targeting the ALK gene. It has achieved striking response rates in patients with tumours harbouring the EML4-ALK gene rearrangement.[669] Many of these responses were sustained, though in vitro studies suggest acquired resistance may result following prolonged treatment.[670] Larger phase III trials are ongoing and will help clarify the clinical role of Crizotinib in the treatment of EML4-ALK positive adenocarcinoma.
1.10 ENDOBRONCHIAL ULTRASOUND

1.10.1 Background & preliminary studies

Transthoracic ultrasound-guided sampling of pulmonary tumours was hampered by the failure of air-filled lung to transmit ultrasound signals. An intrabronchial approach to locating pulmonary tumours was proposed and in 1992 Hürter & Hanrath described use of a flexible sonography probe, originally designed for endovascular examination, to examine central airways and peripheral bronchii.[671] They also described use of a sheath to allow re-instrumentation of peripheral airways in order to perform sampling, and use of a water-filled latex balloon at the tip of the catheter, which allowed the whole circumference to be visualised undisturbed by air. They suggested that endobronchial sonography may be an alternative to fluoroscopy for localising peripheral tumours.[671]

1.10.2 Radial probe ultrasound

The endobronchial ultrasound (EBUS) probe became commercially available in 1999. A miniaturized 20 MHz US probe was fitted with a catheter carrying a water-inflatable balloon at the tip (Olympus UM-BS20-26R). EBUS evaluation of central airways demonstrated a 5 layered cartilaginous bronchial wall and allowed the accurate assessment of the depth of invasion of central airway malignancy.[672] The tool also began to be utilized in bronchoscopic investigation of peripheral lung lesions. Herth et al were the first to describe performance of TBLB guided by radial probe EBUS for investigation of peripheral lesions in a cross-over study and noted it was “at least equivalent to fluoroscopy”, with a nonsignificant trend for EBUS to be better than fluoroscopy for lesions <3 cm in diameter.[673]

Kurimoto et al were the first to describe the sonographic features of peripheral lesions located by radial EBUS, with a high accuracy in determining benign from malignant lesions.[674] These findings were confirmed in 2007 when Kuo et al described
Continuous margin, absence of linear-discrete air bronchogram, and heterogeneous echogenicity as strongly indicative of malignant lesions.[675] The same group then published the definitive paper on use of radial EBUS with use of a guide sheath to ensure as accurate sampling as possible, including use of fluoroscopy to target transbronchial biopsies (see figure 1.5).[676] They were able to achieve a diagnostic yield of 77%, with no reduction in accuracy even when assessing lesions less than 10mm diameter.

Paone then published their randomized study (still the only such study) comparing EBUS- with fluoroscopy-directed TBLB. They found similar diagnostic success in lesions >3cm but markedly improved accuracy with EBUS over conventional fluoroscopy-directed TBLB for lesions <3cm (0.75 v. 0.31, \( p=0.0002 \)).[450] American College of Chest Physicians Clinical Practice Guidelines for the initial diagnosis of lung cancer recognize the ability of radial EBUS to improve diagnostic yield in bronchoscopic investigation of PPLs.[417]

While performance of EBUS-guided TBLB is generally consistent, use of fluoroscopy is not uniform across centres. Yoshikawa et al achieved a diagnostic yield of 62%, with markedly lower yield in lesions <20mm (30% v 86%, \( p<0.01 \)).[677] In addition, lesions in the right middle lobe and lingua had a higher diagnostic yield. The authors concluded that their findings justified the avoidance of fluoroscopy, though noted the reduced yield in RLL lesions was likely due to relocation of the sheath as a result of respiration.[677] Diagnostic yield of EBUS is maintained even for fluoroscopically invisible nodules,[678] suggesting the value of fluoroscopy in performance of radial EBUS is not in locating the lesion. Instead, as radial EBUS is not a real-time procedure, fluoroscopy likely aids by ensuring that sampling is taken from the same location as identified initially by the probe.

Factors influencing the yield of EBUS have been examined previously. The ability to detect the lesion with the probe unsurprisingly is associated with a higher diagnostic yield.[676, 679-683] Even lesions where the probe is positioned adjacent to the lesion are associated with a lower yield.[683] In ability to locate the lesion with the radial probe is associated with a yield of just 4%. [683]
Figure 1.5: Performance of radial probe endobronchial ultrasound, as described by Kurimoto et al. [676]

a) the EBUS probe is inserted into a guide sheath and passed through the working channel of a standard bronchoscope. Segmental airways are examined until the lesion is located (b)

c) When positioned within a mass/nodule a typical US appearance is seen – hyper-echoic continuous margin indicates the interface between solid lesion and surrounding aerated lung.

The EBUS probe is withdrawn, leaving the guide sheath in place (d)

e) biopsy instruments are passed through the guide sheath to perform tissue sampling, under fluoroscopic vision (f)
Proximity of PPL to the pulmonary hilum was reported to be associated with increased diagnostic yield in both studies describing this feature.[681, 684] Five TBLB appears to be associated with the highest diagnostic rate.[683, 685] Increasing lesion size is associated with improved diagnostic yield.[685, 686]

Complications following radial probe EBUS appear very low. Multiple studies have reported complication rates of 0%.[450, 685-687] with pneumothorax being the only significant complication reported in any study. Pneumothorax rates of 0% were commonest, [450, 676, 680, 681, 685-687] though one paper noted a pneumothorax rate of 5%.[688] Overall the rate of pneumothorax appears slightly lower that seen following routine fluoroscopy-guided TBLB.[453]

Recognizing that TBNA sampling of mediastinal lymph nodes was an under-utilized technique, use of radial EBUS was then used to provide image guidance for performance of TBNA. A randomized study by Herth et al confirmed that EBUS guidance improved the yield of TBNA in all but the subcarinal region, where diagnostic yield for conventional (blind) TBNA is highest.[689] The value of EBUS appears in part related to proficiency in performance of conventional TBNA. Earlier studies reported similar yield in radial EBUS-guided TBNA.[690]

Until a more recently published study, all studies examining radial EBUS guidance of TBNA were performed by highly experienced centres,[689-691] and success of radial guidance may in fact have reflected the expertise of this group rather than the value of radial EBUS in mediastinal lymph node sampling. The only other study examining radial EBUS for guidance of TBNA found, as did Herth et al,[689] that yield was improved for nodes in paratracheal and hilar regions. However yield for EBUS-directed TBNA was only 49%.[692] Radial EBUS guidance requires the use of a dedicated ultrasound probe with a balloon catheter, and is not a ‘real-time’ procedure. Its use is limited by similar factors that limit widespread use of conventional TBNA – prolonged time to achieve competency,[556, 557] limited training opportunities,[558] considerable variation in sensitivity according to lymph node size and position,[553, 555] movement of nodes with respiration,[693] and concern regarding and risk of inadvertent vascular puncture.
Uptake of the procedure was consequently slow, and stalled completely following introduction of a dedicated linear array ultrasound bronchovideoscope that allowed real-time performance of TBNA.

1.10.3 Linear probe ultrasound

Endoscopic evaluation of the mediastinum for pre-operative staging of NSCLC was performed as early as 1991, with EUS being more accurate than CT chest in assessment of LN size.[694] Use of EUS-FNA for staging of lung cancer was first described in 1996,[695] and allowed accurate staging of mediastinal lymphadenopathy detected by CT. Pooled diagnostic sensitivity was estimated at 84% and complications were rare.[520] The main limitations to EUS-FNA were two-fold. Firstly, it does not allow examination of the endobronchium, which may have important implications regarding surgical planning for patients in whom tumour resection is planned. Secondly, it is able to sample only a limited number of mediastinal lymph node stations. Stations 2R, 4R, 5, and 6, as well as the hilar lymph nodes cannot be accessed using EUS-FNA.[696] Both of these concerns were surmountable by application of real-time ultrasound-guided needle sampling via the endobronchial tree. Miniaturization of the linear array ultrasound device allowed development of an instrument small enough to be introduced via the larynx into the trachea and led to the introduction of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).

The first description of use of a dedicated bronchoscope with a linear curved-array transducer at its tip was published by Krasnik et al in 2003.[33] An oft-cited paper from Yasufuku et al described performance of real-time TBNA of mediastinal lymph nodes and reported a diagnostic accuracy of 97%.[34] This group published their further experience and demonstrated consistently high diagnostic accuracy, and noted that EBUS-guided TBNA (EBUS-TBNA) was able to obviate invasive staging procedures in a significant proportion of patients.[697] Diagnostic performance was quickly replicated in multiple subsequent studies.[698-701]
The EBUS-TBNA videobronchoscope allows ultrasound visualization of paratracheal and peribronchial structures from within the central airways. A balloon placed over the ultrasound tip is inflated to allow conductance of the ultrasound signal into adjacent structures (figure 1.6a). The ‘scope has a 2mm working channel through which a dedicated TBNA needle may be passed. Following identification of the target lesion, the TBNA needle is advanced through the bronchial wall into the lesion. Puncture is performed with “real-time” visualization of the needle (figure 1.6b). An internal stylet is used to clear bronchial tissue from the needle lumen following puncture of the target lesion. Suction is then applied to the proximal tip of the needle apparatus and specimen collected by moving the tip of the needle backwards and forwards within the target lesion. TBNA may be repeated multiple times from each site, and several sites may be evaluated during a single procedure.

Diagnostic accuracy of EBUS-TBNA is demonstrated to remain very high even in evaluation of lymph nodes <1cm diameter.\cite{702} Comparison with PET staging of the mediastinum revealed a higher diagnostic sensitivity of EBUS-TBNA, with the obvious further advantage of 100% specificity.\cite{703, 704} Importantly, diagnostic performance is uniformly high, with meta-analysis indicating pooled sensitivity for detection of mediastinal metastases of 93%.\cite{705} Optimal diagnostic yield is seen after just 3 TBNA procedures, though this can be lowered by use of on-site cytology, or if a core specimen is obtained.\cite{706}

Mediastinal lymph nodes harbouring metastases are frequently less than 1cm in size,\cite{487, 496} and metastatic foci may exist in only a small portion of the lymph node.\cite{707} Lymph node size <5mm is associated with reduced diagnostic sensitivity.\cite{708}

Sonographic features predictive of malignancy have been described to guide proceduralists in determining which lymph nodes warrant assessment with TBNA, and which component of nodes may yield optimal tissue for assessment. Round shape, distinct margin, heterogeneous echogenicity, and presence of coagulation necrosis sign have been reported as independent predictive factors for metastasis.\cite{709-711}
Sensitivity of EBUS-TBNA in restaging mediastinal lymph nodes remains high, however utility in this setting is slightly reduced by a low negative predictive value.[712-714] This finding is also seen for EUS-FNA.[715] Therefore a negative result in such patients requires confirmation by surgical mediastinoscopy.

Multiple studies suggest that sensitivity of EBUS-TBNA may exceed that of mediastinoscopy, the traditional ‘gold-standard’ method of mediastinal staging,[716, 717] and a landmark study by Yasufuku et al in which 153 patients underwent both
EBUS-TBNA and mediastinoscopy demonstrated no significant difference in sensitivity, negative predictive value, and diagnostic accuracy for mediastinal lymph node staging.[718] Despite this, confirmatory mediastinoscopy following negative EBUS-TBNA in patients with imaging studies suggesting mediastinal metastases is still advocated by multiple authors, based on the relatively low negative predictive value in this patient group. For example, one study reports that 28% of patients with high clinical suspicion of nodal disease, even after negative EBUS-TBNA, had N2 mediastinal nodal metastases confirmed by mediastinoscopy, despite negative EBUS-TBNA.[719] However, other expert practitioners have suggested that, based on the high sensitivity of EBUS and the low yield of mediastinoscopy following negative EBUS, a negative EBUS should allow patients to proceed directly to surgical treatment of their lung cancer.[720]

Use of EBUS-TBNA in lung cancer care is not limited to just staging of lung cancer. It is highly accurate in assessment of parenchymal lesions which abut the central airways,[721] and may also be performed as the initial diagnostic procedure in patients in whom CT imaging suggests the possibility of hilar or mediastinal metastases.[722, 723] In an age of “personalized oncology” the ability to tailor therapy based on tumour gene profiles is becoming increasingly important. EBUS-TBNA allows molecular assessment of malignancy for known genetic mutations,[724, 725] as well as molecular profiles that may predict tumour responses.[726-728]

While the initial description of the technique described performance of EBUS-TBNA under conscious sedation,[34] subsequent larger studies used predominantly general anaesthesia and jet ventilation. Review of the issue by anaesthetist specialists have discussed only introduction of the dedicated convex-probe ultrasound bronchoscope into the airway via an artificial airway (eg. endotracheal tube, laryngeal mask) under general anaesthesia.[729, 730] The optimal conditions for performance of EBUS have not been established, and patient tolerance of EBUS-TBNA performed under conscious sedation is unclear.

Initial reports indicate complications following EBUS-TBNA are rare,[731, 732] with no mortality reported to date. Emerging reports suggest that infective complications
may be a concern,[733] however risk factors for this have not been examined and current guidelines do not address the need for prophylactic antibiotics.
CHAPTER 2: Research hypotheses, aims and methodology

This thesis addresses a number of key issues involved in the implementation of EBUS into routine bronchoscopic practice in the Australian setting. The research presented in this thesis was commenced at a time when endobronchial ultrasound was being introduced into an increasing number of centres worldwide. Initial reports were based solely on experience of the technique in only a few specialized research centres. There remained a number of outstanding questions regarding the optimal performance of the techniques, their safety profile and how they should be integrated into a standard bronchoscopy service, and alongside previous standard techniques for assessment of suspected lung cancer. This thesis addresses several such issues to more clearly define how endobronchial ultrasound is best performed and best incorporated into routine clinical care.

2.1 HYPOTHESES AND AIMS

The body of work presented in this thesis was commenced at a time when endobronchial ultrasound was being used more frequently in an increasing number of centres worldwide. There remained a number of outstanding questions regarding the optimal performance of the techniques, their integration into a standard bronchoscopy service, and their safety profile. This thesis attempted to address several such issues to more clearly define how endobronchial ultrasound is best performed and best incorporated into routine clinical care.

The primary hypothesis was that a systemic study of implementation of this new technology into routine practice would reveal new information about the utility,
operating characteristics, safety and cost effectiveness. Such information was not apparent in original studies of EBUS during its development (described in chapter 1) as these were generally studies examining diagnostic performance in assessment of lung cancer completed in high volume interventional pulmonology centres of world-renown. Furthermore, diagnostic performance & utility in comparison to previous standards of care had not been undertaken.

I hypothesized that (based on studies discussed above) endobronchial ultrasound would prove to be preferable to previous standards of care (mediastinoscopy for linear EBUS, percutaneous biopsy for radial EBUS) based on non-inferior diagnostic performance but a lower complication rate and lower health care costs than current standard sampling techniques.

**A secondary hypothesis** was that a systematic approach such as this may reveal new insights into the pathogenesis of lung cancer. As discussed in the relevant chapter, I hypothesized that sarcoidal granulomas may predict improved disease-specific outcomes. The ease by which EBUS-TBNA is able to sample mediastinal lymph nodes suggests such an approach would have utility in the future in predicting biologic characteristics of lung cancers in individual patients should such a predictive morphologic ‘marker’ be identified.

The specific **aims** of the project were;

1. to determine the safety of using fluoroscopic guidance during performance of radial probe EBUS.
2. to determine the optimal procedure for minimally invasive assessment of peripheral pulmonary lesions, and to identify specific clinicoradiologic features that may aid clinicians in selecting the appropriate technique for individual patients
3. to examine issues arising during the integration of EBUS-TBNA into routine clinical care, including
   a. patient tolerance
b. cost-utility

c. risk of infection complicating EBUS-TBNA

d. inter-observer variability in diagnosis of NSCLC subtype in specimens acquired by EBUS-TBNA

4. to examine the diagnostic and prognostic significance of sarcoidal granulomas in regional lymph nodes of patients with non-small cell lung cancer
2.1.1 Background to study aims

2.1.1.1 Aim 1

To determine the safety of using fluoroscopic guidance during performance of radial probe EBUS

(Aim addressed in chapter 3)

Early studies reporting use of radial probe EBUS to guide transbronchial lung biopsy (TBLB) for investigation of peripheral pulmonary lesions described use of fluoroscopy during performance of TBLB.[676] Due to concerns regarding radiation exposure, performance of EBUS-TBLB without fluoroscopic guidance was suggested and one group concluded that diagnostic yield may not be adversely influenced.[677] However, this study noted a lower yield in lesions in the right lower lobe, and attributed this to movement of the guide sheath as a result of deep respiration. This clearly has the potential to reduce diagnostic yield of EBUS-TBLB, with positioning of the probe/sheath being the strongest predictor of diagnostic success.[683] Furthermore, diagnostic yield of EBUS-TBLB for lesions <2cm is significantly reduced when performed without fluoroscopy,[680] whereas fluoroscopic guidance of EBUS-TBLB may maintain significantly higher yield for lesions <2cm.[676, 683] Our early experience suggested fluoroscopy was a valuable component of EBUS-TBLB,[734] improving targeting of TBLB and therefore diagnostic accuracy and safety of the procedure.

The benefit of using ionizing radiation in medical imaging should always outweigh the risks of the radiation exposure, and significant exposure has been noted in other interventional procedures utilizing fluoroscopic guidance.[735-737] The risk-benefit assessment was unclear as the radiation dose resulting from fluoroscopy during EBUS-TBLB (and resultant attributable radiation risk) was unknown. The aim of this project was to evaluate the effective radiation dose, to both patients and proceduralists, resulting from fluoroscopic guidance of EBUS-TBLB. This information is necessary to understand if the risk of radiation toxicity precludes the use of fluoroscopy during EBUS-TBLB.
2.1.1.2 **Aim 2**

To determine the optimal procedure for minimally invasive assessment of peripheral pulmonary lesions, and to identify specific clinicoradiologic features that may aid clinicians in selecting the appropriate technique for individual patients

(Aim addressed in chapter 4)

Minimally invasive assessment of PPL is most frequently undertaken by either CT-guided percutaneous needle biopsy/aspiration (CT-PNB) or by bronchoscopic methods. Of all widely available adjunct tools in bronchoscopic investigation of PPL, radial probe EBUS guidance appears to be associated with the highest diagnostic accuracy.[676, 677] It is unclear how radial probe EBUS should be incorporated into clinical evaluation of patients with peripheral pulmonary lesions. Clinical acumen may determine the optimal approach to diagnosis in some patients with PPL, however selection of the appropriate invasive technique by treating clinicians is frequently arbitrary, as in a proportion of patients the optimal diagnostic intervention is unclear. No published evidence has directly compared the two commonly used modalities for minimally invasive assessment of PPL. Specific clinicoradiologic features may allow clinicians to determine the optimal initial procedure for investigation of patients with PPL, and we sought to evaluate this in a prospective clinical trial.

The randomized pragmatic trial illustrated the significant heterogeneity that may occur between patient cohorts, and that individual randomized or cross-over trials examining the effect on diagnostic accuracy of variation in clinicoradiologic factors is not feasible given the virtually infinite permutations of these factors. Clinical decision-making incorporating the numerous and complex factors that may influence diagnostic outcomes in evaluation of PPL require clear knowledge of performance characteristics of available procedures. Comprehensive reviews of CT-PNB have previously been published,[17] and numerous studies have described the influence of various clinicoradiologic characteristics on diagnostic accuracy and rates of complications.[473, 684, 738] Diagnostic performance of EBUS-TBLB varies considerably between reports. Factors responsible for these differences have not been examined and a systematic examination of the literature has not been performed. The
aim of performing a meta-analysis of studies examining EBUS-TBLB in evaluation of PPL was to define the performance characteristics of EBUS-TBLB, and to identify any issues that might be responsible for observed heterogeneity in diagnostic performance.

Generalizability of findings from studies with a large number of variables is frequently limited. Assessment of PPL requires consideration of size, lobar location, proximity to pulmonary hilum, bronchus sign, and presence/absence of COPD. Findings from our randomized study hold true for patients with similar clinicoradiologic characteristics but many patients will differ from our cohort based on one or more of the abovementioned characteristics. As described by Lilford et al.,[739] differences in clinical outcome for individuals may be in either probability (ie. likelihood of diagnostic success) or in utility (ie. effect a person is prepared to trade off against the positive outcome of an investigation).

The utility for individual diagnostic procedures may also vary from patient to patient, based on aversion to risk, or to undesired outcomes. Such factors may influence cost-utility or cost-effectiveness analyses.[740, 741] Clinical decision making incorporating all of this information is frequently performed intuitively, however there are numerous studies highlighting the limitations of intuitive reasoning in complex clinical scenarios.[742] The attempt to make complex decisions intuitively inevitably results in gross oversimplifications because it is impossible to incorporate and consider several components of a decision simultaneously.[739] Clinical decision making may be influenced by non-clinical factors such as recent experiences, or minor changes in the ordering or framing of information.[743, 744] This can lead to differences in clinical opinions by individual doctors even when presented with identical information for both diagnosis,[745, 746] and probability assessment.[747, 748] Numerous clinician-held biases may also strongly influence medical decision-making.[749-751]

Health professionals usually undertake complex decision-making intuitively, and in discussion with patients, but formal decision analysis provides an intellectual framework for developing an explicit decision making algorithm which can be criticised and improved.[739] It is able to simulate even complex clinical algorithms, and explicitly capture the uncertainty that is inherent in modeling of any type.[752] It
utilizes Bayesian probabilities together with values assigned to different outcomes to
determine the best course of action.[739] Decision tree analysis therefore represents a
method for synthesising both medical facts (probabilities) and human values
(utilities), which together determine the best course of action.[753]

Performance of decision tree analysis was undertaken with the aim of establishing
which clinicoradiologic factors most heavily influenced cost-benefit and cost-
effectiveness analyses. Such information may be of significant value in assisting
clinicians in selection of the optimal diagnostic procedure when evaluating patients
with PPL.

2.1.1.3 Aim 3
To examine issues arising during the integration of EBUS-TBNA into routine clinical
care
(Aim addressed in chapters 5 and 6)

EBUS-TBNA was developed following miniaturization of the EUS-FNA bronchoscope. This had been used for almost ten years to achieve minimally invasive
per-oesophageal staging of intrathoracic malignancy, including lung cancer.[569]
Recognizing that a majority of lung cancer patients require invasive assessment of the
mediastinum,[29, 731] EBUS-TBNA was developed.[34] Reports to date had
examined diagnostic sensitivity, with consistent results noted in multiple studies, and
meta-analysis indicating a diagnostic sensitivity of 0.93 (95% CI, 0.91-0.94) and
specificity of 1.00 (95% CI, 0.99-1.00).[705]

Widespread uptake of EBUS-TBNA preceded detailed examination of numerous
issues with respect to optimal performance of the procedure, integration into routine
care alongside current diagnostic methods, and alternate indications for performance
of EBUS-TBNA beyond staging of NSCLC.

Original reports describe introduction of the dedicated convex-probe EBUS
bronchoscope into the airway via an artificial airway (eg. endotracheal tube, laryngeal
mask) under general anaesthesia.[729] If the procedure is to be performed under standard bronchoscopic conditions, size characteristics of the instrument necessitate oral rather than nasal insertion. However, per oral introduction of the bronchoscope has been associated with lower patient satisfaction.[754] It is also recognized that bronchoscopists may underestimate patient discomfort during flexible bronchoscopy.[755]

Performance of a poorly tolerated procedure is likely to markedly limit use of a procedure, even despite the excellent diagnostic accuracy and safety of the procedure. We examined patient tolerance of EBUS-TBNA under conscious sedation, as we believed evidence indicating this approach was well tolerated was required before widespread uptake of the procedure under these conditions could be supported.

Early reports suggested diagnostic accuracy of EBUS-TBNA was similar to the historic gold standard of mediastinoscopy.[716] However, capital costs for introduction of EBUS-TBLB are substantial. The feasibility of introduction of the procedure into the Australian setting depend in part on the economic implications and the cost-benefit of EBUS-TBNA versus mediastinoscopy for staging of NSCLC was unknown. We aimed to determine the extent of cost-benefit associated with minimally invasive EBUS-TBNA. Such information will be important in assessment of the economic value of significant capital expenditure necessary to implement EBUS.

Early reports of the safety of EBUS-TBNA suggested an extremely low rate of significant complications.[732] Infective complications following conventional (Wang needle) TBNA have been reported,[756] and multiple case reports emerged describing infective complications at the site of minimally invasive TBNA/FNA.[733, 757-759] Infectious Disease Society of America guidelines regarding endocarditis antibiotic prophylaxis recommend antibiotics only if the respiratory mucosa is to be violated in the setting of a high-risk patient.[760] The risk of infection from EBUS-TBNA appeared higher than for routine bronchoscopy, and the reported cases suggested that TBNA may need to be considered a violation of the respiratory mucosa. However, the rate of bacteraemia during EBUS-TBNA was unknown and it was also unclear if this contributed to development of infection in affected individuals. We aimed to determine bacteraemia rates, and bacteriology, in patients
undergoing EBUS-TBNA for a variety of indications. Such information is important to properly guide prophylaxis and treatment recommendations of infection complicating EBUS-TBNA.

An increasing body of evidence supports the importance of accurate sub-typing of NSCLC in order to guide optimal selection of systemic therapies. Variation in either efficacy or toxicity of both chemotherapeutic [60, 761, 762] and biologic [59, 668] agents for specific histologic subtypes of NSCLC are reported. In addition, molecular abnormalities for which specific biologic treatments exist appear confined to tumours with adenocarcinoma histology.[192, 763] Meanwhile, the ability to acquire both diagnostic and staging information in a single procedure mean many patients undergo EBUS-TBNA as their sole diagnostic procedure. Consequently, at a time where tissue characterization is becoming ever more important, tissue specimen size is becoming ever smaller. Significant inter-observer variability between pathologists in the sub-classification of NSCLC subtypes in small specimens obtained at routine flexible bronchoscopy has previously been observed,[764] and cytologic specimens are subject to significantly higher interobserver variability than histologic specimens.[765] Given the increasing importance of accurate NSCLC sub-classification, we aimed to examine interobserver variability in evaluation of the small volume samples obtained by EBUS-TBNA.

2.1.1.4 **Aim 4**

*To examine the diagnostic and prognostic significance of sarcoidal granulomas in regional lymph nodes of patients with non-small cell lung cancer*

(Aim addressed in chapter 7)

High diagnostic sensitivity of EBUS-TBNA had been reported in multiple studies, though the negative predictive value of the technique in mediastinal staging remained unclear.[520] Early reports had also noted the ability of EBUS-TBNA to demonstrate sarcoidal granulomas in patients with suspected sarcoidosis,[766, 767] Both sarcoidosis as well as localized sarcoideal reactions are recognised to occur in the setting of malignancy,[768] and thus the negative predictive value of pre-operatively
identified granulomatous reactions within regional lymph nodes, obtained by minimally invasive EBUS-TBNA, was unclear. With the aim of addressing this clinical question, we determined the prevalence of sarcoideal reactions within regional lymph nodes in NSCLC, and the frequency of co-involvement of sarcoideal reactions and lymph node metastases in NSCLC.

The pathogenesis of sarcoideal reactions in patients with malignancy is poorly understood, though formation of non-necrotising epithelioid granulomas appears to occur at sites of antigen presentation.[769] The clinical implications of this finding are also uncertain though in Hodgkins Lymphoma sarcoideal reactions have been associated with improved prognosis.[770] Both these observations have prompted the hypothesis that sarcoideal reactions may represent an effective cell-mediated anti-tumour response. Our preliminary work indicated that sarcoideal reactions appear to be isolated to patients with stage I NSCLC.[771] I examined the association between these reactions and disease-free survival though performance of a case-control study.
2.2 RESEARCH METHODOLOGY

Methods for evaluation of results are specific to the study design required to address individual research aims and are therefore presented in detail in each chapter of the thesis. There are two research concepts that require elaboration as they are integral to examination of the effectiveness of novel techniques during integration into/replacement of previous standard techniques and thus have underpinned much of the work undertaken in this thesis. These are discussed in detail below. The setting in which the research was undertaken is described in detail in section 4.4.2.1.

2.2.1 Comparative Effectiveness Research

The traditional clinical trial design – randomized controlled trial (RCT) – is most frequently used to assess efficacy of a new tool, i.e., does this intervention work under ideal conditions? What best assists clinical decision makers is information on effectiveness, i.e., does this intervention work under “everyday” conditions. This is known as effectiveness research. The research methodology to assess effectiveness is often different to that best suited to evaluation of efficacy. This has been highlighted in the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) tool which was developed to help researchers design trials that inform health care decisions.[772] This document outlines 10 domains illustrating the extremes of explanatory (assessment of efficacy) versus pragmatic (assessment of effectiveness) trial designs (see figure 1.7).

Comparative Effectiveness Research (CER) has been defined as “the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care.” Its purpose is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.[773] It is characterized by the study of two or more interventions using a variety of study designs, which allows comparative evaluation of the
effectiveness of these interventions in real-world settings, for diverse patient populations and subgroups, assessing a full range of outcomes.[774]

Pragmatic trials, by virtue of their greater external validity (generalizability) are favoured in conduct of CER.[772] An analysis for the Cochrane database group on CER wrote that CER should directly compare tests or active treatments-so-called head-to-head comparisons-of viable clinical alternatives within the current standard of practice (which in some cases may be no intervention). CER should primarily assess patient-relevant outcomes, but should also compare the economic implications of different approaches to prevention and care.[775]

Published evidence (discussed above) has evaluated the performance characteristics, or efficacy, of endobronchial ultrasound. What is unknown is how such technology compares with methods currently used for diagnosis of PPL and/or mediastinal staging of NSCLC. CER methodology is in this thesis used to undertake a randomized pragmatic trial to assess relative effectiveness of EBUS-TBLB versus CT-guided percutaneous lung biopsy in evaluation of PPL.
<table>
<thead>
<tr>
<th>Participants</th>
<th>Pragmatic trial</th>
<th>Explanatory trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant eligibility criteria</td>
<td>All participants who have the condition of interest are enrolled, regardless of their anticipated risk, responsiveness, comorbidities or past compliance.</td>
<td>Stepwise selection criteria are applied that (a) restrict study individuals to those previously shown to be at highest risk of unfavourable outcomes, (b) further restrict these high-risk individuals to those who are thought likely to be highly responsive to the experimental intervention and (c) include just those high-risk, highly responsive study individuals who demonstrate high compliance with pretrial appointment-keeping and mock intervention.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions and expertise</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental intervention — flexibility</td>
<td>Instructions on how to apply the experimental intervention are highly flexible, offering practitioners considerable leeway in deciding how to formulate and apply it.</td>
<td>Inflexible experimental intervention, with strict instructions for every element.</td>
</tr>
<tr>
<td>Experimental intervention — practitioner expertise</td>
<td>The experimental intervention typically is applied by the full range of practitioners and in the full range of clinical settings, regardless of their expertise, with only ordinary attention to dose setting and side effects.</td>
<td>The experimental intervention is applied only by seasoned practitioners previously documented to have applied that intervention with high rates of success and low rates of complications, and in practice settings where the care delivery system and providers are highly experienced in managing the types of patients enrolled in the trial. The intervention often is closely monitored so that its “dose” can be optimized and its side effects treated; co-interventions against other disorders often are applied.</td>
</tr>
</tbody>
</table>

| Comparison intervention — flexibility | "Usual practice" or the best alternative management strategy available, offering practitioners considerable leeway in deciding how to apply it. | Restricted flexibility of the comparison intervention; may use a placebo rather than the best alternative management strategy as the comparator. |
| Comparison intervention — practitioner expertise | The comparison intervention typically is applied by the full range of practitioners and in the full range of clinical settings, regardless of their expertise, with only ordinary attention to their training, experience and performance. | Practitioner expertise in applying the comparison intervention(s) is standardized to maximize the chances of detecting whatever comparative benefits the experimental intervention might have. |

<table>
<thead>
<tr>
<th>Follow-up and outcomes</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up intensity</td>
<td>No formal follow-up visits of study individuals. Instead, administrative databases (e.g., mortality registries) are searched for the detection of outcomes.</td>
<td>Study individuals are followed with many more frequent visits and more extensive data collection than would occur in routine practice, regardless of whether patients experienced any events.</td>
</tr>
<tr>
<td>Primary trial outcome</td>
<td>The primary outcome is an objectively measured, clinically meaningful outcome to the study participants. The outcome does not rely on central adjudication and is one that can be assessed under usual conditions (e.g., special tests or training are not required).</td>
<td>The outcome is known to be a direct and immediate consequence of the intervention. The outcome is often clinically meaningful but may sometimes (e.g., early dose-finding trials) be a surrogate marker of another downstream outcome of interest. It may also require specialized training or testing not normally used to determine outcome status or central adjudication.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compliance/adherence</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant compliance with “prescribed” intervention</td>
<td>There is unobtrusive (or no) measurement of participant compliance. No special strategies to maintain or improve compliance are used.</td>
<td>Study participants’ compliance with the intervention is monitored closely and may be a prerequisite for study entry. Both prophylactic strategies (to maintain) and “rescue” strategies (to regain) high compliance are used.</td>
</tr>
<tr>
<td>Practitioner adherence to study protocol</td>
<td>There is unobtrusive (or no) measurement of practitioner adherence. No special strategies to maintain or improve adherence are used.</td>
<td>There is close monitoring of how well the participating clinicians and centres are adhering to even the minute details in the trial protocol and “manual of procedures.”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analysis</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Analysis of primary outcome</td>
<td>The analysis includes all patients regardless of compliance, eligibility, and others (intention-to-treat analysis). In other words, the analysis attempts to see if the treatment works under the usual conditions, with all the noise inherent therein.</td>
<td>An intention-to-treat analysis is usually performed. However, this may be supplemented by a per-protocol analysis or an analysis restricted to “compliers” or other subgroups in order to estimate maximum achievable treatment effect. Analyses are conducted that attempt to answer the narrowest, “mechanistic” question (whether biological, educational or organizational).</td>
</tr>
</tbody>
</table>

**Figure 1.7:** Domains illustrating the extremes of explanatory and pragmatic trial design. (from Thorpe *et al.* [772])
2.2.2 Decision Tree Analysis

Results from clinical trials may yield results that assist clinicians in practising evidence-based medicine. However patients in clinical practice may differ from the “average” patient studied in a clinical trial.[776] Furthermore, such studies may produce results that describe the probability of a particular outcome, or the magnitude of a particular outcome. However incorporating these factors into a clinical decision-making model can be difficult. Health professionals usually do this intuitively, but formal decision analysis provides an intellectual framework for developing an explicit decision making algorithm which can be criticized and improved.[739] The attempt to make complex decisions intuitively inevitably results in gross oversimplifications because it is impossible to incorporate and consider several components of a decision simultaneously.[742]

An advantage of decision tree analysis is its capacity to simulate even complex clinical algorithms, such as that for the NSCLC staging. Furthermore, it can explicitly capture the uncertainty that is inherent in modelling of any type. [777] Sensitivity analysis allows outcomes to be modelled across a range of factors (input parameters) that may influence clinical outcomes (outputs).

A further strength of decision analysis is that decisions are based not just on the probability of specific outcomes but also on the value placed on these. It is able to synthesize medical facts (probabilities) and human values (utilities) to maximise expected utility.[753] When the costs of various options are included this is called a cost utility analysis.
CHAPTER 3: Determining optimal performance of radial probe endobronchial ultrasound

3.1 BACKGROUND

Over 80% of lifetime radiation is a result of background “cosmic” radiation, with dosages estimated at 2.4 mSv per year.[84] Exposure to higher doses of ionizing radiation is recognized to increase the risk of numerous malignancies, as well as benign disease.[86] Radiologic imaging for medical purposes is one of the major sources of increased radiation exposure.[87, 88]

Fluoroscopic screening has been used in the performance of bronchoscopy as it has previously been demonstrated to increase diagnostic yield for peripheral lesions.[25] Diagnostic yield for bronchoscopy in the investigation of peripheral lung lesions has been improved further by the introduction of endobronchial ultrasound (EBUS). Initial reports utilized fluoroscopic guidance in addition to EBUS.[676] though more recent studies suggest yield may be unaffected by removal of fluoroscopic guidance.[677] Every effort should be made to minimize the use of ionizing radiation where possible.[778] and if significant risks were posed by radiation doses resulting from fluoroscopic guidance of bronchoscopic procedures, then the risk-benefit equation may suggest fluoroscopy was unwarranted in performance of radial EBUS. The radiation dose received by bronchoscopist, or by patients undergoing bronchoscopy with fluoroscopy, had never been quantified. Therefore the attributable radiation risk was unknown.
3.2 RADIATION DOSE TO PATIENTS AND STAFF DURING FLUOROSCOPICALLY GUIDED ENDOBRONCHIAL ULTRASOUND-GUIDED BIOPSY OF PERIPHERAL PULMONARY LESIONS

3.2.1 Introduction

Due to changes in the epidemiology of lung cancer,[779] a majority of lung cancers are now located in the lung periphery and, therefore, are not visible at routine bronchoscopy.[220] Diagnostic yield of transbronchial lung biopsy without guidance in the investigation of peripheral pulmonary lesions is less than 20%.[23, 24] Diagnostic yield may be improved with use of fluoroscopic guidance to more accurately target the area of interest.[446, 780] More recently endobronchial ultrasound (EBUS) used in the investigation of peripheral pulmonary lesions has allowed accurate localization of such lesions, resulting in diagnostic accuracy of up to 85%.[450]

Initial reports describing the technique utilized fluoroscopic guidance,[676] though a more recent study suggested diagnostic yield of EBUS bronchoscopy may be unaffected by removal of fluoroscopic guidance.[677] However, this report also noted a reduced yield in the right lower lobe and attributed this to inadvertent relocation of the guide sheath during the procedure.[677] There is potential for movement of the EBUS probe after deployment in any lobe due to deep respiration or vigorous coughing. Even movement to a bronchiole adjacent to a mass may compromise diagnostic yield.[683]

As radial-probe EBUS bronchoscopy is not a real-time procedure, we feel that once the lesion has been localized with EBUS, optimal performance of the biopsy is achieved using fluoroscopic guidance, as it allows confirmation that the guide sheath remains in its original position and that the biopsy forceps are passed the correct distance into the lung periphery. This ensures a high diagnostic yield and reduces the likelihood of biopsy forceps being advanced too far, which may result in
pneumothorax. The benefit from using ionizing radiation for medical imaging should always outweigh the risks resulting from exposure to radiation. The radiation exposure from fluoroscopic guidance during bronchoscopy has never been quantified.

In order to quantify the radiation exposure and, therefore, the risk associated with fluoroscopic guidance during EBUS bronchoscopy we calculated the radiation exposure to patients, as well as measuring the radiation dose received by the bronchoscopists, and assistants, in consecutive EBUS bronchoscopy procedures utilizing fluoroscopic guidance.

3.2.2 Methods

We studied consecutive subjects undergoing bronchoscopy with EBUS for the investigation of peripheral pulmonary lesions from July 1st 2007 to January 31st 2008. All patients with pulmonary lesions not endobronchially visible were investigated using both radial probe EBUS as well as fluoroscopic guidance. Procedures were performed as previously described [676] by a single physician (DPS).

3.2.2.1 Measurement of patient dose

Fluoroscopic guidance was performed using a C-arm mobile fluoroscopy system (GE/OEC 9600 mobile fluoroscopy system. General Electric Healthcare, New York, NY). For all bronchoscopy procedures the mobile Image Intensifier was positioned with the x-ray tube located underneath the patient. This is a standard operational procedure and is performed specifically to minimize scattered radiation to radiosensitive organs of staff within the working environment. To estimate the effective radiation received by the patient, the geometry, anatomical area screened, x-ray beam dimensions, peak kilovoltage (kVp), milliAmperes (mA) and fluoroscopy screening time were recorded from the fluoroscopic x-ray equipment at the completion of the procedure. Machine parameters such as fluoroscopic radiation dose rates; and kVp's were measured using a MDH Radcal Corporation model 9095 meter with a Radcal 90X5-6 6 cm³ ion chamber. The Half value layer of the equipment was
also estimated from these measurements. Using these measured parameters and the Monte Carlo software developed by Tapiovaara,[781] the effective dose received by each patient was estimated.

3.2.2.2 Measurement of staff dose

Radiation dose measurements for bronchoscopists were performed using passive personal radiation (film) monitors (National Radiation Laboratory, Christchurch, New Zealand). The film dosimeters can record photon energies ranging between 15 and 180 kilo-electronvolts (keV), and have a minimum reportable dose (threshold) of 50 microsieverts (µSv). Four personal radiation dosimeters were placed identically for both the bronchoscopist and the assistant in the following positions; one overlying the thyroid shield, one over the sternum outside the protective apron, one over the sternum beneath the protective apron, and one posteriorly at waist level, outside the protective apron. The personal radiation monitors (including control) were assessed at three month intervals.

3.2.2.3 EBUS procedure

All procedures were performed under conscious sedation, as previously described,[782] with the patient in the supine position lying on a radiotransparent trolley. Fluoroscopic guidance using a C-arm mobile fluoroscopy system utilized tube potential varying between 60 to 80 kVp, depending on the size of the patient. Fluoroscopy screening parameters (kVp, mA, area screened) were optimized at the beginning of each case and were not altered subsequently for the remainder of each procedure. Fluoroscopic screening was predominantly used to check that the guide sheath had not moved after the lesion had been localized with EBUS and to visualize the forceps whilst specimens were obtained. Transbronchial lung biopsies and cytology brushings were performed in all cases.

The bronchoscopist was positioned at the head of the trolley and remained in this position throughout the procedure. The assistant predominantly stood next to the bronchoscopist but moved away for brief periods to retrieve equipment or handle collected specimens, although this rarely occurred during fluoroscopic screening. All
staff in the procedure room wore lightweight “non-lead” composite aprons covering both front and back. The lead equivalence of the aprons is 0.35mm across the diagnostic x-ray energy range.

Institutional ethics committee approval was sought, and granted, for the performance of this study.

3.2.3 RESULTS

Data was recorded for forty-five consecutive patients who underwent EBUS bronchoscopy for suspected lung cancer in the study period. Mean lesion size was 3.1 ± 1.1 cm. Mean fluoroscopic exposure times recorded for these procedures was 96 ± 55 seconds.

EBUS bronchoscopy was diagnostic in 36 patients (80%). The diagnoses made are listed in table 3.1. Two patients demonstrated resolution of radiologic abnormality on subsequent imaging, confirming a benign nature of the pulmonary lesion.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-small cell lung cancer – 29</td>
<td></td>
</tr>
<tr>
<td>Small cell lung cancer – 3</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis – 2</td>
<td></td>
</tr>
<tr>
<td>Bronchoalveolar cell carcinoma – 1</td>
<td></td>
</tr>
<tr>
<td>Mycobacterium <em>tuberculosis</em> – 1</td>
<td></td>
</tr>
</tbody>
</table>
Of the remaining four patients, two had non-small cell lung cancer demonstrated on subsequent procedures, and two are undergoing radiologic surveillance of pulmonary lesions. One patient experienced transient hypoxia following the procedure, which resolved with supportive care only. He was discharged home the same day. No other complications occurred.

3.2.3.1 Radiation exposure to patients

Sufficient data was recorded to allow calculation of effective radiation dose for 37 patients undergoing EBUS bronchoscopy. A mean effective dose of $0.49 \pm 0.37$ milliSieverts (mSv) (range 0.016–1.3mSv) was recorded. There was significant variation in the patient’s calculated effective dose, as seen in Table 3.2, where quartile values for screening time and effective dose (mSv) are indicated.

Table 3.3 records radiation exposure from other common sources of ionizing radiation (including other medical procedures), for the purpose of comparison with our findings.

3.2.3.2 Radiation exposure to clinicians

Radiation exposure during two three-month intervals were assessed, with 21 and 24 procedures performed in the first and second periods, respectively. Measured radiation doses recorded by passive radiation monitors worn by staff are recorded in Table 3.4. The only positions to record radiation doses above the minimum threshold for the devices were those positioned over the sternum, outside the protective lead apron.
Table 3.2: Patient exposure data during EBUS-GS bronchoscopy

<table>
<thead>
<tr>
<th></th>
<th>Mean (±SD)</th>
<th>1st quartile</th>
<th>Median</th>
<th>3rd quartile</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroscopic screening time (sec)</td>
<td>96 (±55)</td>
<td>44</td>
<td>98</td>
<td>131</td>
<td>250</td>
</tr>
<tr>
<td>Effective dose (mSv)</td>
<td>0.49 (±0.37)</td>
<td>0.18</td>
<td>0.37</td>
<td>0.74</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Table 3.3: Effective radiation doses for common sources of ionizing radiation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Effective dose (mSv)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-hour transatlantic (Frankfurt – Vancouver) airline flight</td>
<td>0.06</td>
<td>[783]</td>
</tr>
<tr>
<td>EBUS bronchoscopy</td>
<td>0.49</td>
<td>-</td>
</tr>
<tr>
<td>Background “cosmic” radiation (over 1 year)</td>
<td>2.4</td>
<td>[784]</td>
</tr>
<tr>
<td>Low-dose CT chest</td>
<td>5</td>
<td>[785]</td>
</tr>
<tr>
<td>CT-guided lung biopsy</td>
<td>6</td>
<td>[786]</td>
</tr>
<tr>
<td>Coronary angioplasty</td>
<td>17</td>
<td>[736]</td>
</tr>
<tr>
<td>CT- pulmonary angiogram</td>
<td>19</td>
<td>[787]</td>
</tr>
</tbody>
</table>

Table 3.4: Recorded staff effective radiation doses

<table>
<thead>
<tr>
<th>Dosimeter location</th>
<th>Dose recorded (µSv)</th>
<th>Total recorded radiation dose (µSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>period 1 (n=21)</td>
<td>period 2 (n=24)</td>
</tr>
<tr>
<td>Thyroid, outside apron</td>
<td>P&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>&lt;50</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>110</td>
</tr>
<tr>
<td>Sternum, outside apron</td>
<td>P</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>&lt;50</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>110</td>
</tr>
<tr>
<td>Sternum, inside apron</td>
<td>P</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>&lt;50</td>
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<td></td>
<td>90</td>
<td>110</td>
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<tr>
<td>Back</td>
<td>P</td>
<td>A</td>
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<td></td>
<td>&lt;50</td>
<td>&lt;50</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>110</td>
</tr>
</tbody>
</table>

<sup>a</sup>P = proceduralist, <sup>b</sup>A = assistant
3.2.4 DISCUSSION

This is the first study describing radiation exposure to patients undergoing bronchoscopy, and to bronchoscopists and their assistants, due to fluoroscopic guidance. Our study demonstrates that patients undergoing EBUS bronchoscopy are not exposed to significant radiation during the procedure. Mean and median effective doses received, which are below 0.5mSv, are equivalent to approximately 10 chest x-ray examinations,[788] and compare favourably to CT-guided lung biopsy, where effective patient doses of 6mSv are received,[786] and CT-fluoroscopy for performance of transbronchial lung biopsy, with reports indicating mean thoracic organ applied doses of 380mSv.[789] It is much lower than the 5 mSv resulting from low-dose CT chest, and significantly less than patient doses associated with other fluoroscopically guided medical procedures such as ERCP (6mSv [735, 737]), vertebroplasty (10mSv [735]), and coronary angioplasty (11 – 17mSv [736]).

The variation in patient effective dose appears to be due to both the size of the patient and the complexity of the individual procedures. Wide variation in effective dose is noted both for routine CXR [788] and fluoroscopically guided interventional cardiac procedures,[790] mainly due to differences in patient size. However, the additional variable of screening time, which can be linearly related to effective dose, is most responsible for the wider variation in effective doses among our patients. Such variation has been noted in previous studies examining fluoroscopy-guided medical procedures such as ERCP [737] and fluoroscopically-guided orthopedic procedures.[791].

Importantly, as well as minimizing patient radiation, our results are consistent with previous reports that confirm EBUS bronchoscopy to be a very safe procedure.[450, 676] This is in contrast to percutaneous lung biopsy, which has a comparable diagnostic yield to EBUS bronchoscopy,[457, 792] but is associated with a pneumothorax rate from 25%-457, 792] to over 40%.[793]

Deterministic side effects due to radiation exposure from fluoroscopy, such as radiation-induced dermatitis or burns,[794] have been reported but are of much less
concern in bronchoscopic procedures utilising mobile image intensifiers due to relatively low entrance skin dose rates and short screening times.[795] Stochastic effects, particularly malignancy, are a potential concern. Knowledge of cancer risk associated with exposure to ionising radiation in excess of background radiation is largely based on studies of Japanese atomic bomb survivors. These groups were exposed to very high amounts of radiation, and experienced higher rates of both solid organ and haematological malignancies.[89, 90] However, a dose-response relationship was seen and no excess rate of solid organ malignancy was observed among the population exposed to <10mSv.[89]

Effective doses to patients undergoing EBUS bronchoscopy are much lower than such radiation doses previously associated with no harm and are more equivalent to a single return intercontinental airline flight.[796] It is also clear that the excess rate of radiation-induced cancer is very small in comparison to the spontaneous cancer incidence risk.[797]

Additionally, linear extrapolation of data from populations exposed to high doses, such as those resulting from atomic bomb exposure, overestimates the cancer risks of low-dose exposures.[91] While biological effects may result from ionizing radiation doses in the diagnostic energy range,[798] the biologic effects of low-dose and high-dose ionizing radiation are not linearly distributed.[799] This allows further reduction in the estimated risk from exposure to fluoroscopy during EBUS bronchoscopy.

For proceduralists, and their assistants, who are exposed to radiation on repeated occasions, our study also provides reassuring results. We confirm that, with adequate protective shielding, bronchoscopists and their assistants are not exposed to significant amounts of scattered radiation from fluoroscopic-guided bronchoscopy procedures. Dosimeters positioned beneath lead protective aprons recorded no radiation dose above the minimum 50μSv threshold. Expected attenuation of ionizing radiation in the diagnostic energy range across shielding of 0.35mm minimum lead equivalence is estimated at 93%.[800] Thus, on the basis of the externally recorded radiation dose of 200μSv recorded over 45 procedures, we conclude that bronchoscopists utilizing fluoroscopic guidance with lead shields of 0.35mm
minimum lead equivalence are unlikely to be exposed to an effective radiation dose not exceeding approximately 0.4μSv per procedure. Shielded thyroid exposure is less than 0.2μSv per procedure.

Recorded effective doses to staff compare favourably to other fluoroscopy-guided medical procedures. CT-guided biopsy results in a proceduralist effective dose of up to 28 μSv per procedure.[786] Effective doses of up to 38μSv per procedure have been reported for diagnostic cardiac catheterization [801] and up to 166μSv per procedure for percutaneous coronary intervention.[802] Interventional cardiologists have been noted to receive a maximum annual dose of up to 2.8mSv despite optimal shielding.[803] To achieve similar, albeit safe, annual doses would require the performance of over 5,000 fluoroscopy-guided bronchoscopies; well beyond even the most prolific bronchoscopist.

Atomic bomb survivors do not provide useful comparison of risk for subjects exposed to much lower doses of radiation, over prolonged periods of time. Recovery from radiation-induced injury is much more effective following low-dose exposures.[93] and low dose rates.[94] Cohorts exposed to occupational radiation are therefore more representative of the risks to which bronchoscopists using fluoroscopy are exposed.

Airline cabin crew experience radiation exposure above background radiation levels due to ionising cosmic radiation. Examination of 19,184 commercial airline pilots with mean annual doses of 2.5mSv in excess of background radiation levels, and cumulative lifetime doses not exceeding 80mSv, demonstrated no increase in all-cause and all-cancer mortality.[99] Nuclear industry workers have experienced no increased incidence of malignancy even following cumulative exposures of <200mSv.[98] McGeoghegan et al recently reported on a cohort of 64,937 nuclear industry workers, with subjects exposed to <10mSv experiencing no adverse health effects at all.[804]

Fluoroscopic procedures are by far the largest source of occupational exposure in medicine,[805] however reports of deterministic injuries resulting from such exposure are rare. Vano et al[806] reported a case series of ophthalmologically confirmed lens
injuries in interventional radiologists receiving estimated lens doses of 450 to 900mSv per year, over several years; vastly in excess of the magnitude of radiation to which interventional bronchoscopists are exposed. Probability of stochastic risks is dependent on radiation dose. Lifetime risk of fatal cancer for bronchoscopists, based on the work of Goodenough,[807] is of the magnitude of $1 \times 10^{-6}$ per procedure. The literature, therefore, clearly supports the assertion that performance of fluoroscopically guided bronchoscopic procedures should not be associated with any adverse outcomes.

3.2.4.1 Study limitations

Effective patient (and staff) doses vary considerably according to fluoroscopy screening time, which is determined by the number of diagnostic specimens taken, and the proficiency of the bronchoscopist.[808] Our results will not be identical to those for other bronchoscopists utilizing fluoroscopy during bronchoscopy as fluoroscopy parameters, most notably screening times, are likely to vary between individual proceduralists and institutions. In addition, doses recorded at such low levels are subject to significant uncertainty. However the magnitude of radiation exposure is very likely to be reproducible and, given the very small amount of radiation we feel our findings of safe levels of radiation exposures are generalizable to all bronchoscopists.

Use of EBUS guidance, in addition to increasing the diagnostic accuracy of bronchoscopic biopsy, is likely to have reduced radiation exposure, as the time required to confidently locate the lesion is reduced. This is valuable in minimizing radiation exposure and additional measures may be used to reduce effective doses to patients even further, such as maximising x-ray tube to patient distance, minimising the patient to image intensifier distance, coning the x-ray beam to the region of interest, minimising the use of electronic magnification, lowering fluoroscopy frame rates, and more judicious use of screening.[778] The International Commission on Radiological Protection notes that the principle aim of medical exposures is to do more good than harm to the patient.[809] In the setting of almost certainly very low patient radiation exposures, we feel there is no rationale to preclude patients from undergoing a single bronchoscopy with fluoroscopy on the basis of safety concerns.
3.2.5 CONCLUSIONS

Adequate shielding of proceduralists’ front and back, and thyroid, using protective garments with a minimum lead equivalence of 0.35mm across the diagnostic energy range result in negligible radiation to proceduralists performing EBUS bronchoscopy with mobile C-arm fluoroscopic guidance.

Effective doses are much smaller than those previously associated with no adverse health outcomes. Concern regarding radiation exposure should not preclude the use of fluoroscopic guidance in the performance of diagnostic bronchoscopy if it is clinically indicated.
CHAPTER 4: Determining the optimal procedure for minimally invasive assessment of peripheral pulmonary lesions

4.1 BACKGROUND

Peripheral pulmonary lesions (PPL) are radiographic abnormalities within the lung parenchyma not visible within central airways at routine bronchoscopy. The differential diagnosis of a PPL is large however in a clinical sense the diagnostic challenge is most frequently framed as “could this be cancer”. The likelihood of PPL representing malignancy varies significantly based on the size & morphologic characteristics of the lesion, and the clinico-demographic characteristics of the patient.[17] Surgical excision is recognized to be the definitive diagnostic procedure,[780] but is unwarranted in the setting of a benign lesion. Minimally invasive diagnosis is therefore frequently sought.

This may be achieved by either bronchoscopic or percutaneous sampling with CT-guidance. Traditionally bronchoscopy was reserved for central airway lesions, where diagnostic yield is known to be high.[780, 810] However, performance of routine bronchoscopy in assessment of peripheral pulmonary lesions was poor, with meta-analysis published in 2003 noting a sensitivity for lesions <2cm diameter of only 33% and some authors noting a diagnostic yield when fluoroscopy was not utilized of as low as 5%.[23] In contrast, percutaneous sampling of peripheral lesions was associated with diagnostic sensitivity of over 90%.[780, 810] American College of Chest Physicians guidelines for the diagnosis of suspected lung cancer published in 2003 [780] made the following recommendations

- In a patient with a central lesion, bronchoscopy is the most sensitive way to confirm a diagnosis of cancer (grade of recommendation = B)
- In the case of a peripheral lung lesion, TTNA has a much higher sensitivity than bronchoscopy. It is the procedure of choice for confirming the diagnosis of lung cancer (grade of recommendation = A)

The availability of radial endobronchial ultrasound (EBUS) markedly improved the diagnostic sensitivity of bronchoscopic investigation of PPL. Bronchoscopy rapidly became a feasible alternative to CT-guided percutaneous needle biopsy (CT-PNB) in part due to the improved yield from bronchoscopy, but also as a result of the favourable safety profile of EBUS-guided transbronchial lung biopsy (EBUS-TBLB). Multiple authors reported consistent improvement in diagnostic yield using radial EBUS, in comparison to historic controls. One group also published a randomized trial indicating superiority of EBUS-TBLB versus traditional bronchoscopic investigation. As a result numerous centres world-wide began to utilize EBUS in their bronchoscopic investigation of PPL.

Performance characteristics of radial EBUS had been reported but no examination had been made of how this new technology should be incorporated into current care. No studies provided evidence from direct comparison between the traditional method for minimally invasive sampling of PPL – CT-PNB – and the novel technique – radial EBUS.

Comparison of these two techniques appeared important in informing clinical decision-making regarding patients with PPL. Information was required regarding complication rates, diagnostic yield, and even cost comparisons. In addition, a measure of ‘utility’ or value placed on a difference would be important in guiding clinicians in care of such patients.
4.2 COMPARATIVE EFFECTIVENESS OF RADIAL PROBE ENDOBRONCHIAL ULTRASOUND VERSUS CT-GUIDED NEEDLE BIOPSY FOR EVALUATION OF PERIPHERAL PULMONARY LESIONS: A RANDOMIZED PRAGMATIC TRIAL

4.2.1 INTRODUCTION

Peripheral pulmonary lesions (PPL) are focal radiographic opacities that may be characterized as nodules (≤3cm) or masses (≥3cm). While referral for lobectomy in patients with a PPL with a very high pre-test probability of malignancy is suggested by some guidelines,[296] resectional biopsy is not risk-free and may not be necessary in a significant number of patients with such lesions.[17] CT screening studies show that up to 34% of such operations are performed for benign nodules.[18-20]

Non-invasive tests such as FDG-PET or dynamic Computerised Tomography (CT) with nodule enhancement cannot distinguish benign from malignant disease with sufficient accuracy.[17] Consequently, attempts at minimally invasive diagnosis are strongly favoured. The two modalities most commonly used to investigate PPLs are CT-guided percutaneous needle biopsy/aspiration (CT-PNB) or bronchoscopy. Bronchoscopy may be limited by poor diagnostic yield,[23, 24] though sensitivity is improved by guidance techniques such as fluoroscopy,[23, 450] virtual bronchoscopy,[686] endobronchial ultrasound (EBUS),[450] or electromagnetic navigation (EMN).[688]

Clinical acumen may determine the choice of initial investigation in many patients with PPL. For example, those with radiographic evidence of probable mediastinal or extra-thoracic metastases are best served by sampling the metastatic disease site.[417] Conversely, PPL with endobronchial involvement are best evaluated via bronchoscopy.[417, 811] Alternatively, expert review of imaging in patients referred for evaluation of PPL may demonstrate that invasive biopsy is not warranted, while in other patients, severe comorbid disease renders tissue diagnosis unnecessary.
However, in a proportion of patients who require tissue diagnosis, the optimal investigation remains unclear. This may be influenced by diagnostic accuracy, complication rates, and costs of individual procedures. Although the individual diagnostic characteristics of both EBUS-guided TBLB (EBUS-TBLB) and CT-PNB are well described, no study has previously directly compared the two tests.

Comparative effectiveness research (CER) was recently defined by the Institute of Medicine as “the generation and synthesis of evidence that compares the benefits and harms of alternative methods to diagnose, treat or monitor a clinical condition”.[783] We performed a randomized trial of EBUS-TBLB versus CT-PNB for the investigation of solitary PPLs, in patients who had no clinical features to mandate or exclude either procedure. We compared the benefits (diagnostic accuracy) and harms (complications) of the two methods in order to guide clinicians in selection of the optimal investigation.

4.2.2 METHODS

Institutional review board approval was granted for the performance of this study. All patients provided informed written consent.

4.2.2.1 Trial design

This study was a prospective randomized pragmatic trial. The continuum between pragmatic and explanatory trials has been previously elucidated, with pragmatic trials noted to be primarily designed to determine the effects of an intervention under the usual conditions in which it will be applied.[772] Given our intention to provide evidence to guide clinicians in selection the optimal investigation of patients with PPLs, the trial was designed according to the PRECIS tool in order to simulate “usual-care” conditions.[772] Such trial designs are well aligned with the purpose of CER.[812] We have adhered to the CONSORT guidelines for optimal reporting of
randomized trials of non-pharmacologic treatment,[813, 814] and the STARD guidelines for reporting studies of diagnostic accuracy.[815]

We hypothesized that the diagnostic accuracy of EBUS-TBLB was non-inferior to that of CT-PNB, but that the complication rate of EBUS-TBLB would be significantly lower than CT-PNB. Non-inferiority was defined a priori as diagnostic accuracy differing by not greater than 10%. Primary study outcomes were procedural complication rates and diagnostic accuracy.

4.2.2.2 Participants
All consecutive patients referred to our multidisciplinary lung cancer service for initial evaluation of solitary PPL, suspicious for lung cancer, were considered for inclusion in the study. The multidisciplinary service is based at Royal Melbourne Hospital, a tertiary referral centre and university teaching hospital. All patients were reviewed in a multidisciplinary meeting (MDM) to ensure that consensus opinion is that investigation is warranted and that either CT-PNB or EBUS would be acceptable modes of initial investigation of the lesion. Clinicians could exclude patients from the study if clinical acumen (on the basis of clinicoradiologic features) suggested a higher diagnostic accuracy or lower complications rate for one of the two procedures, thus making the alternate procedure unacceptable. The following exclusion criteria were applied only to exclude those with PPLs not requiring investigation:
- clinical condition precludes investigation
- lesion <1cm diameter anywhere in lung fields
- Evidence on CT scan of central (endobronchially visible) lesion
- Other clinical site of disease more amenable to tissue diagnosis
- Tissue diagnosis considered unnecessary by MDM

Randomization to either procedure was performed using a computer-based random sequence generator (www.randomization.com). Both subjects and clinicians were unblinded to the randomization outcome. Subsequent investigation in the event of a non-diagnostic procedure was determined by the primary clinician.
Recorded data included patient demographics (age, gender), clinicoradiologic information (lesion size, lobar position, lesion distance from hilum and pleural, final diagnosis) and procedural information (date, diagnostic (Y/N), complications). All data was recorded prior to performance of the diagnostic test.

4.2.2.3 Performance of EBUS-TBLB

Bronchoscopy with EBUS guidance was an established technique at our institution for the investigation of peripheral pulmonary lesions,[782, 816, 817] with approximately 150 procedures completed in the 12 months prior to commencement of the trial. Procedures were performed with topical lignocaine 2% and intravenous sedation, as previously described.[782] All procedures were performed by a single physician (DPS) using a standard videobronchoscope (BF-P160, Olympus, Tokyo, Japan), with a 20-MHz radial EBUS probe (UM-BS20–26R; Olympus, Tokyo, Japan) and guide sheath.

Visible bronchial segments were sequentially examined until the characteristic ultrasound signal indicating presence of solid lesions was demonstrated. The EBUS probe was then removed and sampling instruments (biopsy forceps, cytology brush) introduced through the guide sheath, with sampling performed under fluoroscopic vision. Bronchial washings were taken after performance of TBLB and bronchial brushings. In the event that a PPL was not located, only bronchial washings were performed.

4.2.2.4 Performance of CT-PNB

Computed tomography-guided percutaneous needle biopsy of lung lesions was performed using CT fluoroscopy using a 64 detector CT scanner (Siemens Sensation 64, Siemens Healthcare. Erlangen, Germany). Twelve biopsies were performed by consultant radiologists (JMV, SH) and four were performed by radiology registrars/fellows.

The lung lesion was localized by a limited CT scan through the chest. Lignocaine 1% was injected into the skin and soft tissues to the pleural surface. A coaxial needle
(Bard TruGuide needle, Bard Biopsy Systems. Tempe, AZ, USA) was introduced to the periphery of the PPL and multiple core biopsies (Bard Biopy-Cut needle and Bard Magnum biopsy instrument. Bard Biopsy Systems. Tempe, AZ, USA) were obtained. In fourteen of the fifteen biopsies a 19g coaxial needle and 20g core needle were used. In one patient a 17g coaxial needle and 18g core needle were used.

Following each diagnostic procedure, all patients underwent routine CXR. CT screening of patients following PNB was not performed, and diagnosis of pneumothorax was only made by CXR. Final diagnoses in patients in whom procedures were non-diagnostic were determined either on the basis of a subsequent invasive biopsy procedure, or were presumed benign on the basis of either regression of the PPL during radiologic surveillance, or stability during surveillance of a minimum 12 months duration.

### 4.2.2.5 Statistical analysis

Continuous variables are expressed as mean ± standard deviation, with comparison performed using an unpaired t-test (Welch-corrected). The Mann-Whitney test was used to compare non-parametric values. Categorical variables are presented as simple proportions and compared using Fisher’s exact test. All reported confidence intervals are two-sided. Sensitivity, specificity, and accuracy of the two methods were calculated according to standard definitions, with comparison performed using Fisher’s exact test. Comparison between groups was performed on an as-treated basis. A p-value of less than 0.05 was considered significant. Analyses were performed using GraphPad InStat 3 for Macintosh (GraphPad Software, La Jolla, CA. USA).
4.2.3 RESULTS

From February 7th 2008 until January 22nd 2010, 358 patients were referred to our multidisciplinary lung cancer service for initial evaluation of a PPL. A flowchart illustrating the progression of consecutive unselected patients referred for evaluation of PPL is presented in Figure 4.1. At least one exclusion criteria was met by 259 (72%) patients. A further 14 patients declined, or were unable, to provide consent. Thus 273 (76%) patients were ineligible for randomization (see Figure 4.1).

Clinical acumen resulted in exclusion of 28 patients from the trial. Two patients were preferentially referred for CT-PNB as they had pleurally based PPLs felt to be more amenable to percutaneous sampling. Twenty-six patients were referred preferentially for EBUS-TBLB. Two of these patients were refused by interventional radiologists concerned at the risk of complications from CT-PNB (see Figure 4.2). The remaining 24 patients were declined by their primary clinician; 23 due to concern regarding the risk of pneumothorax complicating CT-PNB in patients with severe COPD or bleeding complicating CT-PNB in patients on anticoagulation, and one on the basis of an expected diagnostic result for EBUS-TBLB in a patient with a peri-hilar pulmonary nodule with a bronchus sign.

Eleven patients also declined to undergo randomization to either procedure. Ten declined CT-PNB due to the risk of pneumothorax, and one patient declined EBUS as CT-PNB could be performed with shorter delay. Three patients were not able to provide consent for inclusion in the trial.

Of the remaining 71 patients, 51 (72%) were randomized. Demographic and clinicoradiologic data for the 51 randomized patients is recorded in Table 4.1.
Figure 4.2: Clinicians were able to exclude patients from randomization if they felt there was an unduly high risk of complications associated with one procedure. Two patients were declined from CT-PNB by interventional radiologists on the basis of a high risk of complications suggested by radiologic appearances. A) CT chest demonstrates a left upper lobe nodule adjacent to an emphysematous bullus, suggesting a high risk of pneumothorax. B) CT/PET demonstrates FDG-avid lesion within the left upper lobe abutting the aortic arch, raising concern regarding vascular trauma complicating the procedure.
4.2.3.1 **Diagnostic performance**

Final diagnoses in all patients undergoing EBUS-TBLB or CT-PNB are recorded in table 4.2. Three patients randomized to CT-PNB did not undergo biopsy: in one, the lesion had resolved by the time of biopsy, a second patient subsequently declined invasive biopsy, and a third patient was referred directly to surgery without biopsy after randomization. Outcome data for all subjects is recorded in Table 4.3. Diagnostic accuracy was similar for both EBUS-TBLB and CT-PNB (87.5% v. 93.3% respectively, \( p=1.0 \)). The 95% confidence interval for diagnostic accuracy of EBUS-TBLB is within the confidence interval for CT-PNB, therefore our results indicate that EBUS-TBLB is non-inferior to CT-PNB for the diagnosis of PPLs.[818]

No clinical factors were noted to influence the diagnostic performance of CT-PNB. For subjects undergoing EBUS-TBLB, multiple factors were associated with improved diagnostic sensitivity (Table 4.4). Diagnostic sensitivity was significantly higher in patients in whom the PPL was located by the probe (22 of 22 v. 5 of 10, \( p=0.001 \)). Ability to locate the PPL with the radial EBUS probe was significantly associated with a diagnosis of primary lung cancer (19 of 28 patients with lung cancer v. 0 of 4 patients with non-lung cancer diagnoses, \( p=0.020 \)). EBUS was significantly more likely to be diagnostic in patients with lung cancer compared to patients with alternate diagnoses (24 of 28 v. 1 of 3, respectively, \( p=0.025 \)). Among patients with primary lung cancer, the ability to locate the PPL with the probe was significantly associated with a positive diagnosis (\( p=0.006 \)).
Table 4-1: Demographic and clinicoradiologic data for randomized patients.

<table>
<thead>
<tr>
<th></th>
<th>EBUS-TBLB</th>
<th>CT-PNB</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>32</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>71 ± 11</td>
<td>67 ± 12</td>
<td>0.193</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>16 / 16</td>
<td>7 / 12</td>
<td>0.36</td>
</tr>
<tr>
<td>Size* (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;2cm</td>
<td>&gt;2cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.8 ± 1.4</td>
<td>4.1 ± 2.1</td>
<td>0.026</td>
</tr>
<tr>
<td>Lobar position*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RUL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>RML</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>RLL</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>LUL</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>LLL</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Distance* (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>from pleura</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>from hilum</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>pleural contact</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.2 ± 2.5</td>
<td>1.6 ± 1.7</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>4.5 ± 2.5</td>
<td>4.9 ± 2.5</td>
<td>0.536</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>5</td>
<td>0.138</td>
</tr>
</tbody>
</table>

* of patients undergoing biopsy (n=16 for CT-PNB)
**Table 4.2:** Final diagnoses in all patients undergoing minimally invasive biopsy

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Method diagnosis established</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic</td>
<td></td>
</tr>
<tr>
<td>EBUS (n = 25)</td>
<td>Adenocarcinoma 14</td>
</tr>
<tr>
<td></td>
<td>Squamous cell lung carcinoma 3</td>
</tr>
<tr>
<td></td>
<td>Small cell lung carcinoma 3</td>
</tr>
<tr>
<td></td>
<td>Large cell lung carcinoma 2</td>
</tr>
<tr>
<td></td>
<td>Non-small cell lung carcinoma 2</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium tuberculosis 1</td>
</tr>
<tr>
<td>CT-PNB (n = 13)</td>
<td>Adenocarcinoma 7</td>
</tr>
<tr>
<td></td>
<td>Squamous cell lung carcinoma 4</td>
</tr>
<tr>
<td></td>
<td>Non-small cell lung carcinoma 1</td>
</tr>
<tr>
<td></td>
<td>Nodular lymphoid hyperplasia 1</td>
</tr>
<tr>
<td>Non-diagnostic</td>
<td></td>
</tr>
<tr>
<td>EBUS (n = 7)</td>
<td>Squamous cell lung carcinoma 2</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma lung 1</td>
</tr>
<tr>
<td></td>
<td>Adenosquamous carcinoma lung 1</td>
</tr>
<tr>
<td></td>
<td>Chondroid hamartoma 1</td>
</tr>
<tr>
<td></td>
<td>Inflammatory mass 1</td>
</tr>
<tr>
<td></td>
<td>Metastatic breast carcinoma 1</td>
</tr>
<tr>
<td>CT-PNB (n = 3)</td>
<td>Inflammatory mass 2</td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma 1</td>
</tr>
</tbody>
</table>

EBUS – endobronchial ultrasound  
CT-PNB – CT-guided percutaneous needle biopsy  
VATS – Video-assisted thoracoscopic surgery  
* all lesions were observed to have resolved on subsequent CT chest.
Table 4.3: Diagnostic performance for detection of lung cancer, and complication rates for the two study groups.

<table>
<thead>
<tr>
<th></th>
<th>EBUS-TBLB</th>
<th>CT-PNB</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic accuracy % (95%CI)</td>
<td>87.5% (71 – 96)</td>
<td>93.3% (68 – 99)</td>
<td>1.0</td>
</tr>
<tr>
<td>Sensitivity* % (95%CI)</td>
<td>86% (68 – 95)</td>
<td>92% (62 – 99)</td>
<td>1.0</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1 (3%)</td>
<td>4 (27%)</td>
<td>0.03</td>
</tr>
<tr>
<td>pneumothorax</td>
<td>1 (3%)</td>
<td>3 (20%)</td>
<td></td>
</tr>
<tr>
<td>admission</td>
<td>1 (3%)</td>
<td>1 (7%)</td>
<td></td>
</tr>
<tr>
<td>ICC</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>deaths</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*sensitivity for the detection of lung cancer

Table 4.4: Comparison of radiologic features of PPLs between patients with lung cancer in whom EBUS-TBLB was diagnostic, versus those in whom EBUS was non-diagnostic. The only factor predictive for a diagnostic procedure was the ability to locate the lesion with the radial EBUS probe.

<table>
<thead>
<tr>
<th></th>
<th>Diagnostic EBUS (n=24)</th>
<th>Non-diagnostic EBUS (n=4)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion size* (mean) SD</td>
<td>30.4 14</td>
<td>27 10</td>
<td>0.69</td>
</tr>
<tr>
<td>Distance* from pleura SD</td>
<td>3.5 2.6</td>
<td>2.0 2.7</td>
<td>0.27</td>
</tr>
<tr>
<td>Distance* from hilum SD</td>
<td>4.0 2.6</td>
<td>5.5 3.1</td>
<td>0.22</td>
</tr>
<tr>
<td>Probe located within lesion</td>
<td>19</td>
<td>0</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*all measured in centimetres
A trend towards significance was seen for difference in sensitivity for PPL ≤6cm from the pulmonary hilum compared to PPL >6cm from the hilum (20 of 21 v. 5 of 8 respectively, \( p=0.058 \)). Lesion size, lobar location, and presence/absence of the CT-bronchus sign were not observed to influence diagnostic performance of EBUS-TBLB (data not shown).

### 4.2.3.2 Complications

There was a significant difference in the overall complication rate between the groups (EBUS 3% v. CT-PNB 27%, \( p=0.03 \)). Pneumothorax was noted in 1 subject in the EBUS group. This was small and self-limiting. Significant haemoptysis and pulmonary haemorrhage, as well as pain, was noted in one subject in the CT-PNB group. This patient required management in hospital and was discharged home after 3 days. Biopsy in this patient was performed using a 17-gauge coaxial needle, with pathologic examination confirming nodular lymphoid hyperplasia. Both the large needle size and the nature of the underlying lesion (CT-PNB confirmed nodular lymphoid hyperplasia) may have contributed to the risk of haemorrhage in this patient. Two further patients undergoing CT-PNB experienced small self-limiting pneumothoraces, and one patient experienced a hydropneumothorax. All complications were managed conservatively, with no patients requiring intercostal catheter insertion.

All complications following CT-PNB were noted in patients in whom the biopsy needle traversed aerated lung, with biopsy of PPLs with pleural contact (n=5) associated with no complications. Complications were seen in two of four procedures performed by radiology registrars/fellows. Comparison with rate of complications in procedures performed by radiology consultants was non-significant (\( p=0.24 \)).
4.2.4 DISCUSSION

This is the first randomized controlled trial to directly compare CT-PNB and EBUS-TBLB for the investigation of PPLs. Our results confirm that both procedures are able to accurately diagnose PPLs. The diagnostic accuracy of the two modalities were comparable, with our results indicating non-inferiority of EBUS-TBLB in comparison to CT-PNB. Inherent in comparative effectiveness research is comparison of both the benefits and harms between the two procedures. Importantly, the complication rate following CT-PNB was significantly higher than that observed following EBUS-TBLB (27% v. 3%, p=0.03). There are practical reasons to suggest why EBUS-TBLB has a significantly lower complication rate, as there is no breach of visceral pleura (as is necessitated by CT-PNB) and biopsy forceps can be localized entirely within the tumour, ensuring injury to surrounding aerated lung is minimized.

Diagnostic sensitivity for both procedures in our study is consistent with previously published studies.[17, 819] A recent meta-analysis confirmed a point sensitivity for detection of lung cancer of 0.73 for EBUS-TBLB in investigation of PPLs, and sensitivity in studies where prevalence of malignancy was greater than 75% was 0.83.[819] No systematic review of CT-PNB for investigation of PPLs has been published but evidence-based clinical practice guidelines observe that sensitivity for detection of malignancy using CT-PNB in most studies exceeds 90%. However, approximately 20% of procedures were non-diagnostic,[17] reflecting the lower yield of CT-PNB in benign conditions.

Our findings suggest that neither modality is uniformly preferable in the investigation of PPLs. If non-inferior in diagnostic accuracy, EBUS-TBLB would be the preferred procedure due to the lower complication rate. While non-inferiority of EBUS-TBLB in evaluation of PPL is demonstrated in our study, this applies only to clinicoradiologically similar PPLs. Clinical and radiologic features affecting diagnostic and complication rates are well described for both EBUS-TBLB and CT-PNB (Table 4.5). Individual randomized or cross-over trials examining the effect on diagnostic accuracy of variation in each of these individual factors is not feasible given the virtually infinite permutations of these factors.
Table 4.5: Evidence-based summary of clinicoradiologic features affecting diagnostic yield & complication rates following invasive biopsy of peripheral pulmonary lesions

- *as well as a higher complication rate, the rate of intercostal tube insertion in the event of a pneumothorax in patients with COPD is also increased. [463, 467, 738, 826, 829]

RML – right middle lobe
RLL – right lower lobe
COPD – chronic obstructive pulmonary disease
EBUS-TBLB – endobronchial ultrasound-guided transbronchial lung biopsy
CT-PNB – CT-guided percutaneous needle biopsy
These results add to data from previous studies regarding the effect of specific clinicoradiologic factors on diagnostic sensitivity or complication rates. Such information may be used to inform a clinical decision-making algorithm to assist clinicians in selection of the most appropriate test. The presence of features that predict a lower diagnostic sensitivity for EBUS-TBLB may lead clinicians to refer patients for evaluation with CT-PNB. Alternatively, clinicoradiologic factors predicting a higher rate of pneumothorax complicating CT-PNB may result in selection of EBUS-TBLB as the primary investigation modality.

A significant number of eligible patients excluded by referring physicians in our study were excluded on the basis of such clinicoradiologic factors, suggesting that many clinicians already make such assessments intuitively.

Cost-effectiveness models may also influence the development of such a clinical algorithm. While diagnostic accuracy appears equivalent, a lower complication rate suggests that EBUS-TBLB may be the preferable test due to a lower morbidity, and lower costs required to manage these complications.

4.2.4.1 Strengths and Limitations
The study was designed as a randomized pragmatic trial in order to replicate usual conditions in which clinical decision-making regarding the choice of investigation for a PPL occurs. We believe the prospective pragmatic study design results in a high degree of external validity. We also carefully defined patient eligibility in order to examine the group of patients with PPL in whom we feel insufficient evidence exists to inform clinical decision-making and in whom the choice between EBUS-TBLB and CT-PNB is frequently arbitrary. We deliberately excluded patients with suspected lung cancer in whom we believe clinical acumen was sufficient to guide initial investigation (eg. patients with endobronchial disease, or suspected distant metastases).

We recognize some limitations to our study. Diagnostic accuracy and complication rates are reported to vary widely for both procedures.[17, 819] The generalisability of our results to other patient cohorts undergoing investigation for PPL is contingent on
individual proceduralists having similar diagnostic sensitivity and complication rates to ours. Significant deviation from our observed outcomes may alter the decision regarding the most appropriate initial investigation for PPLs.

While 14 patients eligible for randomization declined, or were unable, to consent, reasons for failure to randomize were unstated in a further 20 patients. The trial design specified that clinicians may exclude patients from randomization if clinical acumen suggested that one procedure was preferred, and 28 patients were excluded on this basis. We suspect that clinical acumen similarly determined the optimal initial investigation in a significant proportion of these 20 patients. Although selection bias cannot be fully excluded, such a bias would be expected to reduce the observed discrepancy in complication rates. Our findings would therefore remain valid and significant.

We compared CT-PNB with bronchoscopy guided by radial probe EBUS. Other bronchoscopic modalities not included in our study design may be selectively utilized during diagnostic bronchoscopy to further increase diagnostic accuracy. Transbronchial needle aspiration (TBNA) guided by linear probe EBUS may achieve diagnosis via sampling of central parenchymal lesions,[721, 830] or mediastinal and hilar lymph node metastases.[722, 723, 830] EMN is an alternate guidance mechanism however it is very expensive and diagnostic accuracy is not significantly better than EBUS-TBLB.[688] It may be appropriate for selected patients though this remains unclear. Consideration of the potential additional value of these tools should be made when deciding between bronchoscopic and percutaneous approaches to PPL biopsy.

The randomization process resulted in significant differences between the two groups in lesion size (CT-PNB 4.1±2.1 cm v. EBUS-TBLB 2.8±1.4 cm, p=0.026) and in the distance from pleura to the PPL (CT-PNB 1.6±1.7 cm v. EBUS-TBLB 3.2±2.5 cm, p=0.017). The discrepancy in both factors would be expected to favour the CT-PNB arm of the study, with smaller lesion size recognized as a factor in lower diagnostic accuracy for both procedures, and shorter distance between pleura and PPL predicting a lower rate of pneumothorax complicating CT-PNB (see table 4.5). We believe therefore that this does not alter our finding of non-inferiority.
The number of subjects is relatively small, though is consistent with many published interventional bronchoscopy studies. Sample size calculations were performed in order to avoid a type II error (false negative finding) for the primary outcome of complication rates. Given a statistically significant observed difference in complication rates, our subject number, though small, is sufficient to address the primary outcome of complication rates.

4.2.4.2 Implications for future research

Randomized trials in the field of interventional pulmonology are rare, and our results highlight the difficulty of performing such studies. The two major difficulties encountered related to the unequal randomization of subjects (both in terms of numbers per study arm as well as clinical features), and the small proportion of patients screened for trial inclusion that were successfully randomized.

There is a significant chance when randomizing small numbers of subjects that imbalances might be seen between groups.[831] Block (or restricted) randomization may be used to ensure equal numbers of subjects per group, and stratified randomization can be utilized to decrease the odds of significant differences between groups. Response-adaptive (Bayesian) randomization may also allow a reduction in required sample size without impairment of statistical power.[832]

The pragmatic study design used resulted in exclusion of a significant number of patients (Figure 1), including those with clinical stage N2/3 and clinical stage IV disease, as well as those with poor performance status, as we felt the clinical question did not apply to these patient groups. The resultant small proportion of screened patients who were randomized is therefore unsurprising, and is consistent with the proportion of lung cancer patients with localized disease at diagnosis.[29] Future studies may be more effective if performed as multi-centre trials, and may also be required to be more explanatory in design.[772] to optimize subject accrual. Alternatively, further studies examining clinicoradiologic features influencing diagnostic sensitivity and complication rates of EBUS-TBLB and CT-PNB may be more valuable in informing clinical decision-making algorithms. Prospective
validation of any such algorithm would be required prior to their adoption in routine clinical practice.

### 4.2.5 CONCLUSION

Both modalities examined have very good diagnostic accuracy in the investigation of peripheral pulmonary lesions. Our findings suggest that diagnostic accuracy of EBUS-TBLB in evaluation of PPL is non-inferior to CT-PNB. However, clinicoradiologic factors influencing diagnostic accuracy and complication rates should allow clinicians to determine which procedure is most appropriate as the initial investigation for individual patients. Complication rates following EBUS-TBLB are significantly lower than following CT-PNB and as a result, if expected diagnostic sensitivity is equivalent, patients should be preferentially referred for EBUS-TBLB for investigation of PPL. Further studies are required to allow clinicians to accurately assess expected diagnostic accuracy, and complication rates, for individual patients on the basis of clinicoradiologic features.
4.3 RADIAL PROBE ENDOBRONCHIAL ULTRASOUND FOR THE DIAGNOSIS OF PERIPHERAL LUNG CANCER: SYSTEMATIC REVIEW AND META-ANALYSIS

4.3.1 INTRODUCTION

Peripheral pulmonary lesions (PPL) are focal radiographic opacities that may be characterized as nodules (≤3cm) or masses (>3cm). While referral for lobectomy in patients with a PPL with a very high pre-test probability of malignancy is suggested by some guidelines,[296] CT screening studies have shown that 18% – 34% of such operations are performed in patients with benign nodules.[18-20] Consequently, attempts at minimally invasive diagnosis are strongly favoured.

Multiple approaches may be undertaken to establish a tissue diagnosis, including sputum cytology, percutaneous image-guided aspiration/biopsy, and bronchoscopic sampling. Diagnostic yield for routine bronchoscopy for investigation of peripheral pulmonary lesions (ie. lesions not endobronchially visible) may be less than 20%.[23, 24] Diagnostic yield is improved by use of fluoroscopic guidance during performance of transbronchial lung biopsies (TBLB),[23, 25] though varies considerably across reports, from under 45% [23, 452, 833] to over 70%.[449, 834] The highest diagnostic yield for bronchoscopic evaluation of PPLs appears to be associated with use of radial probe endobronchial ultrasound (EBUS).

Radial probe EBUS employs a flexible catheter housing a rotating ultrasound transducer which produces a 360° (“radial”) ultrasound image and was first used to guide TBLB by Herth et al.[673] The transducer is passed into bronchial subsegments until the characteristic ultrasound signal indicating presence of a solid lesion is demonstrated (figure 4.3). TBLB and other methods to sample tissue are then performed from this bronchus.

Numerous groups have now published their experience with EBUS-guided evaluation of PPLs. Synthesis of this information may be valuable to assess the effectiveness and
safety of EBUS-TBLB for the evaluation of PPLs. With this systematic review we sought to establish this through performance of meta-analysis which, to our knowledge, has not previously been performed.

Figure 4.3: Radial probe endobronchial ultrasound image indicating presence of peribronchial mass lesion. The position of the probe is indicated by the central black circle and the hyper-echoic line (arrows) demonstrates the solid tissue-air interface between the peribronchial pulmonary mass lesion (P) and the surrounding lung (L)
4.3.2 METHODS

4.3.2.1 Literature search
A systematic search of the medical literature was performed in December 2009 to identify all studies that used radial probe EBUS for investigation of PPLs. Both Medline and PubMed were searched with a common search strategy (Table 4.6). A manual search of references cited in review papers as well as in all original papers identified by the search was also performed to complete the search.

4.3.2.2 Selection of studies
All articles identified by our search strategy were independently assessed by two authors (DPS, RLM) for inclusion in this review. Discordance was resolved by consensus. Abstracts of all identified articles were initially examined according to pre-established selection criteria. Studies were selected for inclusion in the review only after both reviewers assessed the full text articles. We considered all studies that examined EBUS for the diagnosis of PPLs. Inclusion criteria were;

a) Radial probe EBUS for diagnosis of PPL
b) Diagnoses confirmed histologically, or by close clinical follow-up for at least six months used as the reference standard.
c) Enrolled at least 30 patients

We excluded review articles, non-peer-reviewed papers, and papers not published in English. When multiple papers were published from a single institution we included papers where there were no overlapping study periods. In the event of multiple publications with overlapping study periods, we included only one publication to prevent double counting of the patient cohorts.
Table 4.6: Bibliographic search strategy

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>2.</td>
<td>(Title=bronchoscopic OR Topic=bronchoscopic) OR MeSH Major Topic=bronchoscopic</td>
</tr>
<tr>
<td>3.</td>
<td>(Title=bronchial OR (Topic=bronchial OR MeSH Heading:exp=Bronchii)) OR MeSH Major Topic=bronchial</td>
</tr>
<tr>
<td>4.</td>
<td>(Title=endobronchial OR Topic=endobronchial) OR MeSH Major Topic=endobronchial</td>
</tr>
<tr>
<td>5.</td>
<td>((Title=endobronchial AND Title=ultrasongraphy) OR (Topic=endobronchial AND (Topic=ultrasongraphy OR MeSH Heading:exp=Ultrasonography))) OR MeSH Major Topic=endobronchial ultrasonography</td>
</tr>
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<td>6.</td>
<td>((Title=endobronchial AND Title=ultrasound) OR (Topic=endobronchial AND (Topic=ultrasound OR MeSH Heading:exp=Ultrasonography))) OR MeSH Major Topic=endobronchial ultrasound</td>
</tr>
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<td>7.</td>
<td>(Title=ultrasound OR (Topic=ultrasound OR MeSH Heading:exp=Ultrasonography)) OR MeSH Major Topic=ultrasound</td>
</tr>
<tr>
<td>8.</td>
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<td>9.</td>
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</tr>
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</tr>
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<td>(Title=ultrasongraphic OR Topic=ultrasongraphic) OR MeSH Major Topic=ultrasongraphic</td>
</tr>
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<td>12.</td>
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</tr>
<tr>
<td>13.</td>
<td>#6 OR #5 OR #4 OR #3 OR #2 OR #1</td>
</tr>
<tr>
<td>14.</td>
<td>#11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5</td>
</tr>
<tr>
<td>15.</td>
<td>#14 AND #13</td>
</tr>
</tbody>
</table>
4.3.2.3 **Data extraction**

Two authors (YHK and DPS) extracted relevant data regarding study characteristics and investigation results. Extracted data included the following items: description of study population (age, prevalence of malignancy, lesion size and lobar location); study design (prospective, retrospective or unknown); patient enrolment (consecutive or not); interpretation of the test results (blinded or not); use of guidance modalities.

Further examination of included studies was performed using the QUADAS tool to assess study quality.[835] This is a validated tool that assesses 14 domains of design and the presentation of studies of diagnostic accuracy.

Two-by-two contingency tables were created for each study, with patients categorised into one of four options: true positive, false positive, false negative and true negative.

4.3.2.4 **Statistical analysis**

Cohen’s kappa (κ) co-efficient was calculated using GraphPad quickcalcs (www.graphpad.com/quickcalcs) to determine the inter-observer agreement for selection of studies. Meta-analysis was performed using Meta-DiSc (Version 1.4).[836] *p*-values of <0.05 were considered to be statistically significant. Extracted data was pooled with weighted averages applied, in which the weight of each study was its sample size. As no diagnostic threshold exists for histologic diagnoses, symmetrical summary receiver operating characteristic (SROC) curves as described by Moses and colleagues were constructed to summarize the results quantitatively.[837]

Study heterogeneity was assessed by the *I*² index, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[838] A value greater than 50% may be considered indicative of significant heterogeneity.[839] If heterogeneity was demonstrated, sub-group analysis was performed, according to common methodologic/clinical features of the studies, to identify possible sources of heterogeneity.
Linear regression was performed to analyse relationships between continuous variables using GraphPad Prism 5 for Mac OS X (GraphPad Software, La Jolla, CA. USA).

4.3.3 RESULTS

4.3.3.1 Literature search and study selection
The bibliographic search identified 968 papers for consideration. Following review of abstracts, 24 articles were selected for full text review. Of these, eight were excluded (two papers enrolled less than 30 patients,[816, 840] three papers examined ultrasound features of malignancy but did not report diagnostic performance of EBUS,[675, 841],[842] two papers were not published in English,[843, 844] and one paper was a review article[845]). Therefore 16 studies formed the basis of our systematic review.[450, 673, 676-688, 846] Inter-observer agreement for selection of studies was high, with $\kappa = 0.855$ (95% CI 0.587 – 1.132).

4.3.3.2 Study description and quality assessment
The mean number of participants per study was 89 (median 87, range 30 – 158), with a total of 1,420 subjects. The prevalence of malignancy was reported in 13 studies, with the median study prevalence being 68% (range 50 – 84%), and overall pooled prevalence being 72%. There was wide variation in the conditions under which EBUS-TBLB was performed, with several studies utilizing additional guidance devices including guide sheaths,[676-678, 682-686, 688, 846] fluoroscopy,[676, 682-684, 686] electromagnetic navigation,[688] and virtual bronchoscopy.[685, 686] Study characteristics are recorded in table 4.7. Our application of the QUADAS tool revealed that there were generally low scores in all of the eligible papers (Table 4.7). Only one study performed EBUS-TBLB in comparison to a traditional biopsy method which could serve as a reference standard.[673] As a result, all other studies were only assessable in six of the QUADAS domains. The highest score was only 8 out of a possible 14,[673] the lowest was only 2 (out of a possible 6), with a mean of 3.3. In all studies it was unclear if the spectrum of study subjects was representative of the
patients who would receive the test in practice, and in only seven studies were selection criteria clearly described.

4.3.3.3 Test performance – meta-analysis

Results for sensitivity for detection of malignancy in individual studies ranged from 49% [846] to 88%.[677] Only 13 studies presented data sufficient to allow inclusion in meta-analysis.[450, 673, 676-678, 681-686, 688, 846] (one study did not present raw data,[679] and two studies reported incomplete data[680, 687]). Meta-analysis from these 13 studies (1,090 patients) demonstrated a point specificity for pooled data of 1.00 (95%CI 0.99–1.00). No heterogeneity in specificity was found ($I^2 = 0.0\%$, $\chi^2 = 0.00$ ($p=1.00$)).

The point sensitivity for pooled data was 0.73 (95%CI 0.70–0.76, figure 4.4) and the area under the SROC curve (figure 4.5) was 0.9376 (SE 0.049). Diagnostic odds ratio was 103.75 (46.4–231.7). The results correspond to a positive likelihood ratio of 26.84 (12.60–57.20) and a negative likelihood ratio of 0.28 (0.23–0.36). Significant heterogeneity between sensitivity of individual studies was seen ($I^2 = 75\%$, $\chi^2 = 47.92$ ($p<0.0001$)). To explore the possible source of heterogeneity, subgroup analyses were applied (table 4.8).

No heterogeneity was found among studies with prevalence of malignancy greater than 75% (sensitivity 0.83 (95%CI 0.78–0.88), $I^2 = 37\%$, $\chi^2 = 4.73$ ($p=0.193$)). Further analysis using linear regression demonstrated a weak positive association between prevalence of malignancy and sensitivity ($p=0.0872$). Using the robust regression method,[847] we identified two studies as outliers. The excluded studies were a retrospective chart review performed to “evaluate factors predicting the visualization of EBUS in PPL”,[681] and a prospective series of 100 patients with PPL < 2cm where mean size was just 15mm (range 9 – 20mm).[846] Exclusion of these studies from linear regression analysis demonstrated a significant relationship between prevalence of malignancy and study sensitivity ($Y = 41.1\pm8.1$, $r^2=0.676$, $p=0.002$) (figure 4.6).
Table 4.7: Main characteristics of selected studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. pts</th>
<th>Mean Age</th>
<th>Study design</th>
<th>Prevalence lung cancer</th>
<th>Patient selection</th>
<th>Additional guidance tools</th>
<th>Reference/comparison test</th>
<th>QUADAS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asahina</td>
<td>2005</td>
<td>30</td>
<td>62</td>
<td>unclear</td>
<td>63</td>
<td>Referral for diagnosis of PPL</td>
<td>Guide sheath VB</td>
<td>Histology by alternate means</td>
<td>3</td>
</tr>
<tr>
<td>Chung</td>
<td>2007</td>
<td>158</td>
<td>59</td>
<td>Prospective RCT (EBUS +/- distance)</td>
<td>71</td>
<td>PPL not visible at routine bronchoscopy</td>
<td>Distance measured (57 patients)</td>
<td>Histology by alternate means</td>
<td>3</td>
</tr>
<tr>
<td>Dooms</td>
<td>2007</td>
<td>50</td>
<td>69</td>
<td>Prospective case series</td>
<td>ND</td>
<td>Referral for diagnosis of PPL</td>
<td>nil</td>
<td>ND</td>
<td>2</td>
</tr>
<tr>
<td>Eberhardt</td>
<td>2007</td>
<td>39</td>
<td>53</td>
<td>Prospective RCT</td>
<td>69</td>
<td>Patients with PPL referred to inter. Pulmonol. service</td>
<td>Guide sheath (39)</td>
<td>Surgical resection</td>
<td>3</td>
</tr>
<tr>
<td>Fielding</td>
<td>2008</td>
<td>140</td>
<td>63</td>
<td>Prospective case series</td>
<td>50</td>
<td>Referral for diagnosis of PPL</td>
<td>Guide sheath Fluoroscopy</td>
<td>ND</td>
<td>2</td>
</tr>
<tr>
<td>Herth</td>
<td>2006</td>
<td>54</td>
<td>46</td>
<td>Prospective case series</td>
<td>57</td>
<td>Referral for diagnosis of PPL</td>
<td>Guide sheath</td>
<td>Surgical resection</td>
<td>4</td>
</tr>
<tr>
<td>Herth</td>
<td>2002</td>
<td>50</td>
<td>62</td>
<td>Prospective randomized case crossover study</td>
<td>84</td>
<td>Referral for diagnosis of PPL</td>
<td>nil</td>
<td>Surgical resection</td>
<td>8</td>
</tr>
<tr>
<td>Kurimoto</td>
<td>2004</td>
<td>150</td>
<td>ND</td>
<td>Prospective case series</td>
<td>66</td>
<td>Referral for diagnosis of PPL</td>
<td>Guide sheath Fluoroscopy +/-Angulated curette</td>
<td>Histology by alternate means or Radiol surveillance</td>
<td>3</td>
</tr>
<tr>
<td>Paone</td>
<td>2005</td>
<td>87</td>
<td>65</td>
<td>Prospective RCT</td>
<td>67</td>
<td>Referral for diagnosis of PPL</td>
<td>Nil</td>
<td>Histology by alternate means</td>
<td>3</td>
</tr>
<tr>
<td>Shirakawa</td>
<td>2004</td>
<td>50</td>
<td>68</td>
<td>Prospective case series (v r'spective controls)</td>
<td>50</td>
<td>PPL not visible at routine bronchoscopy</td>
<td>Fluoroscopy +/-Angulated curette Guide sheath (21)</td>
<td>Histology by alternate means</td>
<td>3</td>
</tr>
<tr>
<td>Yamada</td>
<td>2007</td>
<td>155</td>
<td>ND</td>
<td>Retrospective audit</td>
<td>68</td>
<td>ND</td>
<td>Guide sheath Fluoroscopy +/-Angulated curette</td>
<td>Unclear</td>
<td>2</td>
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<td>Yoshikawa</td>
<td>2007</td>
<td>121</td>
<td>66</td>
<td>Prospective case series</td>
<td>84</td>
<td>Referral for diagnosis of PPL</td>
<td>Guide sheath +/-Angulated curette</td>
<td>Histology by alternate means</td>
<td>3</td>
</tr>
<tr>
<td>Asano</td>
<td>2008</td>
<td>31</td>
<td>72</td>
<td>Prospective case series</td>
<td>unclear</td>
<td>PPL not visible at routine bronchoscopy</td>
<td>Guide sheath Fluoroscopy Virtual Bronch</td>
<td>Surgical resection or follow-up to radiologic resolution</td>
<td>3</td>
</tr>
<tr>
<td>Huang</td>
<td>2009</td>
<td>83</td>
<td>60</td>
<td>Retrospective audit</td>
<td>78</td>
<td>Unclear</td>
<td>Distance measured</td>
<td>Histology by alternate means or Radiol surveillance</td>
<td>4</td>
</tr>
<tr>
<td>Yang</td>
<td>2004</td>
<td>122</td>
<td>66</td>
<td>Retrospective audit</td>
<td>100</td>
<td>Patients with confirmed lung cancer</td>
<td>Nil</td>
<td>Histology by alternate means or clinical surveillance</td>
<td>3</td>
</tr>
<tr>
<td>Eberhardt</td>
<td>2009</td>
<td>100</td>
<td>52</td>
<td>Prospective case series</td>
<td>61</td>
<td>PPL &lt; 20mm with CT characteristics of malignancy</td>
<td>Guide sheath</td>
<td>Histology by alternate means</td>
<td>4</td>
</tr>
</tbody>
</table>

PPL = peripheral pulmonary lesion, VB = virtual bronchoscopy, RCT = randomized controlled trial, EMN = electromagnetic navigation, ND = no data available
Figure 4.4: Forest plot of sensitivity of EBUS-TBLB

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asahina 2005</td>
<td>0.74 (0.52 - 0.90)</td>
</tr>
<tr>
<td>Eberhardt 2007</td>
<td>0.72 (0.53 - 0.86)</td>
</tr>
<tr>
<td>Fielding 2008</td>
<td>0.63 (0.51 - 0.74)</td>
</tr>
<tr>
<td>Herth 2006</td>
<td>0.72 (0.55 - 0.85)</td>
</tr>
<tr>
<td>Herth 2002</td>
<td>0.80 (0.65 - 0.90)</td>
</tr>
<tr>
<td>Kurimoto 2004</td>
<td>0.81 (0.72 - 0.88)</td>
</tr>
<tr>
<td>Paone 2005</td>
<td>0.79 (0.68 - 0.88)</td>
</tr>
<tr>
<td>Shirakawa 2004</td>
<td>0.71 (0.49 - 0.87)</td>
</tr>
<tr>
<td>Yamada 2007</td>
<td>0.70 (0.62 - 0.78)</td>
</tr>
<tr>
<td>Yoshikawa 2007</td>
<td>0.88 (0.80 - 0.93)</td>
</tr>
<tr>
<td>Asano 2008</td>
<td>0.85 (0.66 - 0.98)</td>
</tr>
<tr>
<td>Huang 2009</td>
<td>0.60 (0.47 - 0.72)</td>
</tr>
</tbody>
</table>

Pooled Sensitivity = 0.75 (0.72 to 0.78)

Figure 4.5: Summary receiver-operator characteristic curve

Figure 4.6: Results of linear regression examination of relationship between prevalence of malignancy and reported sensitivity of individual studies. Each study is represented by solid black squares. The circles indicate studies detected as outliers. The outliers have not been included in calculation of the regression line illustrated. Study sensitivity was correlated with prevalence of malignancy in patients with peripheral pulmonary nodules. \( Y = 41.1 + 8.1, \ r^2 = 0.676, p = 0.002 \).
Table 4.8: Results of pooled analysis, and heterogeneity

<table>
<thead>
<tr>
<th></th>
<th>No. of studies</th>
<th>No of patients</th>
<th>Pooled sensitivity (95% CI)</th>
<th>Pooled specificity (95% CI)</th>
<th>AUC (SE)</th>
<th>Likelihood ratio – I² (%)</th>
<th>χ² test (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>13</td>
<td>1,090</td>
<td>0.73 (0.70 – 0.76)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.9376</td>
<td>75% (0.046)</td>
<td>30.13 (&lt;0.0001)</td>
</tr>
<tr>
<td>(outliers removed)</td>
<td>11</td>
<td>907</td>
<td>0.76 (0.73 – 0.80)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.9199</td>
<td>55% (0.062)</td>
<td>22.4 (0.013)</td>
</tr>
<tr>
<td>Use fluoroscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>5</td>
<td>526</td>
<td>0.73 (0.68 – 0.78)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.9378</td>
<td>60% (0.081)</td>
<td>9.98 (0.041)</td>
</tr>
<tr>
<td>N</td>
<td>8</td>
<td>564</td>
<td>0.73 (0.68 – 0.77)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.9409</td>
<td>82% (0.075)</td>
<td>37.9 (0.0001)</td>
</tr>
<tr>
<td>Use Guide sheath</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>10</td>
<td>841</td>
<td>0.73 (0.69 – 0.76)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.9407</td>
<td>78% (0.051)</td>
<td>40.6 (&lt;0.0001)</td>
</tr>
<tr>
<td>N</td>
<td>3</td>
<td>249</td>
<td>0.69 (0.63 – 0.75)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.9126</td>
<td>67% (0.114)</td>
<td>9.16 (0.027)</td>
</tr>
<tr>
<td>Without VB</td>
<td>11</td>
<td>1,029</td>
<td>0.72 (0.69 – 0.75)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.9483</td>
<td>78% (0.050)</td>
<td>45.4 (&lt;0.0001)</td>
</tr>
<tr>
<td>Median size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25mm</td>
<td>7</td>
<td>580</td>
<td>0.71 (0.66 – 0.75)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.9356</td>
<td>73% (0.071)</td>
<td>22.2 (&lt;0.001)</td>
</tr>
<tr>
<td>≥25mm</td>
<td>6</td>
<td>510</td>
<td>0.75 (0.70 – 0.79)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.9364</td>
<td>80% (0.066)</td>
<td>24.3 (&lt;0.0001)</td>
</tr>
<tr>
<td>&lt;25mm (outliers removed)</td>
<td>5</td>
<td>480</td>
<td>0.75 (0.70 – 0.80)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.8940</td>
<td>27% (0.124)</td>
<td>5.5 (0.240)</td>
</tr>
<tr>
<td>Prevalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 75%</td>
<td>9</td>
<td>688</td>
<td>0.70 (0.66 – 0.74)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.9127</td>
<td>85% (0.103)</td>
<td>23.05 (0.003)</td>
</tr>
<tr>
<td>&gt; 75%</td>
<td>4</td>
<td>402</td>
<td>0.83 (0.78 – 0.88)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.9338</td>
<td>37% (0.117)</td>
<td>4.73 (0.193)</td>
</tr>
<tr>
<td>&lt;75 % (outliers removed)</td>
<td>8</td>
<td>588</td>
<td>0.73 (0.69 – 0.77)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.8578</td>
<td>20% (0.169)</td>
<td>8.79 (0.268)</td>
</tr>
<tr>
<td>Reference standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology only</td>
<td>7</td>
<td>452</td>
<td>0.79 (0.75 – 0.84)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.9176</td>
<td>33% (0.103)</td>
<td>9.0 (0.174)</td>
</tr>
<tr>
<td>alternate means / not stated</td>
<td>6</td>
<td>638</td>
<td>0.71 (0.68 – 0.76)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.9023</td>
<td>56% (0.118)</td>
<td>16.1 (0.025)</td>
</tr>
</tbody>
</table>

VB = virtual bronchoscopy

*Prevalence = prevalence of malignancy in lesions investigated using EBUS-TBLB
Analysis of studies with prevalence of malignancy less than 75% following removal of studies identified as outliers demonstrated no heterogeneity (sensitivity 0.73 (95%CI 0.69–0.77), $I^2 = 20\%, \chi^2 = 8.8 (p=0.268)$). Therefore, we identify prevalence of malignancy as a possible source of heterogeneity in EBUS-TBLB.

Significant heterogeneity was noted between studies with median lesion size <25mm, and also between studies with median lesion size >25mm (data not shown). Removal of outliers resulted in a finding of no heterogeneity was found between studies with median lesion size <25mm ($I^2 = 13\%, \chi^2 = 5.74 (p=0.332)$), although significant heterogeneity was still seen for studies with median lesion size >25mm. Linear regression analysis demonstrated no significant relationship between prevalence of malignancy and lesion size ($Y = 9.54\pm8.6, \ r^2=0.269, p=0.124$), or between lesion size and study sensitivity ($Y = 9.35\pm9.4, \ r^2=0.186, p=0.161$). Variation in size of PPLs may also contribute to heterogeneity, though the evidence supporting this contention is less clear.

Sub-group analysis according to the means of confirmation of diagnosis of non-diagnostic EBUS-TBLB demonstrated no heterogeneity among studies in whom all subjects underwent histological confirmation by alternate means (sensitivity 0.83 (95%CI 0.78–0.88), $I^2 = 37\%, \chi^2 = 4.73 (p=0.193)$). Significant heterogeneity was noted among studies who used non-histologic methods to determine a diagnosis in subjects with non-diagnostic EBUS-TBLB or studies which did not specify how diagnoses were determined (sensitivity 0.71 (95%CI 0.68–0.76), $I^2 = 56\%, \chi^2 = 16.1 (p=0.025)$).

Several studies reported diagnostic performance based on lesion size. Only two studies presented sufficient data to allow pooling of data.[685, 686] Therefore we were unable to perform meta-analysis. However, ten studies reported overall diagnostic yield for lesions ≤20mm and for lesions >20mm. Pooled statistics demonstrated a diagnostic yield of 56.3% (95%CI 51–61%) and 77.7% (95%CI 73–82%) for lesions ≤20mm (364 patients) and lesions >20mm (367 patients), respectively. This difference was significant ($p=0.007$).
4.3.3.4 Descriptive review

Several studies examined the influence of specific clinical/radiologic features on diagnostic performance. No studies presented sufficiently detailed data to allow meta-analysis sub-groups on the basis of these features. Eight studies examined the effect of lobar position of PPL on diagnostic yield. Yamada et al noted a higher yield for PPLs positioned in the right middle lobe and lingular lobe,[683] Eberhardt et al noted higher yield in right middle and right lower lobes,[846] and Kurimoto et al noted a significantly lower yield for the apicoposterior left upper lobe segment.[676] However, the remaining five studies noted no significant effect of lobar position on diagnostic yield.[679, 681, 683, 685, 688]

While two studies indicated a higher sensitivity for detection of malignant, compared to benign, lesions,[679, 688] six studies reported no difference in diagnostic sensitivity based on lesion pathology.[676, 677, 681, 683, 684, 846]

Unsurprisingly, identification of PPL position by the EBUS probe was associated with higher diagnostic sensitivity in all seven studies that examined this clinical feature.[676, 679-683, 846] In addition, proximity of PPL to the pulmonary hilum was reported to be associated with increased diagnostic yield in both studies describing this feature.[681, 684] Only two studies examined the effect of number of samples taken on diagnostic yield, and both noted an improved yield, to a plateau of 5 biopsies.[683, 685]

4.3.3.5 Complication rates

Complication rates were not reported in two studies.[682, 683] Complication rates in the remaining 14 studies varied from 0% [450, 685-687] to 7.4%.[678] The highest complication rate was noted in a single study and 3 of the 4 patients experiencing complications in this study experienced only minor self-limiting bleeding.[678] No patients in any study experienced bleeding requiring intervention. Pneumothorax rate varied from 0% [450, 676, 680, 681, 685-687] to 5.1%,[688] with a pooled rate of pneumothorax across 14 studies of 1.0% (11 of 1,090). The pooled rate of intercostal catheter drainage of pneumothorax was 0.4%. No deaths were reported in any studies.
4.3.4 DISCUSSION

Narrative reviews on EBUS-TBLB have previously been published,[848] however to our knowledge this is the first systematic evaluation and first meta-analysis of published literature on EBUS-TBLB. The results of our analysis indicate very good diagnostic performance of EBUS-TBLB for evaluation of PPLs. Meta-analysis of 13 studies determined a point sensitivity and specificity of 0.73 (95% CI 0.70–0.76) and 1.00 (95% CI 0.99–1.00), respectively. Heterogeneity in sensitivity of EBUS-TBLB was noted ($I^2 = 75\%$, $\chi^2 = 47.92$ ($p<0.0001$)). Sub-group analysis strongly suggested that the prevalence of malignancy in the patient cohort undergoing EBUS-TBLB is a source of heterogeneity in diagnostic sensitivity among studies.

Our results also support previous observations that yield of EBUS-TBLB is influenced by PPL size. Subgroup analysis suggested variation in lesion size (table 4.8) may explain some of the observed heterogeneity in diagnostic sensitivity, however this remains uncertain as heterogeneity was still seen in studies with median lesion size $\geq25\text{mm}$. Probability of malignancy in PPLs is recognized to increase with increasing lesion size in both clinical studies,[303, 849, 850] and in lung cancer screening studies using low-dose CT chest.[299, 851, 852] This may explain the potential influence of lesion size on diagnostic sensitivity, though regression analysis failed to demonstrate a significant relationship among the studies analysed. Due to limited availability of data in the primary studies included in the meta-analysis, we were unable to determine if lower prevalence of malignancy in smaller nodules contributed to the observation that sensitivity of EBUS-TBLB is reduced for smaller lesions.

Significant variation is noted in the technique of EBUS-TBLB between institutions, particularly with respect to guidance tools (eg. fluoroscopy, guide sheath use etc). We did not identify any such characteristics as influencing sensitivity. The only procedural feature consistently associated with improved diagnostic sensitivity was the ability to locate a PPL with the EBUS probe.
The two modalities commonly utilized to investigate PPLs are bronchoscopy or CT-guided percutaneous needle biopsy/aspiration (CT-PNB). To our knowledge, no systematic review of CT-PNB for investigation of PPLs has previously been published. Recently published evidence-based clinical practice guidelines reviewed CT-guided needle biopsy and observed that sensitivity for detection of malignancy using CT-PNB in most studies exceeds 90%, however approximately 20% of procedures were non-diagnostic,[17] reflecting the lower yield of CT-PNB in benign conditions.

Investigation of PPL with bronchoscopy, while associated with a low complication rate,[296] was previously limited by poor diagnostic performance, even with fluoroscopic guidance. Previous meta-analysis of this technique noted an overall diagnostic sensitivity of 33% for lesions with diameter ≤ 2cm, and 62% for lesions > 2cm.[810] EBUS-TBLB has improved diagnostic yield of bronchoscopic investigation of PPLs to a level more comparable to CT-PNB, with improvement in sensitivity most apparent for smaller lesions. While diagnostic yield in routine bronchoscopy is notably lower for smaller PPLs,[23, 24, 296] we noted a pooled diagnostic yield for PPLs ≤20mm of 56.3% (95%CI 51–61%), which is only slightly reduced in comparison to PPL >20mm (yield 77.7% (95%CI 73–82%)).

While diagnostic yield does not exceed CT-PNB, the major advantage of EBUS-TBLB over CT-PNB is its safety profile. Our meta-analysis demonstrated an overall pneumothorax rate of just 1.0%, and an overall intercostal drain insertion rate of 0.4%. In comparison, many studies describing CT-PNB report pneumothorax rates greater than 25%.[17, 26, 27, 826, 829] and as high as 69%.[853] with many of these patients requiring admission or even intercostal catheter drainage. Pulmonary haemorrhage is less frequent, though still complicates 1 – 10% of CT-PNB.[26, 27]

4.3.4.1 Limitations

The major limitation of our findings is the quality of studies included in the meta-analysis. It is unclear whether the patient populations in individual studies are consistent, as selection criteria were not clear in a majority of studies. Therefore it is unclear if the spectrum of study subjects was representative of patients who would
undergo EBUS-TBLB in clinical practice. This may induce heterogeneity in sensitivity in between studies, and potentially limits the generalizability of our results. In addition, a number of features influencing performance of EBUS-TBNA were not described in most papers included in our meta-analysis. These include bronchoscopist experience, number of biopsies taken, proximity of PPL to central airways, and radiologic appearance of PPLs (eg. solid versus ground-glass opacity).

While two studies determined that lobar location of PPLs may influence diagnostic sensitivity, a majority of studies that examined the influence of lobar position did not detect any effect on sensitivity. No studies presented sufficient data to allow meta-analysis, therefore the effect of lobar position on sensitivity of EBUS-TBLB remains unresolved.

4.3.4.2 Implications for practice and future research

Our analysis calculated a negative likelihood ratio of 0.28 (0.23–0.36) for EBUS-TBLB. It is clear that non-diagnostic EBUS-TBLB should not serve as sufficient reassurance of the absence of malignancy and patients with negative results following EBUS-TBLB should be strongly considered for further investigation to exclude the possibility of cancer.

The relationship demonstrated between prevalence of malignancy and sensitivity of EBUS-TBLB has significant implications for clinical management of incidentally detected pulmonary nodules. It suggests that diagnostic yield of EBUS-TBLB may be influenced by the probability of malignancy for a given patient. The incidence of malignancy in nodules detected by low-dose CT in lung cancer screening trials is much lower than observed in studies included in this meta-analysis, varying from 13% [851] to below 2%. [300, 352] Incidental PPLs are frequently detected on imaging performed for other clinical indications, [11, 854, 855] and such lesions may warrant a different approach to tissue diagnosis than clinically apparent PPLs.

Selection between EBUS-TBLB and CT-PNB may be possible based on clinical and radiologic features of individual patients. For example, radiologic findings may predict a lower sensitivity of EBUS-TBLB (eg. lesions positioned in apicoposterior
bronchial segments,[676] or pleurally based or sub-pleural lesions[681, 684]) or a higher rate of complications with CT-PNB (eg. perihilar lesions,[26, 27, 684, 738, 826] COPD/emphysema,[26, 27, 738, 829] or lesion size.[27, 738, 829]) Other factors such as “bronchus sign”[825] or even clinical models predicting the probability of malignancy in PPLs,[303] may be helpful in determining optimal investigation approaches for individual patients. Future studies are required to inform construction of such a clinical algorithm.

Future studies reporting on EBUS-TBLB need to clearly outline the selection process for inclusion and should ideally describe clinicoradiologic characteristics and include a description of each of these performance issues to allow improved understanding of the features that predict diagnostic yield of EBUS-TBLB. This then could be used to inform clinical decisions regarding the optimal approach to investigation for individual patients. Given the discrepancy in sensitivity and complication rates between EBUS-TBLB and CT-PNB, we suggest economic analyses are also warranted. The lower complication rate of EBUS-TBLB may mean that, despite a lower diagnostic yield, the procedure may still be cost-effective. Such evidence may also guide clinicians in future investigation of patients presenting with PPLs.

4.3.5 CONCLUSIONS

Our study confirms overall test performance characteristics of EBUS-TBLB for investigation of PPLs is very good in the population of patients included in the studies in this review, with excellent specificity, and sensitivity markedly higher than for routine bronchoscopy, though lower than for CT-PNB. However our results indicate an extremely favourable safety profile of EBUS-TBLB, supporting initial investigation of patients with PPLs using EBUS-TBLB. Diagnostic sensitivity of EBUS-TBLB may be influenced by the prevalence of malignancy in the patient cohort being examined. Further methodologically rigorous studies are required to evaluate the generalisability of the results to more clearly defined patient populations. Studies examining the influence on test performance of prevalence of malignancy, as well as other specific clinical and radiologic features, particularly PPL position, are still required.
Peripheral pulmonary lesions (PPL) are focal radiographic opacities that may be characterized as nodules ($\leq 3$ cm) or masses ($> 3$ cm). While referral for lobectomy in patients with a PPL with a very high pre-test probability of malignancy is suggested by some guidelines,[296] resectional biopsy is not risk-free and may not be necessary in a significant number of patients with such lesions.[17] Screening studies using computed tomography (CT) show that up to 34% of such operations are performed for benign nodules.[18-20]

Non-invasive tests such as fluorodeoxyglucose positron emission tomography (FDG-PET) or dynamic CT with nodule enhancement cannot distinguish benign from malignant disease with sufficient accuracy.[17] Consequently, attempts at minimally invasive diagnosis are strongly favoured. This may be achieved by either bronchoscopic or percutaneous approaches.

Percutaneous sampling is generally performed under CT-fluoroscopic guidance. Bronchoscopy may be aided by guidance methods such as fluoroscopy,[23, 450] virtual bronchoscopy,[686] endobronchial ultrasound (EBUS),[450] or electromagnetic navigation (EMN).[688] The highest diagnostic yield is associated with EBUS and/or EMN guidance.[688] Availability of EMN remains very limited, partly owing to the significant expense associated with the technology and ongoing consumable costs.

The performance characteristics of EBUS bronchoscopy and CT-guided percutaneous needle biopsy (CT-PNB) have been well described, although only one study has previously compared the two modalities head-to-head.[856] This study concluded that
the overall diagnostic accuracy of EBUS was non-inferior to CT-PNB, but that the complication rate following EBUS-guided transbronchial lung biopsy (EBUS-TBLB) was significantly lower. In addition to clinical ‘performance’, the optimal test for diagnosis of PPLs may also be influenced by the costs of individual procedures. Costs for EBUS-TBLB and CT-PNB have not been previously reported. In particular, the cost of managing complications, and the influence of this on procedural cost outcomes, is unknown. Such information is highly relevant to clinical decision making.

In this study, we undertook a cost-utility analysis of EBUS-TBLB for management of PPLs, compared to CT-PNB.

4.4.2 METHODS

4.4.2.1 Study site

The Royal Melbourne Hospital in Melbourne, Australia, is a tertiary referral centre for the diagnosis, staging and management of lung cancer, with substantial experience in both EBUS-TBLB and CT-PNB. The hospital serves a catchment of over 600,000 people. Patients with suspected/known lung cancer are managed by a multidisciplinary team comprising respiratory physicians, thoracic radiologists, thoracic surgeons, medical oncologists and radiation oncologists. The MDT manages approximately 300 patients with lung cancer per year.

4.4.2.2 Modelling approach

Decision analysis [739] using specialized software (TreeAge Pro 2009, Excel module. TreeAge Software Inc., Williamstown, MA) was applied to compare the downstream costs of EBUS-TBLB and CT-PNB (Figure 4.7). The analysis accounted for costs of each procedure as well as costs incurred as a result of extra procedures required in the event of a negative result from either modality.
An advantage of decision tree analysis is its capacity to simulate even complex clinical algorithms, such as that for evaluation of PPL. Furthermore, it can explicitly capture the uncertainty that is inherent in modelling of any type.[777]

4.4.2.3 Model population
The modeled population comprised hypothetical patients referred to a multidisciplinary team for evaluation of PPL, for whom the team felt investigation was warranted and that either CT-PNB or EBUS would be acceptable modes of initial investigation of the lesion. This therefore excluded patients with the following features:
- clinical condition precluded investigation
- lesion <1cm diameter anywhere in lung fields
- evidence on CT scan of central (endobronchially visible) lesion
- other clinical site of disease more amenable to tissue diagnosis

4.4.2.4 Health care costs
Unit cost estimates, in Australian dollars (AU$), were based on recorded hospital costs for patients undergoing the above-mentioned procedures at the Royal Melbourne Hospital between 7 February 2008 and 22 January 2010. All patients had provided written consent for inclusion in a randomized pragmatic trial comparing EBUS-TBLB with CT-PNB.[856]

EBUS-TBLB and CT-PNB are performed on an outpatient basis at the Royal Melbourne Hospital. EBUS-TBLB is performed in a day procedure unit, with sedation administered by resident staff from the Respiratory Unit, as previously described.[782] The procedure itself has previously been described [676], using a 20-MHz radial EBUS probe (UM-BS20–26R; Olympus, Tokyo, Japan) and guide sheath. CT-PNB is performed using a coaxial needle (Bard TruGuide needle, Bard Biopsy Systems. Tempe, AZ, USA) and core biopsy instrument (Bard Biopy-Cut needle and Bard Magnum biopsy instrument. Bard Biopsy Systems. Tempe, AZ, USA).
Costs were derived from actual patient data at the Royal Melbourne Hospital. Costing data for each patient admission was obtained from cost weight analysis compiled according to guidelines from the Clinical Costing Standards Association of Australia.[857] Hospital and median costs for EBUS-TBLB and CT-PNB were calculated based upon all patients included in a recently published randomized pragmatic trial. Table 4.9 records summary data for all uncomplicated procedures. Costs for patients in whom complications occurred are recorded in Table 4.10. Costs for thoracoscopic resection were established following an audit of all patients undergoing thoracoscopy/thoracotomy for resection of lung lesions at Royal Melbourne Hospital from 1 July 2007 to 30 June 2008. All costs were updated to 2010/11 levels according to the locally recorded Health Price Index, which reported an increase of 3% per year.[858]

4.4.2.5 Other input parameters

Other input parameters applied to the decision tree analysis are described in Table 4.11. Sensitivity and specificity of EBUS-TBLB for evaluation of PPL was based on our own institutional experience, and a published meta-analysis[856, 859] while data for CT-PNB was based on our reported experience, and on published guidelines.[17, 856]

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n</th>
<th>Median cost</th>
<th>Updated mean cost (±SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS-TBLB</td>
<td>12</td>
<td>$1,318</td>
<td>$1,572 ± $232</td>
</tr>
<tr>
<td>CT-PNB</td>
<td>12</td>
<td>$1,688</td>
<td>$1,569 ± $244</td>
</tr>
</tbody>
</table>

All procedures completed as day-admission cases

*based on local Health Price Index of 3%/year.[857]
Table 4.10: Hospital costs associated with complicated procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>complication</th>
<th>management</th>
<th>Length of stay</th>
<th>Updated cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS-TBLB</td>
<td>Small self-limiting pneumothorax</td>
<td>Conservative*</td>
<td>0</td>
<td>$1,941</td>
</tr>
<tr>
<td>CT-PNB</td>
<td>Small self-limiting pneumothorax</td>
<td>Conservative*</td>
<td>0</td>
<td>$1,952</td>
</tr>
<tr>
<td>CT-PNB</td>
<td>Small self-limiting pneumothorax</td>
<td>Conservative*</td>
<td>0</td>
<td>$1,791</td>
</tr>
<tr>
<td>CT-PNB</td>
<td>Hydropneumothorax</td>
<td>Conservative*</td>
<td>0</td>
<td>$1,905</td>
</tr>
<tr>
<td>CT-PNB</td>
<td>Haemothorax, pulmonary haemorrhage</td>
<td>Admission for analgesia and observation</td>
<td>3</td>
<td>$4,932</td>
</tr>
</tbody>
</table>

*conservative management comprised discharge home if the patient was clinically stable and pneumothorax not enlarging on repeat CXR at 4 hours. Costs include performance of procedure and the cost of next-day CXR and clinical review.

*based on local Health Price Index of 3%/year.[857]

Table 4.11: Parameter values used for variables in performance of decision tree analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-case value</th>
<th>Range utilized for sensitivity analysis</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS-TBLB sensitivity</td>
<td>0.86 0.50</td>
<td>0.60 – 0.88 0.50 – 0.80</td>
<td>[856, 859]</td>
</tr>
<tr>
<td>CT-PNB sensitivity</td>
<td>0.93 0.56</td>
<td>0.65 – 0.94 0.50 – 0.90</td>
<td>[17, 856]</td>
</tr>
<tr>
<td>CT-PNB complication rate</td>
<td>0.27</td>
<td>0.14 – 0.43</td>
<td>[17, 856]</td>
</tr>
<tr>
<td>Prevalence of malignancy</td>
<td>0.87</td>
<td>0.5 – 0.95</td>
<td>[856, 859]</td>
</tr>
<tr>
<td>Mean cost of complications</td>
<td>$327</td>
<td>$300 – $3,363</td>
<td>Current study</td>
</tr>
</tbody>
</table>
4.4.2.6 Sensitivity analysis

Calculations based on the above data constituted a ‘base-case’ analysis, as defined by NICE guidelines.[860] We recognized that model input values may vary significantly across different institutions. For example, diagnostic sensitivity of EBUS-TBLB differs considerably between institutions,[859] and there is significant discrepancy in reported complication rates following CT-PNB.[17] Therefore, a series of one-way sensitivity analyses were undertaken within the range of each parameter recorded in Table 4.3, based on data from recent pooled analyses. The values of these key inputs were varied one at a time, while maintaining the other inputs at ‘base case’ values. Subsequent analysis was undertaken to determine the threshold above which the most cost-beneficial approach remained in comparison to other diagnostic modalities.

Cost may also alter, depending on the severity of the condition, and institutional approaches to management (e.g. in- versus out-patient care, frequency of intercostal catheter insertion). Sensitivity analysis was performed to determine if a threshold cost for complications existed, above which the alternate investigation modality proved more cost-beneficial.

In order to assess the impact of uncertainty more accurately, probabilistic sensitivity analysis was performed using Monte Carlo simulations.[861] With this method, input parameters are assigned a distribution to reflect the nature of uncertainty. Multiple model simulations are then run. With each simulation, one value from every input range is randomly sampled from within a specified data range according to its probability distribution. Multiple outputs are thus generated, and uncertainty ranges are derived from the distributions of these. In our analysis, 10,000 simulations were undertaken.

4.4.2.7 Cost-effectiveness

The above methodology is used to assess the comparative cost-benefit of competing diagnostic strategies for assessment of PPL. Cost-effectiveness requires consideration of quality-of-life measures. Patient preferences with regard to the impact of
procedural complications or anxiety related to waiting for test results have been shown to influence cost-effectiveness analyses for patients with PPL.[740]

Cost-effectiveness outcomes are expressed in cost per quality-adjusted life year ($/QALY), with utility being the measure on which quality adjustment is based. Utility allows adjustment of life-years gained by an intervention when those gained years would be lived in less than perfect health. Extra life-years are given a utility value of between 0 and 1 to account for this. This method is suitable for assessment of chronic health/disease states, although it is not able to assess the cost impact of short-term disease states, such as pain or complications arising from a diagnostic procedure, or the anxiety resulting from a non-diagnostic procedure.[862]

Multiple methods for assessment of the impact of transient disease states have been described. With the time-tradeoff (TTO) technique, a patient decides between a longer period of time in less optimal health versus a shorter period in good health. A variation, the wait-tradeoff (WTO) technique, quantifies patients’ preference for undergoing a particular test or treatment that has associated discomfort or restrictions that the patient may dislike. The patient is asked to trade off extended time with the condition being diagnosed or treated in order to avoid the noxious effects of the test or treatment in favor of a similarly effective test or treatment but one not having side effects.[741] A QALY toll is reflected in the WTO by an individual’s willingness to wait longer to avoid more noxious experiences.[863] and may be measured by disutility, being a the fraction of a year of perfect health a patient would be willing to give up to avoid having to undergo a diagnostic test and to avoid its short-term morbidity.[864] This tool was originally designed for use in states related to diagnostic screening and testing.[865]

Sensitivity analysis was performed for disutility, starting at a theoretical disutility of 0 for both the procedure itself (that is no utility penalty), as well as disutility attributable to complications arising from the procedure. One-way sensitivity analysis was performed to identify theoretical thresholds that may influence cost-effectiveness outcomes.
Figure 4.7: Decision tree illustrating possible clinical pathways following selection of a diagnostic approach.

PPL – peripheral pulmonary lesion

EBUS = endobronchial ultrasound

□ = decision node. *i.e.* The clinician may choose any clinical pathway for an individual patient.

○ = chance node. *i.e.* Either outcome may occur, based on chance. The proportion of patients following each pathway from a chance node is dependent on pre-defined clinical parameters (e.g. Table 3.5)

▼ = terminal node in decision pathway. *i.e.* An individual patient has reached a definitive outcome in their diagnostic pathway.
4.4.2.8 Assumptions

As sensitivity analysis is based on theoretical patients, we were required to make some specific assumptions regarding the theoretical model population. Key assumptions in the analysis were:

- There was a well-defined outcome in each arm of our decision model; that is, pathologic diagnosis of PPL.
- The long-term outcomes (measures of effectiveness) were equivalent in each model arm; that is, treatment and outcomes of all patients was similar regardless of how the diagnosis was determined. As previously recognized [866], a cost-benefit analysis that assumes competing diagnostic strategies have equivalent outcomes and focuses thereafter only on cost outcomes is the most appropriate form of economic analysis to use in this setting.
- Once a diagnosis has been made, the downstream costs of medical care were the same, regardless of how diagnosis was achieved.
- Thoracotomy/thoracoscopy had a diagnostic accuracy of 100% in the evaluation of PPL.
- Pathology costs were identical regardless of method of acquisition of tissue.

4.4.3 RESULTS

4.4.3.1 Base-case analysis

Costs of each procedure based on base-case parameters are recorded in Table 4.12. For the base-case analysis, initial evaluation with CT-PNB was cost-beneficial in comparison to EBUS-TBLB by a margin of $24 (CT $2,724 v. EBUS-TBLB $2,748).

4.4.3.2 Sensitivity analysis

One-way sensitivity analysis identified threshold values at which EBUS-TBLB became more cost-beneficial, which included cost of managing complications exceeding $501 per episode, complication rate of CT-PNB exceeding 40% and
sensitivity of CT-PNB for detection of malignancy falling below 91%. Prevalence of malignancy had no effect on cost-benefit during one-way analysis. Variation in diagnostic yield for benign disease had negligible effect on outcomes for both procedures. The variable which exerted the most influence on cost outcomes was the cost of managing complications. The influence of this is illustrated in Figure 4.8.

Two-way sensitivity analysis was undertaken to explore the interaction between two specific parameters. Threshold values are altered when two parameters are varied making identification of specific values impossible. The variation in cost-outcome with variation in both cost of complications as well as complication rate of CT-PNB is illustrated in Figure 4.9a. Significant interaction was seen in two-way analysis with variation of prevalence of malignancy and sensitivity of EBUS-TBLB for detection of benign disease (Figure 4.9b), and with variation of sensitivity for detection of malignancy for both procedures (Figure 4.9c).

Given the influence of diagnostic sensitivity and complication rates on costs for procedures, we have modelled cost comparisons for hypothetical patient values, with results recorded in Table 4.13. As expected, differing clinical scenarios resulted in different outcomes from cost comparisons. An increase in cost of managing complications above $327 as used for these calculation would result in increasing cost-benefit towards EBUS-TBLB due to the lower complication rate seen with this procedure.

| Table 4.12: Calculated base-case costs of the two diagnostic approaches |
|--------------------------|------------------------------|------------------|
| Variable | Base case cost | Range* |
| EBUS-TBLB | $2,748 | $2,719 – $3,534 |
| CT-PNB | $2,724 | $2,683 – $3,868 |

*range of costs based on diagnostic sensitivity (malignancy) range recorded in table 2 for each procedure.
4.4.3.3 *Probabilistic sensitivity analyses*

Monte Carlo Simulation was performed using triangular distributions of values (lowest – likeliest – highest) as recorded in Table 4.14. Outcomes of probabilistic sampling demonstrate the negligible difference in net costs between the two procedures (Table 4.15). The two procedures differ by a maximum of $132 when comparison of mean, median and 10\(^{th}\) and 90\(^{th}\) centile values are made.

4.4.3.4 *Cost-effectiveness analysis*

Using a theoretical WTO for a non-diagnostic procedure of 20 days (0.05 years), CT-PNB remained the more cost-effective procedure at base-case parameters. One-way sensitivity analysis in the range of values recorded in Table 4.11 revealed that EBUS-TBLB became the more cost-effective procedure if sensitivity of EBUS-TBLB for benign disease exceeded 71%, if sensitivity of CT-PNB (malignancy) was below 89%, or if cost of managing complications exceeded $560. Unlike cost-benefit analyses, no threshold was observed for the complication rate of CT-PNB.

Using a theoretical WTO for a procedural complication of 20 days (0.05 years), CT-PNB remained the more cost-effective approach (CT = $2,778/QALY vs. EBUS = $2,816/QALY) at base-case parameters. One-way sensitivity analyses demonstrated that EBUS-TBLB became the more cost-effective approach if the cost of complications exceeded $489, if the complication rate for CT-PNB exceeded 40%, and if the sensitivity of EBUS-TBLB for detection of benign disease exceeded 65%. The effect in alteration of these two parameters (two-way sensitivity analysis) is demonstrated in Figure 4.10.

As was demonstrated for cost-benefit calculations, the cost of managing complications was the input parameter that most heavily influenced the results of cost-effectiveness comparisons.
**Figure 4.8:** Graphical representation of effect on expected cost of each procedure (Y-axis) during one-way sensitivity analysis (variation) in the cost of managing complications (X-axis) among the modelled population. EBUS-TBLB is cost-beneficial (ie. cheaper) if mean cost of complications exceeds $501 per episode.

**Figure 4.9:** Results of two-way sensitivity analysis (ie. alteration of two input parameters). The most cost-beneficial diagnostic pathway for the combination of the two varied parameters is indicated by the pattern present on the graph. Parameters varied are:

A) Cost of complications versus CT-PNB complication rate
B) Prevalence of malignancy in PPL versus diagnostic yield of EBUS-TBLB for benign PPL
C) Sensitivity of EBUS-TBLB for detection of malignancy versus sensitivity of CT-PNB for detection of malignancy
### Table 4.13: Cost calculations for specific hypothetical patient scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>EBUS-TBLB sensitivity</th>
<th>CT-PNB sensitivity</th>
<th>CT-PNB complication rate</th>
<th>costs EBUS-TBLB</th>
<th>costs CT-PNB</th>
<th>Threshold value for cost complications</th>
<th>References for values used</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLL pleurally-based nodule</td>
<td>0.5</td>
<td>0.97</td>
<td>0.03</td>
<td>$3,366</td>
<td>$2,711</td>
<td>none</td>
<td>[681, 684]</td>
</tr>
<tr>
<td>Peri-hilar RML nodule</td>
<td>0.88</td>
<td>0.85</td>
<td>0.43</td>
<td>$2,929</td>
<td>$3,074</td>
<td>none</td>
<td>[459, 681, 683, 684, 688]</td>
</tr>
<tr>
<td>6cm RUL mass with ‘bronchus sign’</td>
<td>0.9</td>
<td>0.8</td>
<td>0.2</td>
<td>$2,929</td>
<td>$3,106</td>
<td>none</td>
<td>[473, 676, 820, 825]</td>
</tr>
<tr>
<td>1.5cm proximal RLL nodule, FEV1 800mL</td>
<td>0.7</td>
<td>0.7</td>
<td>0.4</td>
<td>$4,699</td>
<td>$4,774</td>
<td>none</td>
<td>[27, 456, 459, 473, 820, 826, 859]</td>
</tr>
</tbody>
</table>

Cost calculations are base-case calculations only. Analysis was performed with assumed ‘cost of complications’ = $327. Cost threshold was determined by one-way sensitivity analysis for ‘cost-of-complications’ from $300 to $3,363.

### Table 4.14: Values used in Monte Carlo simulation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values utilized in triangular probabilistic calculation</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lowest</td>
<td>likeliest</td>
</tr>
<tr>
<td>EBUS-TBLB sensitivity</td>
<td>0.60</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.75</td>
</tr>
<tr>
<td>CT-PNB sensitivity</td>
<td>0.82</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>0.56</td>
<td>0.80</td>
</tr>
<tr>
<td>CT-PNB complication rate</td>
<td>0.14</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean cost of complications</td>
<td>$300</td>
<td>$654</td>
</tr>
</tbody>
</table>
### Table 4.15: Results of Monte Carlo simulation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mean (SD)</th>
<th>10th centile</th>
<th>Median</th>
<th>90th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS-TBLB</td>
<td>$2,843 (301)</td>
<td>$2,482</td>
<td>$2,814</td>
<td>$3,253</td>
</tr>
<tr>
<td>CT-PNB</td>
<td>$2,935 (340)</td>
<td>$2,515</td>
<td>$2,911</td>
<td>$3,385</td>
</tr>
</tbody>
</table>

**Figure 4.10:** Disutility may be measured by the wait-tradeoff (WTO) technique. The most cost-effective procedure may then be determined on the basis of $/QALY. This graph illustrates the results of two-way sensitivity analysis, with cost-effectiveness measured according to disutility arising from procedural complications. A dynamic relationship is evident between the cost of complications and the complication rate of CT-PNB.
4.4.4 DISCUSSION

Our study was conducted in order to determine the most cost-beneficial and cost-effective diagnostic procedure in the evaluation of PPL. Our analysis indicates that the two minimally invasive approaches used in evaluation of PPL differ in cost by negligible amounts, both in evaluation of the base-case scenario and following Monte Carlo probabilistic simulation.

The minimal differences between the two procedures observed in the base-case and probabilistic sensitivity analyses highlight the importance of clinical acumen in determining the most appropriate procedure. The only previously published randomized trial comparing EBUS-TBLB and CT-PNB found that overall diagnostic accuracy of EBUS-TBLB was non-inferior to CT-PNB.[856] However, numerous studies have demonstrated that both diagnostic accuracy and complication rates for both procedures may vary significantly, based on clinical factors (summarized in Table 4.5).

At base-case values, CT-PNB enjoys an advantage by a having higher diagnostic sensitivity, while EBUS-TBLB has a lower complication rate. Specific clinical features are known to influence clinical outcomes, and therefore will have an effect on cost outcomes. Clinical acumen may suggest to clinicians which procedure may serve a patient better (eg. higher diagnostic sensitivity, lower risk of complications) and these factors will, as demonstrated in Table 4.13, also predict favourable outcomes from a cost perspective.

Where cost and clinical outcomes may diverge is in assessment of cost-effectiveness. We have used theoretical values to conduct cost-effectiveness analysis using the WTO method. Modelling has previously indicated that cost-effectiveness of competing strategies depends on patient attitudes about taking risks.[740] To our knowledge, no published studies have examined the disutility value patients place on adverse outcomes, such as complications, or delay in diagnosis due to a non-diagnostic procedure.
Some patients may place a larger ‘cost’ than 20 days (in the WTO methodology) on adverse outcomes, such that thresholds between the two methods may be significantly different that to that recorded in our study. The ‘cost’ of complications versus non-diagnostic procedures may differ considerably, and may be highly dependent on personality type. This also highlights the value of involving the patient in medical decision making, especially when clinical acumen suggests two approaches may be equivalent. Patients may prefer a procedure with higher diagnostic success even at the cost of a higher risk of complications, or more risk averse patients may prefer a procedure with lower morbidity accepting a slightly higher likelihood of a non-diagnostic procedure.

Our analysis has demonstrated some factors that may influence the cost comparison between EBUS-TBLB and CT-PNB. Cost of managing complications was the factor that most influenced cost-benefit results. A higher cost of complications favoured EBUS-TBLB in cost comparisons, due to the lower complication rate associated with this procedure. Cost of complications is likely to vary significantly between institutions, based on clinical practice (eg. admission vs. out-patient care) and cost of delivering care. Individual institutions and health care services may wish to undertake decision tree analysis, based on local clinical and cost data, to determine their specific optimal investigative approach for patients with PPL.

4.4.4.1 Strengths and Limitations

To our knowledge, this is the first cost comparison study of two minimally invasive procedures for evaluation of PPL. It is also the first to describe the cost of specific procedures, and costs associated with complications of these procedures.

Assumptions are required for decision tree analysis, and validity of the analyses is more certain when actual clinical data or variables are used instead of assumptions. Our analyses were well informed by our own local cost and clinical data, and sensitivity analysis allowed us to perform cost comparisons across most clinically realistic values, as described in published literature. We also accounted for the impact that false-negative results and procedural complications might have had.
Bronchoscopic staging of the mediastinum is cost-beneficial in comparison to the previous standard of surgical mediastinoscopy, largely as a minimally invasive approach is supplanting the significantly more expensive surgical procedure.[866] In contrast, we are comparing two minimally invasive procedures which are very similar in cost. Cost-benefit therefore relies on minimizing ‘downstream’ costs and, as illustrated in Table 4.13, we have emphasized the influence that clinicoradiologic factors known to influence procedural outcomes also strongly influence cost outcomes. Decision tree analysis incorporating such information may assist clinical decision-making, though this requires future study.

Our decision analysis model may aid clinicians in guiding local practice, but outcomes may vary considerably between institutions. Availability of local services, or expertise, may be a more pressing issue in determining clinical practice than our findings. Furthermore, individual patient characteristics may determine which specific modalities are most appropriate, regardless of cost concerns. Finally, patient preference will also guide clinical decision making. We attempted to account for the influence of patient preferences using measures of disutility to obtain cost-effectiveness values, but disutility has not been examined previously and should be included in future studies.

4.4.5 CONCLUSIONS

The costs of EBUS-TBLB and CT-PNB to evaluate PPL appear to be equivalent, but specific clinicoradiologic factors known to influence procedural outcomes will influence cost comparisons. Use of disutility scores to obtain QALY values did not significantly alter the outcome of cost-comparisons. Cost-minimization relies on minimizing ‘downstream’ care costs. As a result, clinical acumen and incorporation of published data regarding influence of clinicoradiologic factors on procedural outcomes are likely to identify the most cost-beneficial diagnostic strategy. Further evaluation of patient preferences and their influence on cost-effectiveness are required.
CHAPTER 5: Assessment of the tolerability and safety of EBUS-TBNA

5.1 BACKGROUND

Endobronchial ultrasound-guided transbronchial needle aspiration was developed primarily to allow real-time minimally invasive staging of lung cancer. It was an advance on conventional transbronchial needle aspiration (TBNA) which was performed ‘blind’, ie. puncture of mediastinal structures was not visualized. Conventional (“Wang needle”) TBNA had been described as early as 1978.[549] Only a small minority of pulmonologists perform TBNA,[451, 558, 559] and published data regarding diagnostic accuracy of this method is highly variable.[520, 554] Numerous factors were known to influence diagnostic sensitivity,[553-555] and competency took considerable time to achieve.[556, 557] Consequently, use of conventional TBNA remained limited to a small number of high-volume centres.

With the advent of a procedure with greater diagnostic accuracy,[732] and shorter time to achieve competency [867] there was unsurprisingly a rapid world-wide uptake of this new technology. Numerous studies quickly emerged reporting consistent diagnostic performance and a systematic review noted “no studies….reported important complications”. [732] However, each of these studies were of subjects undergoing EBUS-TBNA for the purpose of staging NSCLC. Therefore safety in other situations was not established. In particular, clinicians were utilizing EBUS-TBNA with minimal training,[867] and greater penetration of the TBNA needle into mediastinal structures may be sought than would have been used for conventional TBNA.[733] This procedure could in some ways therefore be considered more invasive than conventional TBNA and issues regarding bacteraemia, infection risk, and endocarditis prophylaxis remained unexamined.
Similarly, conditions under which EBUS-TBNA could be performed required examination. Original reports describe introduction of the dedicated convex-probe ultrasound bronchoscope into the airway via an artificial airway (e.g. endotracheal tube, laryngeal mask) under general anaesthesia.[729] Routine bronchoscopy, including conventional TBNA, was performed under conscious sedation, with introduction of the scope most frequently occurring via the nasal route. Size characteristics of the linear array EBUS instrument necessitate insertion via the mouth rather than nostrils, however per oral introduction of the bronchoscope has been associated with lower patient satisfaction.[754] In addition, it is recognized that bronchoscopists may underestimate patient discomfort during flexible bronchoscopy.[755] It remained unreported whether such an approach was acceptable to patients.
5.2 INCIDENCE OF BACTERAEMIA FOLLOWING ENDOBRONCHIAL ULTRASOUND-GUIDED TRANSBRONCHIAL NEEDLE ASPIRATION

5.2.1 INTRODUCTION

The recent introduction of endobronchial ultrasound-guided TBNA (EBUS-TBNA) has revolutionized the evaluation of intrathoracic lymph nodes and other paratracheal structures. Since its description in 2004,[34] this minimally invasive bronchoscopic technique has achieved widespread popularity among respiratory physicians and thoracic surgeons and in centres where it is available is now the procedure of choice for mediastinal staging of lung cancer. Its popularity is based in part on its excellent performance characteristics, but equally on its excellent safety profile. Diagnostic accuracy is at least equivalent to mediastinoscopy and significantly higher for certain lymph node (LN) stations,[716] while a recently published meta-analysis noted no important complications among over 1,500 completed procedures.[732]

Infective complications following conventional (Wang needle) TBNA have been reported but prospective studies suggested bacteraemia following conventional TBNA is extremely rare.[756] Two recent reports have illustrated that EBUS-TBNA may be associated with clinically significant infection, due to direct inoculation of oropharyngeal flora into mediastinal tissue by the TBNA needle.[733, 757] We conducted a prospective study to determine the incidence of bacteraemia following EBUS-TBNA in order to inform clinicians regarding the risk of complicating infection. We also performed culture of needles following TBNA in order to identify microbial pathogens responsible for clinical infection following inoculation by TBNA. We demonstrate for the first time that bacteraemia rates following EBUS-TBNA were consistent with rates reported following routine bronchoscopy. Culture of the needles post TBNA identified organisms that routinely colonise the oropharanyx (15/43, 35%). No local infections or complications related to bacteraemia were identified.
5.2.2 MATERIALS AND METHODS

Institutional review board approval was granted for the performance of this study. All patients provided informed written consent.

All patients undergoing EBUS-TBNA for evaluation of mediastinal lesions were considered for inclusion in the study. We applied the following exclusion criteria; current febrile illness; antibiotic therapy in previous fortnight; current respiratory infection, and; indication for prophylactic antibiotics.

EBUS-TBNA was performed under conscious sedation using a dedicated linear array bronchoscope (BF-UC180F-OL8, Olympus, Tokyo, Japan) by a single operator (DPS). Topical anaesthetic using lignocaine 2% was introduced via the working channel of the linear array bronchoscope. A single use TBNA needle (NA-201SX-4022, Olympus, Tokyo, Japan) was used for each patient. To ensure assessment of bacteraemia pertained specifically to EBUS-TBNA, TBNA was performed as the first diagnostic procedure and blood cultures drawn prior to any further diagnostic procedures being performed.

Venipuncture of an antecubital vein was performed within sixty seconds of completion of the final TBNA. 20mL blood was drawn and then divided equally into both aerobic (BD BACTEC Plus Aerobic/F 442192. Becton Dickinson. Maryland, USA) and anaerobic (BD BACTEC Plus Anaerobic/F 442193. Becton Dickinson. Maryland, USA) culture bottles. Specimens were incubated at 35°C in an instrumented blood culture system (BD BACTEC 9240. Maryland, USA). Positive blood culture vials were processed according to the manufacturers instructions.

Following completion of the procedure, 10mL sterile Normal Saline was washed through the TBNA needle lumen into a sterile container and sent for microbial culture. Following centrifugation, material was inoculated onto both horse blood agar and chocolate agar and incubated in CO2 at 35°C for 48 hours. Patients whose blood cultures were positive were immediately contacted by phone to review any symptoms that might suggest clinical infection. All patients underwent detailed clinical review at
the time of scheduled post-procedure review at three to seven days following EBUS-TBNA.

### 5.2.2.1 Statistics

Comparison between patient groups was made using Fisher’s exact test. This test, and confidence intervals, were calculated using online software available at [http://www.graphpad.com/quickcalcs](http://www.graphpad.com/quickcalcs) (GraphPad Software, La Jolla, CA. USA).

### 5.2.3 RESULTS

Forty-five consecutive patients undergoing EBUS-TBNA between March 19th and August 21st 2009 consented to involvement in this study. Two patients met exclusion criteria (one required prophylactic antibiotics, and one had a concurrent febrile illness) therefore 43 patients had samples taken for analysis. Clinical indication for performance of EBUS-TBNA, and final diagnosis, is recorded in table 5.1.

EBUS-TBNA was performed for evaluation of mediastinal lesions at a number of lymph node stations (see table 5.2). Median lesion size was 2.6±0.9 cm (range 0.9 – 3.5 cm). Median number of needle passes performed prior to venisection was 2.3 (range 1 – 4). Sufficient material for pathologic analysis was obtained in 41 patients (95%) and demonstrated a definitive diagnosis in 33 patients, with TBNA from eight patients demonstrating normal lymphoid tissue.

Peripheral blood cultures taken within sixty seconds of TBNA were positive in 3 patients (7.0% 95%CI 1.7–19.3%). All organisms identified typically colonise the oropharynx. Bacteria isolated and clinical features of these three patients are recorded in table 5.3. No statistically significant relationship was seen between presence of bacteraemia and lesion size, number of needle aspirations performed, or underlying pathology. Bacteraemia was even noted for one patient, undergoing EBUS-TBNA for evaluation of suspected mediastinal recurrence of breast carcinoma, in whom
inadequate samples were obtained. None of the three bacteraemic patients had clinical features suggestive of infection, and no complications were seen among our cohort.

Culture of needles following TBNA was negative in 28 patients (65%), Cultures were positive in 15 patients (35%) with growth of multiple anaerobic and aerobic organisms, typical of upper respiratory tract flora, in fourteen patients and a pure growth of Streptococcus *mitis* in one patient. Needle culture was negative in all three patients in whom bacteraemia was identified.

**Table 5.1:** Indication for performance of EBUS-TBNA, and final diagnoses

<table>
<thead>
<tr>
<th>Indication</th>
<th>Final diagnosis</th>
<th>(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staging of known NSCLC*</td>
<td>Adenocarcinoma</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>NSCLC*</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Large cell carcinoma</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sarcoidal granulomas</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Normal lymph node</td>
<td>6</td>
</tr>
<tr>
<td>Mediastinal evaluation of suspected locally advanced</td>
<td>Small cell lung carcinoma</td>
<td>4</td>
</tr>
<tr>
<td>NSCLC*</td>
<td>Squamous cell carcinoma</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Granulomatous inflammation</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Normal lymph node</td>
<td>2</td>
</tr>
<tr>
<td>Suspected sarcoidosis</td>
<td>Sarcoioids</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Normal lymph node</td>
<td>1</td>
</tr>
<tr>
<td>Isolated mediastinal/hilar lymphadenopathy</td>
<td>Hodgkin’s disease</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Breast carcinoma metastases</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Metastatic melanoma</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Carcinoid tumour</td>
<td>1</td>
</tr>
</tbody>
</table>

*NSCLC – non-small cell lung cancer*
Table 5.2: Lymph node stations sampled.

<table>
<thead>
<tr>
<th>Lymph node station*</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>4R/4L</td>
<td>13</td>
</tr>
<tr>
<td>10R/L</td>
<td>7</td>
</tr>
<tr>
<td>2R</td>
<td>1</td>
</tr>
<tr>
<td>1L</td>
<td>1</td>
</tr>
</tbody>
</table>

*Mountain & Dresler lymph node station classification.[868]

Table 5.3: Clinical features of patients with confirmed bacteraemia following TBNA.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>Location of lesion*</th>
<th>Size (cm)</th>
<th>Number of needle aspirates performed</th>
<th>Final diagnosis</th>
<th>Bacterial isolate</th>
<th>Clinically significant infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>62</td>
<td>7</td>
<td>2.4</td>
<td>2</td>
<td>Insufficient material#</td>
<td>Actinomyces spp.</td>
<td>No</td>
</tr>
<tr>
<td>M</td>
<td>77</td>
<td>10L</td>
<td>3.1</td>
<td>1</td>
<td>Metastatic melanoma</td>
<td>Streptococcus salivarius</td>
<td>No</td>
</tr>
<tr>
<td>M</td>
<td>26</td>
<td>7</td>
<td>1.9</td>
<td>2</td>
<td>Granulomatous inflammation</td>
<td>Streptococcus mitis</td>
<td>No</td>
</tr>
</tbody>
</table>

*Mountain & Dresler lymph node station classification.[868]

#confirmed metastatic adenocarcinoma of breast by subsequent surgical biopsy.
5.2.4 DISCUSSION

This is the first report to describe the frequency of bacteraemia following EBUS-TBNA, which appears comparable to the rate of bacteraemia associated with routine flexible bronchoscopy. We have recorded a bacteraemia rate of 7% among patients undergoing EBUS-TBNA for evaluation of mediastinal and hilar lesions, though importantly none of our patients experienced any clinically significant infective complications. The risk of bacteraemia did not appear to depend on lesion size, or the underlying pathology being sampled. It is also interesting to observe that bacteraemia may even occur despite an inadequate sample being retrieved by the procedure. The exact cause of bacteraemia following EBUS-TBNA remains unclear.

The rate of bacteraemia following routine flexible bronchoscopy varies between reports from 0% to 6%. Yigla and co-workers previously observed bacteraemia in 6% of patients undergoing bronchoscopy – comparable to our observed bacteraemia rate – and noted no association between bacteraemia and performance of procedures (eg. brushings, biopsy) and suggested that bacteraemia may result from bacterial mucosal penetration above the vocal cords, or alternately due to bronchial mucosal trauma following introduction of the bronchoscope. This is supported by the observation in both human and animal studies that bacteraemia may be seen in over 30% of patients undergoing rigid bronchoscopy, in which mucosal trauma is significantly greater than that seen for flexible bronchoscopy.

It is of interest to observe that bacterial culture of the TBNA needle washings was negative in all three patients in whom bacteraemia was demonstrated. This may be a result of the reduced sensitivity of the agar culture method used for the needle washing compared with the bactec system used for detecting bacteraemia. It is also possible that bacteraemia in our patients was a result of introduction of the bronchoscope per se and that performance of TBNA did not measurably increase the risk of bacteraemia. This is also consistent with the observation that, while infections at the site of needle puncture following conventional TBNA have been reported, the only study to examine bacteraemia rates following conventional TBNA observed
no bacteraemia in 50 procedures.[756] In comparison to a routine bronchoscope (through which conventional TBNA is performed), the EBUS-TBNA bronchoscope is larger, less manoeuvrable, and has poorer video optics (including a 30 degree viewing camera). This increases the likelihood of pharyngeal and glottic contact during introduction of the bronchoscope through the upper airway and may explain the higher bacteraemia rate we observed in comparison to those undergoing conventional TBNA.[756]

Similarly, bacteraemia rates following upper gastrointestinal endoscopic ultrasound (EUS) are similar whether FNA is performed or not.[877] Observed incidence of bacteremia following EUS is equal to that seen in routine gastroscopy (6%),[878, 879] and for both procedures, biopsy or other endoscopic operation does not appear to increase the likelihood of bacteremia.[878, 879]

Epstein and co-workers previously reported polymicrobial contamination of conventional TBNA needle contents in all patients examined.[876] Our findings also indicate that contamination of the TBNA needle by oropharyngeal flora is common. We also observe that the majority of reports describing clinically significant infection following either TBNA or EUS-FNA describe infection of relatively avascular tissue.[733, 757-759, 876] During insertion of the bronchoscope through the oropharynx suctioning is very difficult to avoid while establishing a view of the larynx. Contamination of the bronchoscope channel lumen should be assumed for all EBUS-TBNA procedures. While insertion of the bronchoscope through an endotracheal tube (under general anaesthetic) may avoid this, intubation itself is associated with a bacteraemia rate of over 10%.[880] and the very low observed incidence of infection complicating EBUS-TBNA should not influence sedation practice.

Guidelines from the American Heart Association for the prevention of infective endocarditis acknowledge that respiratory tract procedures may cause transient bacteremia with a wide array of microorganisms, but that the risk of antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic antibiotic therapy.[760] Our findings suggest that, given a comparable bacteraemia rate to routine flexible bronchoscopy, recommendations for use of prophylactic antibiotics
for the prevention of infective endocarditis in patients undergoing EBUS-TBNA should not differ from those for routine bronchoscopy. Current guidelines recommend antibiotic prophylaxis for bronchoscopic procedures only in patients with cardiac conditions associated with the highest risk of adverse outcome from endocarditis.[760]

We identify some limitations of our study. Blood cultures were taken at only one time-point. However, rates of bacteraemia following dental procedures are highest immediately after the procedure, and fall dramatically after just two to five minutes.[881] Therefore, the likelihood we have missed bacteraemic events occurring after our venisection seems very low. We excluded patients with fever, and no patients were immunocompromised at the time of EBUS-TBNA. Such patients may be at higher risk of bacteraemia, or infective complications. Finally, culture of needle washings was performed by inoculation onto agar plates. The sensitivity of this method is less than 100% and it is likely our finding under-estimates the true rate of needle contamination by oropharyngeal bacteria.

This study cannot inform comment on the exact risk of local infections. Although bacterial contamination of the TBNA needle was demonstrated in 35% of patients, none developed evidence of clinically significant infection. Oropharyngeal commensal bacterial contamination of the TBNA needle is almost certainly a common event in EBUS-TBNA. Despite this, only two reports describe clinically significant infections complicating EBUS-TBNA,[733, 757] suggesting local infection at the site of TBNA is either extremely rare, or potentially under-recognized and/or under-reported.

Given the assumed needle contamination, we believe patient factors influence the risk of local infection during EBUS-TBNA more so than procedural factors. Previous reports note that infection following conventional TBNA or EUS-FNA are seen only following direct needle inoculation of relatively avascular or necrotic tissue.[733, 758, 759, 876, 882] Future larger prospective studies are required to determine which lesions pose the highest risk of local infection. Further evaluation of the cause of bacteraemia in EBUS-TBNA is also warranted, comparing bacteraemia rates
following TBNA with rates following bronchoscope insertion, prior to performance of TBNA.

5.2.5 CONCLUSION

In conclusion, we observe a low rate of bacteraemia following performance of EBUS-TBNA, comparable to that previously reported following routine flexible bronchoscopy. Bacteraemia appears likely to be due to insertion of the bronchoscope itself rather than due to performance of TBNA. Contamination of the TBNA needle by oropharyngeal flora is common and may predispose patients to clinically significant infection at the site of TBNA puncture, though this appears rare.
5.3 PATIENT SATISFACTION DURING EBUS-TBNA PERFORMED UNDER CONSCIOUS SEDATION

5.3.1 INTRODUCTION

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) allows minimally invasive evaluation of intrathoracic lymph nodes as well as other paratracheal structures.[716] Diagnostic accuracy is at least equivalent to mediastinoscopy in the evaluation of mediastinal lymph node metastases in lung cancer.[716] In centres where EBUS-TBNA is available it has supplanted mediastinoscopy as the procedure of choice for the investigation of mediastinal or hilar lesions and, as such, the procedure is being performed increasingly frequently.

Original reports describe introduction of the dedicated convex-probe ultrasound bronchoscope into the airway via an artificial airway (eg. endotracheal tube, laryngeal mask) under general anaesthesia.[729] Given the probable cost savings of performing EBUS-TBNA under conscious sedation, as opposed to full anaesthesia, many pulmonology units may plan to institute such a service in an ambulatory setting. Size characteristics of the instrument necessitate insertion via the mouth rather than nostrils, however per oral introduction of the bronchoscope has been associated with lower patient satisfaction.[754] In addition, it is recognized that bronchoscopists may underestimate patient discomfort during flexible bronchoscopy.[755] Therefore, we have evaluated patient satisfaction in those undergoing EBUS-TBNA under conscious sedation, and present findings of our study in this report.

5.3.2 METHODS

Institutional review board approval was granted for the performance of this study and all patients gave informed consent.
We prospectively examined patient satisfaction and tolerance in consecutive patients undergoing EBUS-TBNA for the diagnosis and/or staging of mediastinal or hilar lymphadenopathy from July to October 2008. Patients were referred for EBUS-TBNA by a pulmonologist after review in our multidisciplinary lung clinic. Patients were excluded only if the procedure was performed under general anaesthesia, or if cognitive impairment precluded completion of the questionnaire.

5.3.2.1 Performance of EBUS-TBNA

All procedures were performed by a single physician (DPS) using a dedicated linear array bronchoscope (BF-UC160F-OL8, Olympus, Tokyo, Japan). Co-Phenylecaine (Lidocaine 50mg/mL & Phenylephrine 5mg/mL) was applied to the oropharynx and the bronchoscope was then introduced per orally through a bite-block. Topical lidocaine 2% was applied routinely via the bronchoscope during introduction of the bronchoscope through the vocal cords and trachea.

Intravenous sedation was given by a dedicated physician using a combination of midazolam, fentanyl and/or propofol. Agents and doses used were at the discretion of the physician administering sedation, with titration to effect throughout the procedure.

5.3.2.2 Patient questionnaire

Patient wakefulness was assessed using the modified Aldrete score.[883] Patients completed the self-administered questionnaire two to four hours after completion of the procedure only if their modified Aldrete score was 19 or 20. They were advised that this was an anonymous survey and that their responses could not be connected to them. Completed questionnaires were placed in a sealed envelope and paired with a physician-completed demographic and procedural questionnaire.

Patients recorded their willingness to return for this procedure again in the future, were it necessary, using five-point Likert scales, as previously used to assess tolerance of bronchoscopy;[754, 884, 885] (definitely not, probably not, unsure, probably would, definitely would return).
Patients noted the degree of recall of the procedure, using a five-point scale and were also asked to assess, using a three point scale (none, a small amount, a significant amount), their degree of discomfort from anaesthetic throat spray; bronchoscope insertion; shortness of breath; cough; throat pain; and chest pain.

5.3.2.3 Procedural and demographic data

Data relating to performance of the procedure were recorded, including clinical indication for procedures, number of prior bronchoscopic procedures, doses of anaesthetic agents administered during EBUS-TBNA, procedure time, number of TBNAs performed, complications and final diagnosis resulting from the procedure.

5.3.2.4 Statistical analysis

Comparisons of categorical data were analysed using Chi-squared test for trend, and comparison of means was performed using an unpaired t-test. Analyses were performed using GraphPad InStat 3 for Macintosh (GraphPad Software, La Jolla, CA. USA).

5.3.3 RESULTS

Forty-one consecutive patients undergoing EBUS-TBNA completed a patient satisfaction questionnaire, with all completed within four hours of the procedure. No patients had previously undergone EBUS-TBNA. Two patients were excluded from the study. Cognitive impairment precluded informed consent in one patient, and one procedure (performed on a 14 year-old paediatric patient) was performed under general anaesthesia. No patients were denied EBUS-TBNA on medical or anaesthetic grounds. Demographic data and lymph node stations sampled for all 41 patients are recorded in table 5.4. EBUS-TBNA yielded a positive diagnostic yield in 37 patients (90%), with one procedure yielding normal lymphoid tissue and three patients yielding non-diagnostic specimens. No major complications were noted. Transient hypoxia and transient hypotension were each noted in one patient.
### Table 5.4: Demographic data of patients completing satisfaction questionnaire

<table>
<thead>
<tr>
<th></th>
<th>Male / Female</th>
<th>24 (59%) / 17 (41%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td></td>
<td>66 ± 12 years</td>
</tr>
<tr>
<td>Lymph node stations evaluated*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2R/L</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>4R/L</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>10R/L</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>11R/L</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Number of TBNA punctures (mean)</td>
<td>3.6 (range 1 to 6)</td>
<td></td>
</tr>
<tr>
<td>Procedure duration (± SD)</td>
<td>31 ± 8 minutes (range 18 – 45)</td>
<td></td>
</tr>
</tbody>
</table>

*Multiple lymph node stations sampled in ten patients. Lymph node stations were classified according to the system described by Mountain & Dresler.¹⁶

### Table 5.5: Doses and combinations of agents used to achieve sedation during EBUS-TBNA performed under conscious intravenous sedation

<table>
<thead>
<tr>
<th>Medications combinations</th>
<th>Number of patients</th>
<th>Medication doses (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam / Fentanyl</td>
<td>13</td>
<td>3.8±1.4mg / 75±28µg</td>
</tr>
<tr>
<td>Midazolam / Propofol</td>
<td>4</td>
<td>2.0±1.3mg / 220±205mg</td>
</tr>
<tr>
<td>Fentanyl / Propofol</td>
<td>2</td>
<td>62±18µg / 240±57mg</td>
</tr>
<tr>
<td>Midazolam / Fentanyl / Propofol</td>
<td>22</td>
<td>3±1.3mg / 75±24µg / 130±75mg</td>
</tr>
</tbody>
</table>
Mean dose of topical lidocaine was 332±51mg. Combination and doses of intravenous sedative medication varied widely (see table 5.5). All patients scored 19-20 on the modified Aldrete score when first asked to complete the questionnaire.

Forty patients (98%) reported they would “definitely return” for EBUS-TBNA in the future if required, and one (2%) patient reported they would “probably” return for such a procedure.

Frequency and severity of reported symptoms are recorded in table 5.6. The most commonly reported symptom was cough (71%), which was most prominent on introduction of the bronchoscope through the vocal cords. Cough did not interfere with performance of TBNA in any patients. Ten patients (24%) reported no symptoms as a result of their procedure. Twenty-four patients (59%) recalled nothing of their procedure, with patients receiving propofol significantly more likely to report no recollection of the procedure than those receiving midazolam and fentanyl without propofol (p=0.001). Degree of recall for the remaining patients was noted as; no details – 4 (10%); some details – 6 (15%); most details – 4 (10%), and; all details of the procedure – 3 (7%). Recall was not significantly related to reporting of symptoms.

**Table 5.6:** Frequency & severity of reported symptoms during performance of EBUS-TBNA.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Likert scale of symptom severity</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Small amount</td>
</tr>
<tr>
<td>Anaesthetic throat spray</td>
<td>30 (73)</td>
<td>9 (22)</td>
</tr>
<tr>
<td>Discomfort during scope insertion</td>
<td>32 (78)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>33 (80)</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Cough</td>
<td>12 (29)</td>
<td>21 (51)</td>
</tr>
<tr>
<td>Throat pain</td>
<td>30 (73)</td>
<td>11 (27)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>37 (90)</td>
<td>4 (10)</td>
</tr>
</tbody>
</table>
Routine bronchoscopy performed under conscious intravenous sedation has previously been associated with high levels of willingness to return for the procedure suggesting good tolerance of the procedure.[754] Our results confirm that performance of EBUS-TBNA under conscious sedation may be associated with extremely high levels of patient satisfaction and provide strong reassurance that such practice is safe and well tolerated by patients. Ninety-eight percent of our patients reported they “definitely would” return for such a procedure if required in the future which, to our knowledge, is the highest reported satisfaction level described in the published literature for any form of bronchoscopy.

Previous authors have suggested EBUS-TBNA is best performed under general anaesthesia via an artificial airway.[729] The dedicated linear-array bronchoscope required for performance of EBUS-TBNA is larger than routine bronchoscopes (6.9mm diameter), and has a fixed non-flexible tip. This necessitates insertion via an oral route. Lechtzin et al previously reported lower satisfaction levels in patients undergoing routine bronchoscopy with per-oral insertion,[754] however all these patients had failed attempts at per-nasal introduction of the bronchoscope suggesting that failed nasal insertion is responsible for reduced satisfaction levels, rather than per-oral insertion per se. Our findings indicate oral bronchoscope insertion under conscious sedation may be equally well tolerated.

Satisfaction levels with bronchoscopy have varied across reports, from 52% to 98%.[885, 886] It is possible EBUS-TBNA is less stimulating than bronchoalveolar lavage or transbronchial lung biopsy, which may explain our extremely high satisfaction levels. However, our aim with administration of sedation was to aim for moderately deep anaesthesia and we feel this is responsible for such high satisfaction levels among our patients. Importantly we have also shown that use of moderate doses of sedative agents is associated with an excellent safety and satisfaction profile.

Flexible bronchoscopy may be performed safely without sedation, with one randomized study suggesting patient tolerance is not affected by use of...
sedatives.[887] However, as few as 27% of patients receiving placebo sedation in this study reported a willingness to return for the procedure, and generalizability of findings from this study are difficult due to very low doses of sedation used in the treatment arm.[887] Hirose et al reported just 12% of patients would “definitely return” following bronchoscopy performed under sedation with intramuscular pentazocine, with a weight-based dose equivalent to morphine 5mg.[884] This low dose may be sub-sedative and, therefore, likely to be associated with lower levels of patient tolerance.

In contrast multiple studies have suggested that routine use of sedation improves patient tolerance of FB.[755, 885, 888-892] Most recently, Silvestri et al described a significantly higher proportion of patients expressing willingness to be treated again following sedation for bronchoscopy with higher doses of a novel sedative drug, fospropofol,[891] indicating use of sedation is associated with better patient tolerance of bronchoscopy. Not surprisingly, a survey of Pulmonologists in the United Kingdom noted just 0.1% of those regularly performing bronchoscopy do so without sedation.[893] Indeed, the British Thoracic Society recommend all patients undergoing FB be offered sedation unless clear contra-indications exist.[894]

We identify some limitations of our study. There was no control group and sedation regimens were not uniform. Therefore we cannot definitively comment on patient tolerance with respect to routine bronchoscopy, or with use of specific sedation regimens. We also recognize that having a physician focussed on sedation may provide a more satisfactory procedure, and that this facility is not available in all centres performing EBUS-TBNA. However, our intent was to describe patient satisfaction in those undergoing EBUS-TBNA, rather than identify optimal sedation practice. Our results provide reassuring evidence that when performed under conscious sedation EBUS-TBNA may be associated with high levels of patient satisfaction. Our results indicate that this is true regardless of the sedation regimen used.

We have recorded satisfaction at only one time-point. However, Maguire et al noted no difference in patient satisfaction reported immediately following bronchoscopy and one month after the procedure.[885] Therefore we feel that assessment at two to four
hours post-procedure is reliable. Furthermore, we have not determined if satisfaction varies according to whether the physician providing sedation is an anaesthetist or non-anaesthetist. While non-anaesthetist sedation for flexible bronchoscopy is safe, we are not aware of any studies examining patient tolerance of non-anaesthetist administered sedation for bronchoscopic procedures and feel this warrants further study.

Finally, all procedures were performed by a single physician. Satisfaction levels may be expected to vary between individual proceduralists and institutions. While satisfaction levels reported among our patients may not be experienced by all persons performing EBUS-TBNA, our results do afford confidence to those electing to perform EBUS-TBNA under conscious sedation that it is feasible to do so safely and with satisfaction levels at least as high as those previously recorded for routine bronchoscopy.

5.3.5 CONCLUSION

EBUS-TBNA may safely be performed under conscious intravenous sedation. Such practice is associated with very high levels of patient satisfaction, and reported satisfaction appears to be independent of the sedation regimen used. Prospective trials are required to determine the optimal combination of sedative agents in patients undergoing bronchoscopy, and to confirm that sedation for bronchoscopy may safely be administered by non-anaesthetic physicians.
CHAPTER 6: Issues in the integration of EBUS-TBNA into routine care – comparison with current standards of care

6.1 BACKGROUND

Early studies examining performance of EBUS-TBNA almost exclusively described performance in the staging of NSCLC. Benefits of EBUS-TBNA in comparison to the historic gold-standard – surgical mediastinoscopy – were assumed based on the fact that a minimally invasive bronchoscopic procedure was replacing invasive surgery. Mediastinoscopy was still viewed as the ‘gold-standard’ and international guidelines recommended mediastinoscopy be performed in the event of a ‘negative’ EBUS-TBNA procedure given the uncertain negative predictive value of EBUS-TBNA. This has clear implications for cost-benefit analysis as accurate comparison should always include downstream costs such as cost of subsequent procedures in the event of non-diagnostic testing.

The value of EBUS-TBNA lay largely in its minimally invasive nature however this posed some concern regarding the utility of the small sample sizes of tissue retrieved by the 22-gauge TBNA needle. Examination of cytology specimens is known to have some limitations in comparison to histology specimens (as acquired at surgery) especially where appreciation of tissue architecture is important in determining diagnoses, or sub-classifications within specific diagnoses. Increasingly, EBUS-TBNA was the sole method by which diagnostic tissue was obtained in patients with advanced lung cancer. Recent evidence has emphasized the importance of accurate
determination of NSCLC subtype in selection of optimal therapy for patients with advanced NSCLC.[895, 896] The comparison between EBUS-TBNA and the current standards of care was unknown.
6.2 COST-BENEFIT OF MINIMALLY INVASIVE STAGING OF NON-SMALL CELL LUNG CANCER: A DECISION TREE SENSITIVITY ANALYSIS

6.2.1 INTRODUCTION

Accurate staging of non-small cell lung cancer (NSCLC) is critical for its optimal management. Assessing the involvement of mediastinal lymph node stations is the most common dilemma facing clinicians staging NSCLC, as treatment strategies differ significantly according to the presence or absence of mediastinal lymph node metastases (MLNM). The superiority of Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) integrated with computed tomography (CT) chest (PET/CT) over other non-invasive imaging modalities is well established in the staging of NSCLC and has been shown to be cost-effective.[897, 898] However, guidelines recognize that PET/CT is associated with a positive predictive value of less than 90%,[30] and therefore emphasize the need to pathologically confirm FDG-avid mediastinal lesions so as not to deny patients potentially curative surgical treatment.[30, 520]

Pathological assessment of mediastinal lymph nodes may be performed by either surgical or minimally invasive means. Mediastinoscopy has long been the gold standard for evaluation of the mediastinum. However, it is invasive and carries a low but significant risk of complications.[525-527] Since 1983, transbronchial needle aspiration (TBNA) via bronchoscopy has been available for the minimally invasive assessment of mediastinal lymph nodes,[31] but a significant false negative rate has limited uptake in clinical practice.[555, 558] Recently, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has been established as a minimally invasive technique for the assessment of mediastinal lymphadenopathy.[34] Diagnostic accuracy is comparable to surgical mediastinoscopy but with a significantly lower complication rate.[705] Furthermore,
in contrast to mediastinoscopy, EBUS-TBNA is better able to access to the subcarinal region,[716] and can evaluate hilar lymph nodes and provide endobronchial assessment of patients with known or suspected NSCLC.

The Royal Melbourne Hospital in Melbourne, Australia, is a tertiary referral centre for the diagnosis, staging and management of lung cancer, with substantial experience in all the above modalities used for mediastinal staging in NSCLC. Based on cost estimates at this institution, we sought to establish the most cost-beneficial method of staging NSCLC patients in whom non-invasive imaging with PET/CT have demonstrated suspected MLNM.

6.2.2 METHODS

6.2.2.1 Modelling approach
Decision analysis [739] using specialized validated software (TreeAge Pro 2009, Excel module. TreeAge Software Inc., Williamstown, MA) was applied to compare the downstream costs of EBUS-TBNA, conventional TBNA and surgical mediastinoscopy (Figure 6.1). The analysis accounted for costs incurred as a result of extra procedures required in the event of a negative result by conventional TBNA or EBUS-TBNA.

An advantage of decision tree analysis is its capacity to simulate even complex clinical algorithms, such as that for the NSCLC staging. Furthermore, it can explicitly capture the uncertainty that is inherent in modelling of any type.[777]

6.2.2.2 Model population
The modeled population comprised hypothetical patients who had diagnosed NSCLC and required mediastinal evaluation following detection of abnormalities on non-invasive staging with PET/CT. As recommended by expert guidelines,[509, 899] all patients with confirmed stage III NSCLC would be referred for non-surgical
management of disease. Patients with early stage disease (stage I and II) were referred for surgical resection.

6.2.2.3 Health care costs

Unit cost estimates, in Australian dollars (AU$), were based on recorded hospital costs for patients undergoing the above-mentioned procedures at the Royal Melbourne Hospital between 1 July 2007 and 30 June 2008. Mediastinoscopy at the Royal Melbourne Hospital is performed as a day procedure under general anaesthesia. EBUS-TBNA and conventional TBNA are also performed on an outpatient basis, under conscious sedation. EBUS-TBNA is performed with a dedicated single-use TBNA needle (NA-201SX-4022, Olympus, Tokyo, Japan).

At the Royal Melbourne Hospital during the period specified, conventional TBNA was only performed as a component of diagnostic bronchoscopy. Therefore, associated costs included those associated with procedures other than TBNA. If TBNA had been performed solely for staging of mediastinal lymph nodes, it would have been under identical conditions to EBUS-TBNA, with the only exception being the use of a different needle to perform TBNA. We therefore based costs of conventional TBNA when performed solely for staging of NSCLC on costs observed for EBUS-TBNA, discounted due to the lower cost of the TBNA needle ($145 cheaper).

All patients undergoing either mediastinoscopy, thoracotomy or EBUS-TBNA in the period 1 July 2007 to 30 June 2008 were identified. Hospital records were reviewed to identify those undergoing these procedures specifically for the purpose of staging or treatment of histologically proven NSCLC. Patients with diagnoses other than NSCLC were excluded from cost calculations, as were those undergoing mediastinoscopy or thoracotomy for reasons other than staging of NSCLC with intent for curative resection.
Figure 6.1: Decision tree illustrating possible clinical pathways following selection of one of the four diagnostic approaches being evaluated.

MLNM = mediastinal LN metastases

Procedures are denoted as positive (+) or negative (-) for metastases

EBUS = endobronchial ultrasound

TBNA = transbronchial needle aspiration

☐ = decision node. *i.e.* The clinician may choose any clinical pathway for an individual patient.

○ = chance node. *i.e.* Patients may experience either outcome, based on chance. The proportion of patients following each pathway from a chance node is dependent on predefined clinical parameters. For example, the proportion of patients following the MLNM+ branch, versus the MLNM- branch, is dependent on the underlying prevalence of MLNM.

△ = terminal node in decision pathway. *i.e.* An individual patient has reached a definitive outcome in their diagnostic pathway.
Numbers of patients undergoing each procedure during 2007/8 at Royal Melbourne Hospital, and median costs associated with each diagnostic approach are summarised in Table 6.1. No patients in whom costs for mediastinoscopy were calculated had previously undergone EBUS-TBNA. Calculations were based on real costs using the 2007/8 price level. Costs were derived from actual patient data at the Royal Melbourne Hospital and then updated to 2009/10 levels according to the locally recorded Health Price Index, which reported an increase of 3% per year. Hospital costing data for each patient admission was obtained from cost weight analysis compiled according to guidelines from the Clinical Costing Standards Association of Australia.

Estimated costs for mediastinoscopy and EBUS-TBNA were comparable to those previously estimated in a prior economic evaluation of these procedures in the Australian Health Care system. Yap et al had examined the economic impact of addition of FDG-PET staging to routine mediastinoscopy in NSCLC patients, while a Commonwealth Advisory Committee estimated the approximate cost of EBUS-TBNA in order to determine an appropriate Medicare reimbursement rate for performance of the procedure in Australian hospitals.

6.2.2.4 Other input parameters

Other input parameters applied to the decision tree analysis are described in Table 6.2. Sensitivity of EBUS-TBNA for detection of mediastinal metastases (N2/3 disease, according to the IASLC lung cancer staging system) for analysis was based on our own institutional experience. Sensitivity for mediastinoscopy and conventional TBNA was based on recent pooled analyses by Detterbeck et al. Prevalence of mediastinal nodal metastases in PET-positive mediastinal lesions was based on a recent pooled analysis by Silvestri et al.

6.2.2.5 Sensitivity analysis

Calculations based on the above data constitute a “base-case” analysis, as defined by NICE guidelines. We recognized that model input values may vary significantly across different institutions. For example, the prevalence of MLNM will vary...
depending on the staging modality used, and is likely to be lower among patients in whom only CT imaging is used for mediastinal staging. Furthermore, sensitivity of EBUS-TBNA is likely to vary according to institution and operator, as there is a recognized learning curve for operators being introduced to the technique.[1] Yield of conventional TBNA varies according to lymph node size and position.[553, 555] Therefore, a series of one-way sensitivity analyses were undertaken within the range of each parameter recorded in Table 2, based on data from recent meta-analyses.[705, 732]. The values of these key inputs were varied one at a time, while maintaining the other inputs at ‘base case’ values. Subsequent analysis was undertaken to determine the threshold above which the most cost-beneficial approach remained in comparison to other diagnostic modalities. Finally, as procedural costs may also vary across institutions (for example, if performed under general anaesthesia or as an in-patient procedure), one sensitivity analysis assumed a cost for EBUS-TBNA that was 50% higher ($2,042). As sensitivity analysis is based on theoretical patients, we were required to make some specific assumptions regarding the theoretical “modeled” population.

6.2.2.6 Assumptions

Key assumptions in the analysis were as follows:

- There was a well-defined outcome in each arm of our decision model; that is, the detection of stage III disease.

- The long-term outcomes (measures of effectiveness) were equivalent in each model arm; that is, the survival of all patients with stage III disease is similar regardless of how the extent of disease was determined. As recognized by Harewood et al.[903] a cost-benefit analysis, which assumes that competing diagnostic strategies have equivalent outcomes and focuses thereafter only on cost outcomes, is the most appropriate form of economic analysis to use in this setting.

- The downstream costs of medical care for patients with stage III disease were the same in all arms, once the extent of disease had been established, regardless of how this was achieved.

- The specificity of all procedures examined for the detection of lymph node metastases was 100%, as indicated in published literature.[520]
• Given the higher sensitivity of both EBUS and mediastinoscopy in comparison to PET/CT,[703, 904] all mediastinal lymph nodes detected by PET/CT were sampled.
• Thoracotomy and lymph node dissection detected all patients with N2/3 disease for patients in whom TBNA and/or mediastinoscopy returned false negative results (ie. the sensitivity of thoracotomy for detection of N2/3 metastases was 100%)
• Pathology costs were identical regardless of method of acquisition of tissue.
**Table 6.1:** Hospital costs associated with each procedure
(calculated from hospital data 2007/8)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n</th>
<th>Mean length of stay (range)</th>
<th>Median cost</th>
<th>Mean cost (+SD)</th>
<th>Updated mean cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS-TBNA</td>
<td>12</td>
<td>1 (1-1)</td>
<td>$1,318</td>
<td>$1,320 ± $204</td>
<td>$1,361</td>
</tr>
<tr>
<td>Mediastinoscopy</td>
<td>10</td>
<td>1 (1-1)</td>
<td>$5,324</td>
<td>$5,131 ± $787</td>
<td>$5,290</td>
</tr>
<tr>
<td>Thoracoscopy/thoracotomy</td>
<td>17</td>
<td>9.3 (6 – 17)</td>
<td>$22,048</td>
<td>$22,628 ± $5,969</td>
<td>$23,327</td>
</tr>
</tbody>
</table>

*based on local Health Price Index of 3%/year.[900]

**Table 6.2:** Parameter values used for variables in performance of decision tree analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline sensitivity for detection of mediastinal lymph node metastases</th>
<th>Range utilized for sensitivity analysis</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS-TBNA</td>
<td>0.90</td>
<td>0.79 - 0.96</td>
<td>[42, 705, 905]</td>
</tr>
<tr>
<td>Conventional TBNA</td>
<td>0.78</td>
<td>0.56 – 0.93</td>
<td>[520]</td>
</tr>
<tr>
<td>Mediastinoscopy</td>
<td>0.82</td>
<td>0.68 – 0.92</td>
<td>[520]</td>
</tr>
<tr>
<td>Prevalence mediastinal metastases†</td>
<td>0.85</td>
<td>0.63 – 0.96</td>
<td>[30]</td>
</tr>
</tbody>
</table>

#range based on published systematic reviews
† prevalence in patients staged N2/3 positive by FDG-PET/CT.
6.2.3 RESULTS

6.2.3.1 Base-case analysis
For the base-case analysis, initial evaluation with EBUS-TBNA (with negative results being surgically confirmed) was found to be the most cost-beneficial approach ($2,961) in comparison to EBUS-TBNA not surgically confirmed ($3,344), conventional TBNA ($3,754) and mediastinoscopy ($8,859) (Table 6.3).

6.2.3.2 Sensitivity analysis
One-way sensitivity analyses demonstrated that initial evaluation with EBUS-TBNA remained the least costly approach down to a MLNM prevalence of just 30% (Figure 6.2), an implausibly low percentage in patients with lymphadenopathy detected by PET/CT.[30, 494] A clinical approach whereby negative EBUS-TBNA results were not surgically confirmed was the least costly approach when lymph node prevalence was under 79%.

While base case analysis indicated that surgical confirmation of negative EBUS-TBNA results to be the most cost-beneficial approach to mediastinal staging, variation in the sensitivity of EBUS-TBNA revealed that it was cost-beneficial not to confirm negative results when sensitivity was greater than 0.93 (Figure 6.3). Threshold analysis revealed that EBUS-TBNA (without confirmation of negative results) remained the least costly alternative provided sensitivity was greater than 17% (Figure 6.3). It also demonstrated that conventional TBNA became the most cost-beneficial approach if sensitivity exceeded 88%. In the absence of EBUS-TBNA, conventional TBNA remained cheaper than mediastinoscopy, provided sensitivity of TBNA was greater than 15% (data not shown). One-way sensitivity analysis varying all parameters across the range noted in Table 6.2 demonstrated that the sensitivity of EBUS-TBNA had the largest impact on cost in analysis of our decision tree (data not shown).
Cost savings are related to avoidance of more expensive surgical procedures. A higher rate of negative results by either EBUS-TBNA or conventional TBNA (due to lower sensitivity or lower prevalence of MLNM) may alter the outcome of analyses. In two-way sensitivity analyses which varied both the prevalence of MLNM and the sensitivity of EBUS-TBNA, EBUS-TBNA remained the least costly approach across plausible ranges for both lymph node metastasis prevalence and sensitivity of EBUS-TBNA. The choice as to whether to surgically confirm negative EBUS-TBNA results varied as a function of sensitivity of EBUS-TBNA and lymph node prevalence (Figure 6.4).

Analysis on the basis of a cost for EBUS-TBNA that was 50% higher than noted at our institution ($2,042) demonstrated that EBUS-TBNA, with surgical confirmation of negative results, remained the least costly approach ($3,642, versus TBNA $3,754 and mediastinoscopy $8,593).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base case cost</th>
<th>Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS-TBNA (surgically confirmed negative results)</td>
<td>$2,961</td>
<td>$2,477 – $3,848</td>
</tr>
<tr>
<td>EBUS-TBNA (without confirmation of negative results)</td>
<td>$3,344</td>
<td>$2,154 – $5,524</td>
</tr>
<tr>
<td>Conventional TBNA</td>
<td>$3,754</td>
<td>$2,565 – $5,498</td>
</tr>
<tr>
<td>Mediastinoscopy</td>
<td>$8,859</td>
<td>$6,876 – $12,756</td>
</tr>
</tbody>
</table>

*Range of costs based on diagnostic sensitivity range recorded in table 6.2 for each procedure.
Figure 6.2: Graphical representation of effect on expected value of each diagnostic pathway during one-way sensitivity analysis with variation in prevalence of lymph node metastases among modeled population. Surgical confirmation of negative EBUS-TBNA results is cost-beneficial above a MLNM prevalence of 0.79. This figure illustrates the effect of variation in prevalence of MLNM of the modeled population on the overall cost of each specific diagnostic pathway.

Figure 6.3: Graphical representation of effect on expected value of each diagnostic pathway during one-way sensitivity analysis with variation in sensitivity of EBUS-TBNA.

Figure 6.4: Two-way sensitivity analysis with variation in prevalence of lymph node metastases, and sensitivity of EBUS-TBNA. The most cost-beneficial diagnostic pathway for the combination of the two varied parameters is indicated by the pattern present on the graph. Across all parameter values for MLNM prevalence, and sensitivity of EBUS-TBNA examined, EBUS-TBNA remained the most cost-beneficial diagnostic modality, therefore mediastinoscopy and conventional TBNA are not represented in this graph. The value of surgical confirmation of negative results varied according to parameter values, as demonstrated.
Our study sought to determine economic outcomes resulting from alternate investigative approaches to pathologic staging of NSCLC patients with suspected MLNM. We demonstrated that, in addition to previously demonstrated safety and diagnostic advantages, EBUS-TBNA is also very likely to be associated with significant cost reduction in the evaluation of suspected MLNM in comparison to mediastinoscopy. Our analysis may even underestimate the cost-benefit of EBUS-TBNA as we have not accounted for costs due to the expected higher complication rate in patients staged using mediastinoscopy. Importantly, EBUS-TBNA remains the most cost-beneficial approach across a broad range of parameters, including a sensitivity for detection of disease of 20%, which is far below that recorded in published literature.[705, 732] Cost savings were calculated at approximately $5,721 per patient in comparison to mediastinoscopy and $799 per patient in comparison to conventional TBNA.

Our findings further strengthen the case for the use of EBUS-TBNA as the first line investigation modality for the pathological evaluation of mediastinal lymphadenopathy in patients with known or suspected NSCLC. We found EBUS-TBNA to be cost beneficial in comparison to conventional TBNA, consistent with a recently published study comparing EBUS-TBNA with conventional TBNA for mediastinal staging of NSCLC.[902] Although cheaper to perform than EBUS-TBNA, the lower sensitivity and negative predictive value of conventional TBNA mean a larger proportion of patients require confirmatory mediastinoscopy prior to potentially curative lobectomy, which significantly increases the overall cost.

Notably, conventional TBNA remains more cost-beneficial than mediastinoscopy for patients provided the institutional sensitivity for TBNA is greater than 20%. Yield of conventional TBNA varies according to both lymph node station and size, though it is invariably greater than 20%, regardless of station.[553, 555] From a cost perspective, therefore, use of conventional TBNA is limited not by yield, but only by the preparedness of the proceduralist to use it.
The need for surgical confirmation following negative EBUS-TBNA in the management of NSCLC patients remains unclear. Earlier expert guidelines recommended confirmation of negative results from EBUS-TBNA due to concerns regarding false negative results.[520] However, more recent studies suggest the sensitivity and negative predictive value of EBUS-TBNA may be higher than mediastinoscopy,[520, 705, 716, 732] and the clinical imperative to surgically confirm negative results has recently been challenged by some experts.[906] Despite this, our results suggest it remains cost-beneficial to confirm negative results obtained by EBUS-TBNA in patients staged with PET/CT. The economic value of surgical confirmation of EBUS-TBNA is dependent on the prevalence of lymph node metastases (which will influence the proportion of negative results). Therefore this is an issue that may vary from institution to institution, and particularly according to the mode of non-invasive staging. CT-detected mediastinal lymphadenopathy is associated with a significantly lower prevalence of metastases,[30, 907] and from an economic standpoint, it is more cost-beneficial not to confirm negative EBUS-TBNA results among this group.

Three previous studies have performed cost analyses of various approaches to mediastinal staging of NSCLC. Medford et al examined actual hospital costs associated with performance of EBUS, and concluded that use of EBUS may substantially reduce community health care costs.[908] However they limited analysis to EBUS only and did not examine the potential value of conventional TBNA. The authors did not completely account for costs related to false negative outcomes and, furthermore they examined only observed costs so the effect of variation in input parameters remains unknown.

Costs in both remaining studies were based on medical reimbursement rates, rather than overall costs of care. Kunst et al examined use of EBUS-TBNA in The Netherlands and found, as we have, that it was more cost-beneficial in comparison to conventional TBNA.[869] Our analysis significantly extends their findings as they calculated costs for alternate diagnostic approaches but did not perform a decision tree analysis and assumed 100% prevalence of mediastinal metastases, and a sensitivity of 100% for mediastinoscopy. Our analysis also included downstream health costs, whereas those of Kunst et al were limited to physician and consumable costs.
associated with performance of the procedure. Furthermore, we demonstrated via one- and two-way sensitivity analysis that EBUS-TBNA remains the least costly approach regardless of lymph node metastasis prevalence, and a sensitivity for EBUS-TBNA as low as 20%.

Harewood et al examined the cost-effectiveness of EBUS-TBNA in comparison to EUS-FNA, mediastinoscopy and combined EBUS-TBNA/EUS-FNA in the mediastinal staging of known NSCLC in Florida (United States).[903] This study performed cost calculations using several baseline parameters that do not accord with published data. An assumed sensitivity of 69% for EBUS-TBNA was in line with their own reported institutional sensitivity for EBUS-TBNA,[909] but was significantly below that recorded in numerous studies of EBUS-TBNA,[705, 732] including in patients with a radiologically-,[702] and even PET-negative,[910] mediastinum. Sensitivity analysis reported by the authors indicated that EBUS-TBNA was the least costly approach if sensitivity exceeded 71% - a figure below our expected range for this parameter. Similarly, they assumed a sensitivity of conventional TBNA of just 36%, whereas Detterbeck et al calculated a pooled sensitivity of 78% for conventional TBNA and noted just one of 17 studies with a reported sensitivity below 50%.[520] Finally, they presumed a prevalence of mediastinal metastases of 30%. This was based on their own previous report which differs markedly from most published figures.[30, 494] Other limitations of their study include that they did not calculate costs associated with further investigations that might necessarily follow a negative biopsy by conventional TBNA or EBUS-TBNA, and that their calculations were based on a reimbursement rate for EBUS-TBNA greater than triple that for EUS-FNA – a scenario not relevant to Australia, nor most other countries.

6.2.4.1 Strengths and Limitations

The strengths of our study include the comparison between multiple staging modalities, including comparison of diagnostic approaches whereby negative EBUS-TBNA may or may not be surgically confirmed. Assumptions are required in the performance of decision tree analysis, and validity of the analyses is more certain when actual clinical data or variables are employed instead of assumptions. We have
used actual cost and clinical data to inform our calculations. We have also accounted for the impact that false negative results might have. Finally, our sensitivity analyses, based on published meta-analyses, allow examination of cost outcomes across a wide variety of clinical parameters, including prevalence of lymph node metastases and sensitivity of EBUS-TBNA.

Exact cost comparisons will vary according to local rates of remuneration, complication rates, and even diagnostic performance. The published literature indicates that complication rates and diagnostic performance of all examined procedures will vary only minimally between institutions. However, remuneration and other costs (e.g., admission, pathology) may vary significantly and, therefore, our results may not apply to all institutions. Our results are also specific to patients with CT- or PET/CT-detected lymphadenopathy. Analyses are likely to differ significantly in patients with a normal-appearing mediastinum where the prevalence of lymph node metastases is just 10%. [910]

Conditions under which procedures are performed may also influence cost analyses. For example, EBUS-TBNA may be performed under general anaesthesia, may utilize on-site cytologic specimen evaluation, or may use new TBNA needles for each lymph node station sampled rather than commencing TBNA from the highest stage lymph node site (N3) and performing subsequent TBNA from lower stage stations (N2 then N1). Each of these would be expected to be associated with higher costs. Given the disparity in base-case costs between EBUS-TBNA and mediastinoscopy, it seems unlikely that even use of all these approached would result in mediastinoscopy becoming more cost-beneficial than EBUS-TBNA for mediastinal staging of NSCLC.

Finally, we have not included capital costs in our analysis. Capital costs for EBUS-TBNA, which requires purchase of a dedicated videobronchoscope, provide some impediment to widespread use of EBUS-TBNA. However, given the estimated cost savings (compared to a mediastinoscopic staging approach) of $5,721 per patient, and approximate purchase costs of AU$90,000, purchase of a convex probe bronchoscope for EBUS-TBNA would be cost-neutral after performance of just 16 procedures. Callister et al similarly concluded that capital costs would be quickly recovered, using
hospital reimbursement rates to calculate significant savings to the public health system through use of EBUS-TBNA in preference to mediastinoscopy.[911]

Our decision analysis model may aid clinicians in guiding local practice, but the availability of local services, or expertise, may be a more pressing issue in determining clinical practice than our findings. Furthermore, individual patient characteristics may determine that specific modalities are most appropriate, regardless of cost concerns. Finally, patient preference may also guide clinical decision-making.

6.2.5 CONCLUSION

In conclusion, our study confirms that the least expensive modality for mediastinal staging of NSCLC patients is EBUS-TBNA, with cost-minimization achieved by surgical confirmation of negative results, provided the prevalence of lymph node metastases is greater than 79%. In the absence of EBUS-TBNA, conventional TBNA is cheaper than mediastinoscopy, provided the sensitivity of TBNA is higher than 15%. Given the demonstrated equivalence (and likely superiority) of EBUS-TBNA in diagnostic performance in comparison to mediastinoscopy, and its favourable safety profile, our demonstration of the cost advantage of EBUS-TBNA in diagnosis of mediastinal metastases in patients with NSCLC provides yet more rationale for its clinical use.
6.3 INTEROBSERVER AGREEMENT IN DETERMINATION OF NON-SMALL CELL LUNG CARCINOMA SUBTYPE IN SPECIMENS ACQUIRED BY EBUS-TBNA

6.3.1 INTRODUCTION

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was first developed to allow minimally invasive mediastinal staging of patients with known non-small cell lung cancer (NSCLC).[34] More recently, it has been used to obtain diagnostic tissue in patients suspected of having lung cancer in whom CT or positron emission tomography (PET) suggest mediastinal or hilar metastases.[722, 723, 830] Such an approach allows both diagnostic and staging information to be obtained in a single procedure, thereby expediting the management process, and is predicated upon the high diagnostic sensitivity of EBUS-TBNA.[705] Consequently, an increasing number of patients may have treatment decisions based solely upon small volume tissue samples obtained at EBUS-TBNA.

Recent studies have demonstrated that NSCLC subtype determines the choice of systemic therapy in patients with advanced NSCLC,[895] and the need for molecular characterization of tumours.[896] Significant inter-observer variability between pathologists in the subclassification of NSCLC subtypes in small specimens obtained at routine flexible bronchoscopy has previously been observed, with only ‘fair’ agreement observed among pathologists examining NSCLC in endobronchial biopsies.[764] Cytologic specimens are subject to significantly higher interobserver variability than histologic specimens.[765] Given the increasing importance of accurate NSCLC subclassification we believed it was important to examine the interobserver variability in evaluation of the small volume samples obtained by EBUS-TBNA.
6.3.2 MATERIALS AND METHODS

Institutional review board approval was granted for the performance of this study.

6.3.2.1 Patients

From the time of inception of EBUS-TBNA at our two tertiary referral centres, we have prospectively recorded demographic and detailed clinical information for all completed procedures. After performing a retrospective review of this database, we identified a convenience sample of 60 consecutive patients who underwent EBUS-TBNA for staging/diagnosis of known/suspected NSCLC.

6.3.2.2 Performance of EBUS-TBNA

Consultant respiratory physicians experienced in performance of EBUS-TBNA performed EBUS-TBNA. A dedicated linear array bronchoscope (BF- UC180F-OL8, Olympus, Tokyo, Japan) was used to visualize pathologic LNs, as directed by CT chest findings, before performance of EBUS-TBNA using a 22-gauge needle (NA-201SX-4022, Olympus, Tokyo, Japan). A maximum of three needle passes were performed with initial material transferred to the slides for rapid on-site cytologic evaluation performed by a cytotechnician. All subsequent material placed in formalin solution to allow the preparation of a cell block for histologic evaluation and immunohistochemical analysis.

6.3.2.3 Specimen processing

Cytology slides were fixed in 95% ethyl alcohol and Papanicolaou stain was used to stain all the slides. Material in formalin was centrifuged down to a pellet and 3% molten agar was added, then solidified and processed as a cell block by tissue processor. Serial levels were cut and placed on slides before staining with Haematoxylin and Eosin (H&E). Immunohistochemical stains used were at the discretion of the pathologist at the time of original reporting of the specimen; however, they mostly consisted of panels including CK5/6 (DAKO, dilution 1:50), p63 (DAKO, dilution 1:500), CK7 (Novocastra, dilution 1:120) and TTF1 (Novocastra, dilution 1:300). In some cases markers of neuroendocrine differentiation
such as CD56 (Novocastra, dilution 1:50), chromogranin A (DAKO, dilution 1:800) and synaptophysin (DAKO, dilution 1:400) were also used. Immunohistochemical stains were prepared by Leica Bond automated immunostainer (Leica Microsystems, Wetzlar, Germany).

6.3.2.4 Pathology review

Three pathologists with experience in the reporting of lung cancer pathology specimens independently reviewed each specimen. All three are consultant anatomical pathologists with a minimum 10 years experience. Each regularly attends Australian and International meetings in pulmonary pathology, though none are specialist pulmonary pathologists or pulmonary cytopathologists. All are regularly involved in multidisciplinary lung cancer meetings at their institution.

All specimens were deidentified and reviewed in random order. Smear, H&E, and immunohistochemical specimens were reviewed without reference to other specimen types obtained from the same patient. Previously described cytologic criteria were used for the diagnosis of each tumour subtype.[912, 913]

Diagnoses were recorded on a specifically designed pro-forma, first utilized by Burnett et al.[764] and outlined in the IASLC/ATS/ERS guidelines for classification of NSCLC in small biopsy/cytology specimens.[51] Pathologists were also asked to record on the form whether they were confident, or had some doubt regarding the diagnosis. Final diagnoses were classified as one of:

- NSCLC
- adenocarcinoma
- Squamous cell carcinoma (SCC)
- Not otherwise specified (NOS)
- Small cell lung carcinoma (SCLC)

Diagnoses of large cell carcinoma have been included in the ‘Not Otherwise Specified’ (NOS) category. In a 2010 review, Travis et al noted that NSCLC-NOS is a more appropriate term than ‘large cell carcinoma’ in small biopsy specimens, though recognized that the terms are frequently used interchangeably.[914]
Evaluation of agreement using Kappa statistics does not require any assumption about the "correct" diagnosis, therefore no separate confirmation of diagnoses determined by EBUS-TBNA was sought.

6.3.2.5 **Statistical methods.**
Summary statistics were used to describe patient groups. Kappa (κ) statistics were used to calculate inter-observer agreement. Degree of agreement was determined according to the widely used scale first described by Landis & Koch.[915] Categorical data was analyzed using a two-sided Fisher’s exact test. A p-value of 0.05 was considered significant. Statistical analysis was performed using GraphPad Instat 3 for Macintosh (GraphPad Software, La Jolla, CA. USA).

6.3.3 **RESULTS**
Sixty consecutive patients undergoing EBUS for evaluation of suspected/known primary lung cancer were identified. H&E specimens were available for all 60 patients, with matched ‘smear’ and IHC specimens available in 49 and 36 patients, respectively. Kappa scores for each specimen type are summarized in Table 6.4.

6.3.3.1 **Cytology smears**
All three pathologists gave concordant diagnoses after examination of smear specimens in 19 of 49 cases (39%). Substantial agreement was seen in differentiation of SCLC from NSCLC (κ = 0.701, 95%CI 0.420 – 0.982). Only slight agreement in determining NSCLC subtypes was seen (κ = 0.095, 95%CI -0.164 – 0.355).

All three pathologists expressed confidence in their diagnosis in 13 of 49 (27%) ‘smear’ specimens, with complete concordance in diagnosis seen in all 13 cases (κ = 1.0). In contrast, where at least one pathologist expressed doubt, concordance was seen in only 6 of 36 cases (17%). Agreement was reduced for this group of specimens,
with moderate agreement in differentiation of SCLC from NSCLC ($\kappa = 0.426$, 95%CI 0.097 – 0.948), and agreement in determination of NSCLC subtype less than that expected due to chance alone ($\kappa = -0.194$, 95%CI -0.418 – 0.030).

### 6.3.3.2 Haematoxylin & Eosin specimens

All three pathologists gave concordant diagnoses following examination of H&E specimens in 33 of 60 cases (55%). In 23 cases, agreement was seen between 2 of three pathologists, while in 4 cases of NSCLC, different subtypes were reported by each pathologist for the specimens studied (see Figure 6.5). Final diagnoses for specimens where at least 2 of 3 pathologists concurred are recorded in table 6.5.

Almost perfect agreement was seen in differentiating SCLC from NSCLC ($\kappa = 0.814$, 95%CI 0.562 – 1.067). Fair agreement in determination of NSCLC subtype between the three pathologists was seen ($\kappa = 0.278$, 95%CI 0.075 – 0.481).

In 26 of 60 cases, all three pathologists expressed confidence in their diagnosis, with concordant diagnoses made in 21 of these 26 cases (81%). In contrast, where doubt was expressed by at least one pathologist, concordance was seen in only 11 of 34 cases (32%). The comparison was highly significant ($p=0.0002$). The two most frequent sources of doubt identified were the poor differentiation of the tumour, and a paucity of cells present for pathologic examination.

Inter-observer agreement for the subtyping of NSCLC was almost perfect when all three pathologists reported confidence in their results ($\kappa = 0.881$, 95%CI 0.655 – 1.0). In contrast, only slight agreement was observed when at least one pathologist expressed doubt regarding their diagnosis ($\kappa = 0.143$, 95% CI -0.119 – 0.405).

### 6.3.3.3 Immunohistochemistry

Complete agreement in differentiating SCLC from NSCLC following immunohistochemical analysis was observed following examination of IHC specimens. Overall agreement for determination of NSCLC subtype was moderate ($\kappa = 0.564$, 95%CI 0.338 – 0.740).
**Table 6.4:** Interobserver agreement for each specimen type. Overall agreement is recorded, as well as agreement according to the degree of confidence expressed by the pathologists in their diagnosis.

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>Inter-observer agreement</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kappa (95% CI)</td>
<td>All pathologists confident</td>
<td>Doubt</td>
</tr>
<tr>
<td><strong>Smear</strong></td>
<td>0.095</td>
<td>1.0 (1.0 – 1.0)</td>
<td>0.194 (-0.418 – 0.030)</td>
</tr>
<tr>
<td></td>
<td>(-0.164 – 0.355)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Haematoxylin &amp; Eosin</strong></td>
<td>0.278</td>
<td>0.881 (0.655 – 1.0)</td>
<td>0.143 (-0.119 – 0.405)</td>
</tr>
<tr>
<td></td>
<td>(0.075 – 0.481)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immunohistochemistry</strong></td>
<td>0.564</td>
<td>1.0 (1.0 – 1.0)</td>
<td>0.330 (-0.015 – 0.675)</td>
</tr>
<tr>
<td></td>
<td>(0.338 – 0.740)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 6.5:** Final diagnoses in 56 of 60 NSCLC specimens examined. In four cases of NSCLC each pathologist reported a different histologic subtype as their final diagnosis.

<table>
<thead>
<tr>
<th>Diagnoses where agreement between three pathologists seen (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
</tr>
<tr>
<td>adenocarcinoma</td>
</tr>
<tr>
<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>SCLC</td>
</tr>
<tr>
<td>Carcinoid</td>
</tr>
<tr>
<td>Benign</td>
</tr>
</tbody>
</table>

| 25 | 14 | 11 | 6 | 1 | 1 |

<table>
<thead>
<tr>
<th>Diagnoses where 2 of 3 pathologists concurred (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
</tr>
<tr>
<td>adenocarcinoma</td>
</tr>
<tr>
<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>NOS</td>
</tr>
<tr>
<td>Small cell lung carcinoma</td>
</tr>
</tbody>
</table>

| 22 | 11 | 8 | 3 | 1 |
Al three pathologists expressed confidence in their diagnosis following examination of IHC specimens in 19 of 36 cases (53%), with complete concordance of diagnosis seen between all three pathologists for these 19 cases (κ = 1.0, 95%CI 1.0 – 1.0). In contrast, in the 17 cases where at least one pathologist expressed ‘doubt’ regarding the final diagnosis, concordance was seen in only 9 (53%), with the difference in concordance rates being highly significant (p=0.0008). Doubt was expressed by a pathologist for a total of 33 specimens out of 108 IHC examinations undertaken. Specific sources of doubt were recorded for 20 of these, the commonest (14) being an inadequate panel of IHC stains performed to fully characterize the NSCLC subtype.

Diagnoses recorded for IHC were discordant with H&E diagnoses for the same pathologist in 5, 6, and 11 cases for individual pathologists. The most frequent revision of diagnosis was from SCC on H&E to adenocarcinoma after IHC analysis (7 cases, of 22 overall discordant cases) (see figure 6.6). IHC specimens were available for 20 of 34 cases (58%) for which ‘doubt’ regarding NSCLC subtype was expressed by the pathologist following examination of H&E specimens. Use of IHC resulted in confident diagnoses being made by all three pathologists in 10 of the 20 specimens (50%). Agreement for specimens where at least one pathologist expressed ‘doubt’ following examination of H&E specimens was significantly improved with use of IHC (from κ = 0.143, 95%CI -0.119 – 0.405, to κ = 0.494, 95% CI 0.118 – 0.871).

IHC specimens were available for 14 of 24 (58%) where all three pathologists were ‘confident’ of their H&E diagnosis. No pathologists altered a diagnosis of SCLC made on five H&E specimens. Despite confidence in their H&E diagnosis, at least one pathologist altered their final NSCLC subtype diagnosis following IHC analysis in 3 of 9 cases (33%, 95%CI 12 – 65%).

Inter-observer agreement varied when H&E diagnoses for NSCLC specimens were compared to IHC diagnoses made by the same pathologist. One pathologist demonstrated complete concordance between H&E and ‘paired’ IHC specimen diagnoses; one pathologist altered their H&E following review of IHC specimens in one case (κ = 0.609, 95%CI -0.114 – 1.332), and one altered their diagnosis in 3 cases (κ = 0.308, 95%CI -0.332 – 0.947)
**Figure 6.5:** Demonstrates a smear specimen where each pathologist identified a different NSCLC subtype. Pathologist interpretation of the papanicolau-stained specimen (x400) included:

"a reasonably cohesive group of malignant cells with possible papillary structures and mildly pleomorphic eccentric nuclei, some with prominent nucleoli, suspicious for adenocarcinoma."

"spindling of the tumour cells with streaming within the groups as well as dense keratin-like material in the background indicative of squamous cell carcinoma."

and

"cellular sheets with homogeneous non-orangophilic cytoplasm, and oval to elongated nuclei with hyperchromasia and some nucleoli, consistent with NSCLC-NOS."

**Figure 6.6:** Cytology smear specimens stained by Papanicolau staining showing (1a) Necrotic tumour cells (x200) mimicking keratinised squamous cells with shrunken dark nuclei and orangeophilic cytoplasm, and (1b) Tumour cells (x400) appearing squamoid in appearance with dense cytoplasm and irregular hyperchromatic nuclei. IHC of corresponding cell block specimen demonstrates TTF-1 positivity (1c). Cells were also CK7 positive but CK5/6 and p63 negative. Final diagnosis for this patient was adenocarcinoma.
6.3.4 DISCUSSION

The distinction between NSCLC subtypes is becoming increasingly important in determining optimal treatment. This is due to recent studies that have shown either increased efficacy or toxicity of chemotherapeutic [60, 761, 762] and biologic [59, 668] agents in particular histologies, and the association of molecular abnormalities such as EGFR and EML4-ALK gene abnormalities with adenocarcinoma histology.[192, 763] For this reason, an understanding of the reliability of NSCLC subtype as determined by EBUS-TBNA is critical to guide future clinical decision-making in patients in whom the only diagnostic tissue has been obtained by EBUS-TBNA. To our knowledge, no studies have previously examined inter-observer agreement in interpretation of NSCLC obtained by EBUS-TBNA.

Our findings indicate that there is very high inter-observer agreement between pathologists in distinguishing between NSCLC and SCLC (κ=0.814, 95% CI 0.562–1.067). However, agreement is lower for determination of NSCLC subtype. The agreement seen for both determination of NSCLC subtype (κ=0.278, 95% CI 0.075–0.481) and distinction of SCLC from NSCLC is consistent with agreement previously reported for bronchial biopsy specimens.[56, 764, 916]

Two factors appear to improve inter-observer agreement. Firstly, pathologist confidence in their diagnosis appears to be associated with improved inter-observer agreement. Concordance in final diagnosis was significantly higher among the three pathologists when all were ‘confident’ of their diagnosis, (H&E p=0.0002, IHC p=0.0004). Inter-observer agreement was also higher when all three were ‘confident’ in their diagnosis (κ=0.881 v. κ=0.143). Secondly, IHC appears to increase pathologist confidence in their diagnosis. In 20 cases where previously on H&E examination at least one pathologist had expressed ‘doubt’, IHC allowed all three pathologists to be ‘confident’ in their diagnosis in 10 of these cases (50%). This in turn improved inter-observer agreement for these specimens (κ=0.494 v. κ=0.143).

The diagnosis NSCLC-NOS has been used to convey the difficulty in confidently determining the NSCLC subtype. The proportion of “NOS” as the histologic
diagnosis in NSCLC has increased over time which may be due to increasing use of minimally invasive means to achieve diagnosis.[57] Small volume specimens may be paucicellular or have an absence of tissue architecture, making identification of tumour subtype more difficult.[917] Use of IHC stains may potentially overcome this by identifying differentiation (eg. squamous or glandular differentiation) and by more accurately characterizing the differentiation of the limited cellular material present.

Consistent with our findings, previous studies have noted a decreased proportion of NSCLC-NOS diagnoses made on small volume samples with use of IHC studies,[918] indicating improved ability to subtype NSCLC specimens as a result of IHC. Despite this, there are still a number of patients where confident diagnoses could not be made. This may reflect poor differentiation of underlying tumour rather than the limitations of EBUS-TBNA as inter-observer agreement has previously been reported to be lower in poorly differentiated tumours.[919]

Our results highlight the importance of use of the NSCLC-NOS diagnosis to accurately convey pathologist doubt regarding the NSCLC subtype. Our results strongly suggest that ‘doubt’ in the subtype diagnosis is associated with a low inter-observer agreement and, by inference, the accuracy of NSCLC subtyping is likely to be low. For this reason, inclusion of a measure of pathologist confidence within the diagnostic report may be of value to clinicians. Our results also support performance of the minimum IHC panel of stains (when possible), as recommended by the IASLC/ATS/ERS guidelines to maximize the likelihood of a ‘confident’ diagnosis.[51]

Original reports confirming the excellent diagnostic accuracy of EBUS-TBNA in evaluation of the mediastinum did not compare NSCLC subtype diagnoses to those obtained at surgical resection.[34, 698, 699] Therefore while diagnostic accuracy of EBUS-TBNA for detection of NSCLC matches,[717] or even exceeds,[716] that of mediastinoscopy, the accuracy in determination of NSCLC subtype remains unclear. One study examined accuracy of EBUS-TBNA in subtype determination in 23 specimens (retrospectively selected from over 1,800 EBUS-TBNA procedures performed).[920] However, in 19 of these comparison was made solely with other small volume biopsies (eg. transbronchial biopsy or CT-guided FNA). Diagnostic
accuracy in interpretation of small volume specimens obtained at routine bronchoscopy has previously been suggested to be as low as 50% for identification of NSCLC subtype.[56] making use of these as ‘gold standard’ measures highly problematic. Furthermore, the authors have not examined interobserver variability in discordant diagnoses, which we have demonstrated to be significant for EBUS-TBNA specimens. Of note, consistent with our findings, the study reported that accuracy was improved with examination of H&E slides, and improved further with use of IHC.[920]

A more recent study examined the accuracy of fine needle aspirate cytology (FNAC) specimens in differentiating squamous from non-squamous NSCLC.[921] The authors retrospectively reviewed 474 patients who had NSCLC diagnosed by FNAC and identified 186 who had tissue retrieved by other means and noted good agreement between cytologic and histologic diagnoses \((\kappa = 0.755)\). The study did not use IHC to achieve cytologic diagnosis nor did the authors examine interobserver variability in cytologic diagnosis, which our study suggests may be significant, and for 60% of patients only endobronchial biopsies were available as the reference test. Given the significant inter-observer variability [764] and limited diagnostic accuracy [56] for such specimens, the clinical utility of these findings is uncertain.

Given the poor inter-observer variability, our results suggest that subtype-specific therapies should not be based on ‘smear’ diagnosis alone unless the classic cytologic features of squamous cell carcinoma, adenocarcinoma or small cell carcinoma are present. If a confident diagnosis of a NSCLC subtype cannot be made on examination of “smears” alone, examination of a H&E specimen coupled with use of the minimum panel of IHC as recommended by the IASLC/ATS/ERS guidelines [51] is suggested. Prior to commencement of subtype-specific therapies, review of such specimens in a multidisciplinary setting may inform clinicians of the level of confidence a pathologist has in a particular diagnosis and the manner in which the diagnosis was made eg. examination of smears alone versus use of IHC panel.
6.3.4.1 **Limitations**

Pathologists involved in the study were experienced, but not expert pulmonary pathologists. Inter-observer agreement and ‘confidence’ may differ based on the experience of reporting pathologists. While agreement may higher between experienced pulmonary pathologists, inter-observer agreement noted in this study is comparable to that reported by Burnett and co-workers among pathologists not experienced in evaluation of lung pathology.[764] This suggests our findings may accurately represent clinical practice in the majority of centres worldwide where anatomical pathologists report of EBUS-TBNA specimens rather than specialist pulmonary pathologists.

We have not attempted to examine the accuracy of EBUS-TBNA. While histologic specimens would constitute the ‘gold standard’, the intrinsic heterogeneity of NSCLC [51] means that even surgically resected specimens are subject to less than perfect inter-observer agreement.[765, 922] The fact that EBUS-TBNA demonstrated NSCLC in these patients means that further biopsy was clinically unnecessary. Prior biopsy specimens, if present, would also mostly be small volume specimens (eg. TBLB), where poor accuracy has previously been reported.[56] Any retrospective analysis comparing EBUS-TBNA diagnosis with surgical diagnosis will have several inherent biases as only a select minority of patients will have surgical tissue available. The question of accuracy is answerable only through a prospective study.

Furthermore, previous studies have suggested that no more than 30% of lung carcinomas are of a single cell type.[923] Heterogeneity may mean that discrepant diagnoses in some cases are likely. Therefore the optimal assessment of accuracy may in fact be consensus among multiple pathologists. While some experts have suggested that cytology ‘smears’ may provide greater nuclear and cytoplasmic resolution than histology,[917] our results suggest that this is most likely to be achieved through H&E examination and use of IHC staining, rather than simply relying on a ‘smear’ diagnosis.

A standardized panel of immunohistochemical markers was not used. Use of IHC markers was at the discretion of the pathologist at the time the biopsy was performed.
Forty percent of samples were not analysed immunohistochemically. The reason some specimens were not subject to IHC analysis remains unknown, and it is unknown if this would alter the recorded inter-observer agreement. However, improvement in agreement is clearly demonstrated through use of IHC and we believe the absence of IHC analysis for a minority of specimens does not significantly alter the findings of the study. IHC analysis of Papanicolaou-stained smear specimens is possible,[924] though is less reliable for examination of Diff-Quik prepared smears.[925] The inter-observer variability in reporting of such specimens remains unknown.[925]

6.3.5 CONCLUSIONS

In summary, our findings confirm very high agreement between pathologists of differentiation of SCLC from NSCLC in specimens obtained by EBUS-TBNA. We also confirm only slight inter-observer agreement in determination of NSCLC subtype based on cytology smear specimens, and fair agreement following examination of H&E specimens obtained by EBUS-TBNA. Agreement in NSCLC subtyping is improved when pathologists feel confident in their diagnosis, and both confidence and inter-observer agreement may be improved with use of IHC.

Our results highlight the value of IHC analysis of low volume specimens to confirm histologic subtyping in patients prior to commencement of therapy with divergent clinical outcomes based on tissue subtypes. Finally, it is important that clinicians are aware of the degree of pathologist confidence in the tissue diagnosis prior to commencement of subtype-specific therapy for NSCLC. Inclusion of a measure of pathologist confidence within reports may be of value to treating clinicians.
CHAPTER 7: Diagnostic and prognostic significance of sarcoidal reactions demonstrated by EBUS-TBNA in regional lymph nodes of patients with non-small cell lung cancer

7.1 BACKGROUND

Sarcoidosis is a systemic granulomatous disease of undetermined aetiology. The ATS/ERS/WASOG statement on sarcoidosis describes it as a diagnosis of exclusion best supported by the following three elements: i) compatible clinical and radiologic findings; ii) tissue biopsy specimen that reveals non-caseating epithelioid granulomas; and iii) the absence of known granulomagenic agents.[926]

Studies had demonstrated the ability of EBUS-TBNA to demonstrate epithelioid granulomas, thereby confirming the diagnosis of sarcoidosis in patients with clinical suspicion of systemic sarcoidosis. However, preliminary experience with EBUS-TBNA in staging of NSCLC had also demonstrated epithelioid granulomas. Malignancy was first recognized to be ‘granulomagenic’ a century ago,[927] and sarcoidal reactions most commonly affect lymph nodes draining cancers. Their significance remains unclear, though their presence does predict a better outcome in haematologic malignancy.[770] They may also occur in a ‘peri-tumoural’ distribution and consequently, the negative predictive value (NPV) of sarcoidal reactions in regional lymph nodes of NSCLC patients was unknown. That is, if sarcoidal reactions are present, can mediastinal lymph node metastases be reliably excluded. Given the very small volume of lymph node sampled by EBUS-TBNA this was a critical question to answer. Not only was their NPV unknown, their incidence and their clinical significance in lung cancer had never been described.
7.2 SARCOIDAL REACTIONS IN REGIONAL LYMPH NODES OF PATIENTS WITH NON-SMALL CELL LUNG CANCER: INCIDENCE AND IMPLICATIONS FOR MINIMALLY INVASIVE STAGING WITH ENDOBRONCHIAL ULTRASOUND

7.2.1 INTRODUCTION

Accurate pre-treatment staging is crucial to direct appropriate management of patients with non-small cell lung carcinoma (NSCLC). The absence of metastatic involvement of mediastinal lymph nodes indicates a better prognosis and such patients are optimally managed with curative resection. Conversely, current management guidelines indicate that optimal management of patients with mediastinal involvement does not include surgery and such patients may be managed with induction therapy or with combination chemoradiotherapy.[509] Minimally invasive mediastinal lymph node staging may be performed using EBUS-TBNA.[703] It has a very high sensitivity and specificity, and recent reports indicate it is equivalent to mediastinoscopy in evaluation anterior paratracheal lymph nodes, and superior in evaluation of the sub-carinal and posterior tracheal regions.[716]

Our multidisciplinary lung cancer service routinely uses EBUS-TBNA for minimally invasive staging of NSCLC. We recently experienced one patient in whom fluorodeoxyglucose positron emission tomography (FDG-PET) suggested the presence of hilar and mediastinal lymph node metastases but in whom specimens obtained at EBUS-TBNA demonstrated non-necrotising granulomas. Mediastinal resection at the time of curative lobectomy confirmed the presence of sarcoidal granulomas and, importantly, the absence of lymph node metastases.

In addition to staging the mediastinum in the setting of proven intrapulmonary NSCLC, EBUS-TBNA is able to demonstrate the presence of benign granulomatous disease, such as sarcoidosis.[766, 767, 928] Both sarcoidosis as well as localized
sarcoidal reactions are recognised to occur in the setting of malignancy,[768] and thus the negative predictive value of pre-operatively identified granulomatous reactions, obtained by minimally invasive EBUS-TBNA, is unclear. This will depend on the pre-test probability of such reactions in NSCLC and, most importantly, the frequency of co-involvement of the two diseases. In this paper we describe the frequency of sarcoidal reactions in patients undergoing evaluation of, or surgical resection for, NSCLC. We also report on the frequency of co-involvement of sarcoidal reactions with metastatic NSCLC in regional lymph nodes in order to allow clearer conclusions to be drawn about patients in whom sarcoidal granulomas are detected on specimens obtained via EBUS-TBNA during pre-operative staging for NSCLC.

7.2.2 METHODS

Institutional review board approval was granted for the performance of this study. We examined a prospectively collected cohort of consecutive patients undergoing EBUS-TBNA for staging of suspected or confirmed NSCLC. Only those clinically staged as N2 or N3, by CT chest or FDG-PET, underwent EBUS-TBNA. EBUS-TBNA was performed using a dedicated linear array videobronchoscope (BF-UC180F-OL8, Olympus, Tokyo, Japan) under conscious sedation. Lymph nodes of interest were visualised using EBUS prior to real-time TBNA using a 22-gauge needle. On-site cytological evaluation was utilised, with confirmation of the presence of diagnostic malignant material leading to cessation of the procedure. In the absence of such confirmation, a maximum of 3 needle passes was made at any single nodal station.

We also performed a retrospective audit of all patients undergoing surgical treatment for lung cancer, or staging with mediastinoscopy for NSCLC between July 1st 2003 & August 31st 2008. Chart review was undertaken to identify demographic characteristics of patients, as well as details regarding their malignancy, including surgical procedure undertaken, histological sub-type and final pathological staging of the malignancy. Staging was performed according to the TNM staging system (sixth edition)[929] with pre-operative staging for all patients including imaging with FDG-PET.
Patient histories for those in whom sarcoidal reactions were noted were reviewed to ascertain any past history of sarcoidosis, or other granulomatous diseases (eg. tuberculosis, leprosy, pneumoconiosis) and ancillary tests such as serum ACE and gallium scanning. The pattern of sarcoidal involvement was recorded according to site (ie. primary tumour or lymph nodes) and specific lymph node stations involved. Lymph node stations were classified according to the system described by Mountain & Dressler.[868]

7.2.2.1 Statistics
Analysis of categorical data was performed using a two-sided Fisher’s exact test, and analysis of means between groups was performed using the Mann-Whitney test. Calculations were made by GraphPad Instat 3 for Macintosh (GraphPad Software, La Jolla, CA. USA).

7.2.3 RESULTS

Fifty patients underwent EBUS-TBNA for staging of suspected or confirmed lung cancer. Only one patient had non-necrotising granulomas identified. Two patients had inadequate specimens, two patients had normal lymphoid tissue identified, with the remaining 45 demonstrating NSCLC (39 patients) or small cell lung cancer (6 patients). Findings were confirmed surgically by lymph node dissection in the two patients in whom EBUS-TBNA revealed normal lymphoid tissue, and in the patient in whom EBUS-TBNA demonstrated non-necrotising granulomas.

We identified 187 patients who underwent surgical assessment or management for NSCLC. No patients had received pre-operative chemotherapy or radiotherapy. Seventeen underwent staging mediastinoscopy, 151 underwent lobectomy and 19 underwent pneumonectomy. A mean 3.1 lymph node stations were dissected at surgery.
The mean age of these patients was 66, with 71% male. Histologic and staging information is recorded in table 7.1.

Sarcoidal reactions were seen in regional lymph nodes of eight (4.3%) of patients. None of these patients had a prior history of sarcoidosis or other granulomatous diseases. None of the eight patients with granulomatous reactions in regional lymph nodes had cancer in these or any surrounding lymph nodes.

The incidence of sarcoidal reactions did not appear to differ according to size of primary tumour, the histological type or the age of the patient. However, all eight sarcoidal reactions occurred in patients with stage I disease (IA – 6, IB – 4), with an incidence in this group of 7.7%. This distribution was statistically significant (Stage I v Stages II-IV, p=0.02).

Of the eight patients with sarcoidal nodal reactions, four were staged N0 following FDG-PET. Two patients demonstrated low-grade mediastinal FDG-avidity demonstrated in a classic sarcoid “lambda” pattern, with one of these patients staged N0 by CT size criteria. Of the remaining two patients, one demonstrated high grade hilar FDG avidity, with low-grade symmetrical mediastinal and pulmonary apical uptake and the other demonstrated focal high intensity FDG-avidity in the subcarinal region, and low-grade avidity in bilateral hila (Figure 7.1). No patients exhibited any extrathoracic FDG-avid lesions on PET scanning.

Median time since surgery for the eight patients with sarcoidal granulomas in mediastinal lymph nodes is 36±18 months (range 13 – 62). All patients remain alive and have no evidence of recurrent malignancy or granulomatous disease.
<table>
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<tr>
<th>Histological sub-types</th>
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<tr>
<td>Sarcomatoid carcinoma</td>
<td>IV* - 3</td>
</tr>
<tr>
<td>Small Cell Lung Carcinoma</td>
<td>Limited (small cell) - 6</td>
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</tbody>
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²NSCLC = Non-small cell lung carcinoma

⁴Staging performed according to Mountain & Dressler classification, 6th edition[929]

*all patients had solitary cerebral metastases

**Figure 7.1:** Staging FDG-PET from NSCLC patient demonstrating high uptake in large peripheral right tumour and high uptake in the subcarinal region (white arrowhead), as well as low-grade uptake in bilateral hilar regions (black arrow). Mediastinal dissection demonstrated widespread sarcoïdial reactions in all node stations sampled, including subcarinal station.
This study demonstrates that granulomatous inflammation may be seen in patients with lung malignancy and appears to occur only in early stage disease. The overall incidence of sarcoidal reactions occurring in regional lymph nodes of NSCLC patients was 4.3%. However, such findings were confined to patients with Stage I disease, with an incidence in this group of 7.7%. None of 76 patients with Stage II-IV disease demonstrated sarcoidal reactions in regional lymph nodes (p=0.02). Most importantly, we did not identify any patients in whom sarcoidal granulomas occurred together with malignant disease in the same or surrounding lymph nodes.

This is the highest reported rate of nodal sarcoidal reactions in the setting of lung cancer we have identified in the literature. Two Japanese studies have noted incidence rates of 1.2% and 1.3% in the setting of NSCLC.[930, 931] Incidence of sarcoidosis in Japan is much lower than many other ethnicities which may explain the higher incidence of sarcoidal reactions among our cohort.[932] In 1975 Laurberg reported an incidence of 3.2% among 734 Danish patients with lung malignancy,[933] noting, as have we, that sarcoidal reactions were seen only in patients with stage I disease. Other authors have also noted a significantly increased incidence in Stage I disease,[930, 931] though very rare occurrence in stage II and III disease has been reported.[930, 931]

Consensus statements on Sarcoidosis note it to be a multisystem disease, and stipulate that granulomas of known causes and local sarcoid reactions must be excluded.[902] Potential stimuli are likely to be multiple,[934] resulting in a heterogeneous clinical picture,[935] and malignancy may be one such stimulus.[936] Conversely, sarcoidal reactions may occur locally,[937] with a different underlying pathogenesis – the granulomas of sarcoidal reactions have been noted to differ both morphologically and immunologically from those in sarcoidosis.[938]

The relationship between sarcoidosis and malignancy has been debated by many authors. An increased incidence of sarcoidal reactions in lung cancers and other malignancies has been recognized,[939, 940] as has the development of sarcoidal
reactions [941] and sarcoidosis following treatment for malignancy.[941, 942] Whilst earlier reports indicated increased rates of cancer among sarcoidosis patients,[943, 944] recent studies have suggested this may be due to misclassification demonstrating no increased incidence of cancer.[943, 945-947]

As our patients do not show evidence of systemic involvement, and given a likely cause for sarcoidal reactions is present (NSCLC), we do not identify any of our patients as having sarcoidosis. Furthermore, sarcoidosis seems unlikely to be responsible for observations in our cohort given the very high incidence rate, in comparison to a general population incidence in Australia of 3.41 to 6.34 per 100,000.[948]

Interaction with the tumour seems the likely aetiology of sarcoidal reactions in our patients. Though other authors have noted, as we have, no association with histological subtype,[930, 931] Laurberg noted a preponderance of squamous cell tumours and postulated that the slower growth and higher tendency to necrosis of this tumour type may result in a more vigorous and longer-lasting stimulation of the regional lymph nodes.[933] Sarcoidal reactions arising due to such stimulation may even be associated with a good prognosis due to the anti-tumour effect of such immune activity.[770, 931, 949] Certainly, post-operative survival, according to disease stage, in NSCLC is not adversely affected by the presence of sarcoidal reactions, and in early stage disease, a trend (p=0.07) towards improved survival has been noted.[930] Our findings are consistent with this theory, with all patients with sarcoidal reactions having pN0 status (p=0.02).

Of crucial value to the interpretation of granulomatous histology demonstrated by EBUS-TBNA is our finding of no episodes of co-involvement of metastatic disease with sarcoidal reactions, and most authors have reported similar findings.[931, 933, 949] Only Tomimaru et al have described micrometastases in 4 of 22 patients with NSCLC who had sarcoideal histology demonstrated on post-operative mediastinal lymph node specimens.[930]

The prognostic significance of micrometastases is uncertain, however Marchevsky et al reported identical survival between NSCLC patients staged pN0 and those
demonstrating micrometastases in N1 nodal stations.[547] The presence of micrometastatic mediastinal lymph node disease in patients staged cN0 predicts a prognosis more similar to pN0 rather than pN2,[950] with reported 5 year reported survivals of up to 67%;[575, 576] identical to survival reported for cN2 pN0 NSCLC patients.[951]

Interestingly, we observed a lower frequency of sarcoidal reactions (2%) among patients undergoing EBUS-TBNA than might be expected on the basis of our reported 4.3% prevalence in post-surgical specimens. However, of the 48 patients in whom EBUS-TBNA returned adequate tissue specimens, 45 demonstrated metastatic lymph node involvement. Our results, and those of others,[931, 933, 949] indicate sarcoidal reactions should not be seen in patients with metastatic involvement of lymph nodes. Therefore, the granulomatous reactions were seen in one of the three patients in whom mediastinoscopy did not demonstrate malignant involvement of lymph nodes.

Furthermore, invasive staging of mediastinal lesions is prompted by the outcome of non-invasive staging tests, such lymph node size on CT chest, or FDG-avidity seen on PET scanning.[30] Terstein et al reported positive FDG-PET findings in just 5 of 29 patients (17%) with Scadding Stage 0 and 1 sarcoidosis.[952] Consistent with this, 50% of patients in our cohort demonstrating mediastinal lymph node granulomas were staged by non-invasive means, including FDG-PET, as cN0. Under current guidelines,[520] such patients would not be referred for pre-surgical staging and consequently those with Stage 0, or Stage I with low-grade FDG-avidity, are under-represented in patients referred for EBUS-TBNA.

Therefore, we do not identify any evidence that would argue against recommending patients with NSCLC and sarcoidal reactions demonstrated on EBUS-TBNA for surgical management. Consistent with our conclusion, such findings have previously been reported in patients with prior histories of non-pulmonary malignancy, and suspected mediastinal cancer recurrence. Average follow-up of 10 months in eight patients in whom EBUS-TBNA revealed granulomatous inflammation demonstrated clinical stability,[941] indicating such findings are very likely to be a true negative finding for the absence of malignant lymph node involvement.
7.2.4.1 Limitations

Our post-surgical cohort was performed as a retrospective chart review. Pathologists may not have reported granulomas, instead focusing on the clinically important question regarding the presence or absence of metastatic disease. However, we feel this is unlikely as reports are descriptive and inclusive, with “normal nodal tissue seen” reported in association with negative nodal findings, and comments regarding the degree of invasion in the presence of lymph node metastases.

All patients with sarcoidal reactions had Stage I disease confirmed surgically, however systematic nodal clearance was not performed routinely in all patients. While not all nodes were cleared we feel this does not detract from the absence of co-involvement of sarcoidal reactions with metastatic disease in resected lymph nodes noted among our patients.

Our observations do not allow improved understanding of why sarcoidal reactions in NSCLC are associated with early stage disease. We suspect such reactions are effective cell-mediated anti-tumour immune responses which occur in a small proportion of patients in early phases of the establishment of metastases. Immune down-regulation following tumour invasion of lymph nodes is well recognized [953, 954] and it is possible that changes in tumour behaviour result in improved immune evasion, with subsequent loss of stimulus and, therefore, regression of sarcoidal granulomas. We feel the mechanisms of granuloma formation in such patients is an important area of future research may allow improved understanding of effective anti-tumour responses.

Sarcoidal granulomatous histology may also be seen with numerous other diseases. Degree of suspicion of diseases such as tuberculosis, Mycobacterium Avuim Complex, or histoplasmosis as the cause of granulomatous histology will need to be based on clinical likelihood of such a condition. If pre-test suspicion exists, specimens should be sent for dedicated microbiological analysis in addition to routine cytology and pathology. In patients with low pre-test probability of such alternate diagnoses, and in the absence of diagnostic microbiological specimens, we feel a finding of non-
necrotizing granulomas should be sufficiently reassuring to allow referral for surgical management.

7.2.5 CONCLUSIONS

Sarcoidal reactions in regional lymph nodes may be seen in lung cancer, and appear to be limited to early stage malignancies. A significant proportion of these are radiologically and metabolically occult. On the basis of our results, it appears that metastatic involvement by NSCLC is not seen in lymph nodes exhibiting sarcoidal granulomatous reactions. Therefore, a finding of non-necrotising granulomas on EBUS-TBNA of intrathoracic lymph nodes in the setting of known lung cancer is reliable and should serve to indicate the absence of lymph node metastases.
SARCOIDAL REACTIONS IN REGIONAL LYMPH NODES OF EARLY STAGE NON-SMALL CELL LUNG CARCINOMA PATIENTS PREDICT IMPROVED DISEASE-FREE SURVIVAL: A PILOT CASE-CONTROL STUDY

7.3.1 INTRODUCTION

Localized sarcoidal reactions have been noted in numerous malignancies, including lymphoma, gastric carcinoma and breast carcinoma,[770, 955-957] both in the primary tumour and in regional lymph nodes. We have previously noted that such reactions may also occur in non-small cell lung cancer (NSCLC).[771] The pathogenesis of such reactions is poorly understood, though formation of non-necrotising epithelioid granulomas appears to occur at sites of antigen presentation,[769] suggesting they represent a cell-mediated anti-tumour response. That such immune responses may be effective anti-tumour mechanisms is supported by the observation that sarcoidal reactions predict improved prognosis in Hodgkin’s Lymphoma.2

We have reported that sarcoidal reactions appear to be isolated to patients with stage I NSCLC,[771] and we postulated such histologic evidence of anti-tumour immunity may predict improved survival following surgical resection of such tumours. As sarcoidal reactions are relatively uncommon, we performed a case-control study to evaluate the association between these reactions and disease-free survival.

7.3.2 PATIENTS AND METHODS

Institutional review board approval was granted for the performance of this study. All patients undergoing surgical lobectomy and lymph node dissection at Royal Melbourne Hospital between July 1st 2003 and June 30th 2009 were identified.
following a retrospective review of hospital records. Patients undergoing sub-lobar resection or pneumonectomy were excluded due to the higher risk of disease recurrence associated with these procedures.[54, 213, 540, 958-960] A case-control chart review was undertaken to identify demographic characteristics of patients within this cohort, as well as details regarding their malignancy, including surgical procedure undertaken, histological sub-type and final pathological staging of the malignancy. Staging was performed according to the TNM classification of the International Association for the Study of Lung Cancer staging project (seventh edition),[28] with pre-operative staging for all patients including imaging with fluorodeoxyglucose Positron Emission tomography (FDG-PET).

Patients were excluded from the cohort if mediastinal sampling had not been performed, as true N-status could not be ascertained, or if they had undergone sub-lobar resection. Eligible cases were then identified following review of pathologic reports from the time of surgical resection. Reports were examined to determine the presence or absence of sarcoidal reactions in both resected lymph nodes as well as resected lung tissue. Chart review of identified cases was performed to exclude the presence of clinical sarcoidosis. Controls drawn from the same cohort were frequency-matched (2:1) to identified cases on the basis of tumour T-stage and N-stage, gender, and age (± 5 years).

Pathologic review of cases was performed to confirm the presence of granulomas, and to evaluate their morphology and location within the lymph node. A granuloma is defined in this study as a discrete nodular aggregate of epithelioid histiocytes. Immunochemical staining with a pan-cytokeratin marker AE1/3 (Dako Corporation, Glostrup, Denmark) was performed to exclude the presence of micrometastatic disease. Given the recognized variation on survival of lung adenocarcinoma, based on histopathologic subtype,[51] all cases of adenocarcinoma were reviewed and subtyped.

### 7.3.2.1 Statistical analysis

Wilcoxon signed rank test for was used for comparison of continuous variables between case and control groups. Tests were two-sided, with p < 0.05 considered to
be significant. Disease-free survival was analysed using the Kaplan-Meier method and comparison between the two groups performed using the log-rank test. Calculations were performed by GraphPad Prism 4.03 (GraphPad Software, La Jolla, CA, USA).

7.3.3 RESULTS

170 patients underwent surgical resection of NSCLC during the specified time period. Nine patients had wedge resections performed, and four further patients did not have sampling of mediastinal lymph nodes performed and were excluded from the cohort. From the remaining 157 patients, eight had granulomatous inflammation identified during pathology examination of resected mediastinal lymph nodes (Figure 7.2a). Median lesion size in these eight patients was 30mm (range 13 – 60). Pathology reports revealed one patient had scattered peri-tumoural granulomas noted within the lobectomy specimen, but no other evidence of sarcoidal reactions. Another patient had focal areas of sarcoideal granulomas noted in the resected parenchyma. No patients had any clinicopathologic findings to suggest the presence of systemic sarcoidosis. Sixteen control patients, matched according to criteria described above, were selected from the remainder of the cohort. Selected demographic and clinical details of the two groups are recorded in Table 7.2.

All patients were confirmed pathologically to have an absence of metastatic involvement of mediastinal and hilar lymph nodes. No significant difference was noted between the two groups in age, gender proportion, T-stage, histological subtype or duration of post-operative follow-up.

Immunohistochemical analysis with a pan-cytokeratin marker demonstrated an absence of micrometastatic nodal disease in all patients. Pathologic review of primary tumour specimens in patients diagnosed with adenocarcinoma demonstrated that all had invasive non-mucinous adenocarcinoma, and none were of the lepidic-predominant sub-type. Pathologic review of resected lymph nodes confirmed the presence of well-formed non-necrotising granulomas in all cases. Granulomas were randomly distributed in central as well as peripheral regions of the lymph nodes. The
granulomas were often accompanied by florid sinus histiocytosis, with granulomas and sinus histiocytosis occupying at least 50% of the nodal parenchyma, and involving all the lymph node stations in a similar fashion, in most cases.

Features of sarcoidosis, such as a ring of fibrosis, or inclusions (eg. asteroid, Schaumann, Hamazaki-Wesenberg bodies, calcium oxalate crystals) were absent. No foreign bodies/material was seen, and Ziehl-Neelsen and Grocott stains indicate an absence of organisms. Scattered multinucleated non-Langhans’ giant cells were identified in most cases, though in much fewer numbers compared to those seen in mycobacterial infection.

Table 7.2: Demographic and clinical characteristics of study subjects

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<tr>
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<th>Cases (n=8)</th>
<th>Controls (n=16)</th>
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<td>Age (years)</td>
<td>65 (13)</td>
<td>62 (8)</td>
<td>0.641</td>
</tr>
<tr>
<td>Gender (F / M)</td>
<td>2 / 6</td>
<td>4 / 8</td>
<td>NS</td>
</tr>
<tr>
<td>Size (mm) (median (range))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T stagea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Histology:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>3</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>4</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>FEV1 (litres) (mean ± SD)</td>
<td>2.4 (0.7)</td>
<td>2.0 (0.4)</td>
<td>0.438</td>
</tr>
<tr>
<td># with disease recurrence</td>
<td>0 (0%)</td>
<td>7 (44%)</td>
<td></td>
</tr>
<tr>
<td>Median follow-upc (months) (mean ± SD)</td>
<td>42.5 (40 ± 21)</td>
<td>50 (45 ± 15)</td>
<td>0.469</td>
</tr>
</tbody>
</table>

a – T-stage according to TNM classification of the American Joint Committee for Cancer Staging and Revised International System for Staging Lung Cancer (seventh edition),

b – All patients were staged T3 on the basis of chest wall invasion.

c – patients without disease recurrence.
No disease recurrence was noted among identified cases. In contrast, confirmed disease recurrence occurred in seven (44%) control patients, at a median time of 11 months following surgery (range 7 – 45). Recurrence occurred in 3 (37%, 95%CI 13–69%) patients staged T1, 1 (25%, 95%CI 3–71%) patient staged T2 and 3 (75%, 95%CI 28–96%) patients staged T3. Figure 7.3 demonstrates Kaplan-Meier disease-free survival curves for the two groups. Difference in survival was statistically significant ($p=0.044$, $\chi^2=4.051$). As recurrence was noted in only 44% of control patients, median disease-free survival was unable to be calculated.
Figure 7.2: Histopathology images (original magnification x200) demonstrating the appearance of:
A) sarcoidal granulomas – epithelioid histiocytes are seen within the lymphoid tissue forming a tight granuloma (G), including multinucleate giant cells (arrows).
B) sinus histiocytosis – linear aggregates of histiocytes are seen within the lymph node sinuses (arrowheads) surrounding germinal centres (GC).

Figure 7.3: Kaplan-Meier curve illustrating disease-free recurrence (DFR) of patients with pN0 NSCLC. DFR was significantly lower in control subjects who did not have sarcoidal reactions present in regional lymph nodes ($p=0.044$, $\chi^2=4.051$).
7.3.4 DISCUSSION

Our observations indicate that in patients undergoing definitive surgical resection of early stage NSCLC the presence of sarcoidal reactions in regional lymph nodes may be associated with a reduced rate of disease recurrence, compared to those without this pathologic finding. This is the first published report describing such an association in NSCLC. Previous reports have noted improved prognosis in patients with sarcoidal reactions in Hodgkin’s Lymphoma.[770, 961] To our knowledge, only one study has examined prognostic significance of this phenomenon in other solid organ malignancies, noting sarcoidal reactions in regional lymph nodes of patients with gastric carcinoma had no influence on prognosis.[957]

The pathogenesis of tumour-related sarcoidal reactions is not well understood. Kurata et al suggested that sarcoid reactions represent a T-cell–mediated immune response. Epithelioid granulomas seen in sarcoidal reactions were notable for the presence of dendritic cells,[769] a cell type observed to polarize pathogenic Th1 T lymphocytes in lymph nodes of sarcoidosis patients.[962] As lymph nodes are sentinels for antitumor immunity, antigen presentation to T lymphocytes by dendritic cells is likely to occur at this site. Chronic antigen stimulation in such clinical settings is likely to result in T-lymphocyte stimulation of monocytes to form epithelioid granulomas.[963]

Our morphologic findings are similar to those of Kurata et al who compared the granulomas of sarcoidosis with tumour-related sarcoidal granulomas.[769] They noted occasional giant cells, and an absence of Schaumann bodies or intracellular calcifications. They also noted sarcoid reactions only in nonmetastatic nodes. They also noted occurrence of granulomas in all zones of the lymph node, though observed some cases where sarcoidal reactions were confined to just the T-zone. They concluded that tumour-related reactions may originate in T-zones, where antigen presentation takes place, and that reactions may then spread into the rest of the node. Our pathologic findings are consistent with this hypothesis.

While the effect of sarcoidal reactions on clinical outcome of NSCLC has not previously been described, other clinical studies have noted that anti-tumour immune
reactions may influence survival following surgical resection of NSCLC. Two studies have described improved survival in NSCLC patients in whom lymph nodes exhibited sinus histiocytosis (SH). SH is a histologic finding describing histiocytic (macrophage) infiltration of the marginal and medullary sinuses of lymph nodes (Figure 7.2b). Several authors have suggested that SH represents a tumour-host reaction, potentially of the delayed hypersensitivity type.

Kurata et al also demonstrated that tumour-related sarcoideal reactions begin within lymph node sinuses – where SH is seen – but that subsequent growth and progression of epithelioid giant cells (EGC) occurs within lymph node T-zones, where antigen presentation predominantly occurs. We postulate that SH and sarcoideal reactions are a continuum of anti-tumour cell-mediated immunity, with sarcoideal reactions indicating a more potent and sustained response when compared to SH. An improved DFS may then be potentially expected for patients with sarcoideal reactions, when compared to SH, though the infrequency of the event among our cohort precludes examination of this question and this remains to be studied in future research.

Several studies also illustrate the potential influence of immune activity on tumour progression. Inflammatory and cytokine gene signatures in non-cancerous lung tissue have been shown to influence prognosis of NSCLC or the likelihood of regional lymph node metastases. Similarly, density of tumour-infiltrating lymphocytes correlates with disease recurrence rates and overall survival in NSCLC patients.

Variation in immune response appears to be influenced significantly by the cancer itself. Chemotaxins expressed constitutively by tumours allow recruitment and polarization of multiple immune cell types to assist in migration and vascular/lymphatic invasion. Dendritic cells may be depleted or blocked at an immature stage both at the tumour site, and in regional lymph nodes, resulting in impairment of antigen presentation, co-stimulation, and migratory responses. Kohrt et al noted that regional lymph node immune profiles in breast cancer patients changed independent of nodal metastases, and concluded that impairment of the immune response is likely a critical step in lymph node invasion by tumour, and may precede microscopic metastasis detection.
There appears to be significant potential for immune responses such as we have observed to be greater than simply a passively observed phenomenon – stimulation of host anti-tumour cell-mediated immunity to respond to tumour antigens in the same way naturally seen in patients with tumour-related sarcoidal reactions may have significant therapeutic benefit. Dendritic cell activation, via cytokine stimulation, or ex vivo exposure to tumour antigens, has been used to stimulate cytotoxic anti-tumour T-lymphocyte immunity. Induction of such responses has demonstrated clinical benefit in multiple solid organ malignancies.[976, 977]

With enhanced understanding of tumour-immune system interactions on cancer behaviour, immune profiling of regional lymph nodes may be extremely valuable in guiding individualized patient therapy, based on expected biologic characteristics of individual tumours. Epithelioid granulomas may be demonstrated by EBUS-TBNA both in sarcoidal reactions complicating NSCLC,[771] as well as in sarcoidosis, [905, 978, 979] and even in patients with a prior history of cancer.[941] Molecular analysis of low-volume specimens obtained by EBUS-TBNA has been performed successfully,[724, 726] suggesting that immune profiling of EBUS-TBNA specimens may be possible. This potentially exciting area requires future study.

7.3.4.1 Limitations

This is a small retrospective case-control study, with all the limitations inherent in such methodology. Numerous clinical and pathologic factors are known to influence outcome following early stage NSCLC, including age, gender, histology and FEV1.[120, 213, 959, 980-982] We performed matching of controls in order to minimize the likelihood of confounding, however due to the size of our cohort, the study is likely to be underpowered to detect a significant difference between groups in clinical or pathologic factors. Therefore, larger trials, controlled for these factors, are required to confirm results of our pilot study.

Duration of post-resection follow-up is not uniform, varying from 12 to 60 months. It is possible that some patients may experience recurrence in the future. Boyd et al recently reported median time to recurrence in resected NSCLC was 13 months, with
75% of documented disease recurrence occurring in less than 2 years.[619] With post-surgical follow-up greater than 2 years in 76% of our cohort, we suggest that additional disease recurrence is likely to be very low. Also, observed disease recurrence rates reflect previously published data for stage I disease suggesting our results are consistent with expected clinical behaviour.

Our study does not determine how long sarcoïdal reactions, or their anti-tumour effect, may persist. Our data, and that of others,[769, 930, 931, 933] indicates that sarcoïdal reactions form prior to the development of established metastases in NSCLC. It remains unclear if this response is reversible, though the recognized immunomodulatory ability of cancers means that, given sufficient time, alteration in local environment is likely to result, leading to a pro-tumoural state, with subsequent establishment of metastases.

7.3.5 CONCLUSION

Our pilot case-control study suggests that the presence of sarcoïdal reactions within regional lymph nodes of NSCLC patients predicts a lower rate of disease recurrence following definitive surgical resection. Larger case-control studies and prospective studies are needed to confirm our findings. It is likely that sarcoïdal reactions represent an effective anti-tumour immunity, though the exact mechanism by which this is achieved remains to be elucidated. Future studies should also focus on the ability of EBUS-TBNA to evaluate immune profiles in regional lymph nodes of NSCLC patients in a minimally invasive fashion.
CHAPTER 8: Concluding discussion

Work presented in this thesis was undertaken in evaluation of a novel technique – endobronchial ultrasound – and how this technique should be introduced into routine clinical care. This required clarification of methodologic issues for optimal performance of EBUS procedures, as well as examination of the role EBUS alongside previous standard techniques for evaluation of peripheral pulmonary lesions (radial EBUS) and/or hilar & mediastinal lymphadenopathy (EBUS-TBNA).

8.1 REVIEW OF STUDY AIMS

8.1.1 Aim 1: Does the radiation dose resulting from fluoroscopic guidance of transbronchial lung biopsy (TBLB) preclude its use in performance of radial probe endobronchial ultrasound?

Concerns regarding radiation exposure resulting from fluoroscopic guidance during transbronchial lung biopsy led to some authors suggesting TBLB be performed without such guidance. No assessment of effective radiation dose had been made previously, though some other medical procedures utilizing fluoroscopy were known to be associated with significant effective doses. [735, 736]

Results of this study demonstrated that patients received a median effective dose of 0.49mSv – approximately 10 times that of a conventional chest x-ray,[788] below the yearly background dose of ‘cosmic’ radiation,[784] and well below doses previously associated with no adverse health outcomes.[804]

Findings indicate that concern regarding radiation exposure should not preclude the use of fluoroscopic guidance in the performance of diagnostic bronchoscopy if it is clinically indicated. Any tool that increases diagnostic accuracy of the procedure should be utilized in the interest of minimizing radiation exposure as non-diagnostic
procedures are likely to be followed by CT-guided sampling of peripheral lesions. Such procedures have been associated with median effective radiation doses of 6mSv.[786]

Efforts should always be made to keep radiation doses as low as reasonably achievable.[809] Future study should therefore examine ways to minimize radiation doses further, through measures such as maximising x-ray tube to patient distance or minimising the patient to image intensifier distance, and more judicious use of screening.[778] Most importantly, shortening procedure times and minimizing the number of overall procedures will have the largest effect of radiation doses associated with investigation of PPL, mandating quality training of proceduralists to enhance proficiency and efficiency and to ensure optimal selection of procedures for evaluation of those with PPL.

8.1.2 **Aim 2: What is the optimal procedure for minimally invasive assessment of peripheral pulmonary lesions**

Assessment of PPL is a common clinical scenario. Reflected in published guidelines from 2003 regarding diagnosis of suspected lung cancer is the traditional view that bronchoscopy has minimal utility in assessment of PPLs.[780] The introduction of radial probe EBUS has markedly improved diagnostic yield of bronchoscopic investigation of PPL, to the point where revision of the above-mentioned guidelines published in 2007 advised “radial EBUS can be considered in preference to percutaneous sampling.”[417] Despite this no studies had directly compared the two modalities most commonly used in assessment of PPL. It remained unclear if one was preferable to the other, and what patient characteristics might aid clinicians in selection between the two procedures.

The prospective randomized trial was designed as a pragmatic trial, to most accurately reflect ‘real-world’ clinical situations,[772] and to afford the greatest degree of external validity (generalizability). Findings suggested that EBUS-TBLB was non-
inferior to CT-PNB in assessment of PPL, but with a lower rate of complications. The study is likely to have some selection bias, with only a minority of eligible patients undergoing randomization. In addition, alterations in proceduralist proficiency and in clinicoradiologic features of PPL under investigation would be very likely to alter outcomes of such a trial were it held in different settings. The virtually infinite permutations of all these parameters indicate trials yielding comprehensive guidance for all patients with PPL are unlikely. Instead I suggested that development

Comprehensive reviews of CT-PNB have previously been published,[17] and numerous studies have described the influence of various clinicoradiologic characteristics on diagnostic accuracy and rates of complications.[473, 684, 738] Diagnostic performance of EBUS-TBLB varies considerably between reports, and factors responsible for this have not been thoroughly elucidated. Systematic review and meta-analysis determined a point sensitivity for pooled data of 0.73 (95%CI 0.70–0.76). Significant heterogeneity in sensitivity of individual studies was seen ($I^2 = 75\%$, $\chi^2 = 47.92$ ($p<0.0001$)) and sub-group analysis suggested prevalence of malignancy, and size of lesion as possible sources of inter-study heterogeneity.

An understanding of clinical parameters influencing outcomes of each procedure is valuable in selecting the optimal procedure. Incorporation of such information during medical decision-making is frequently intuitive, though numerous studies have examined limitations of intuitive reasoning in complex clinical scenarios.[742] Decision tree analysis represents a formal method for synthesising both medical facts (probabilities) and human values (utilities), which together determine the best course of action.[753] It also allows cost-utility to be incorporated into decision-making.

The decision tree analysis conducted to examine the most cost-beneficial and cost-effective procedure in assessment of PPL noted that costs of EBUS-TBLB and CT-PNB to evaluate PPL appear to be equivalent, but that specific clinicoradiologic factors known to influence procedural outcomes will influence cost-benefit outcomes. It is clear that cost-minimization relies on minimizing ‘downstream’ care costs for either procedure and that future research should ideally examine ways to further improve diagnostic accuracy, or minimize complication rates, of each procedure.
8.1.3 **Aim 3: Issues in the integration of EBUS-TBNA into routine clinical care**

8.1.3.1 **Assessment of the tolerability & safety of EBUS-TBNA**

Widespread uptake of EBUS-TBNA preceded detailed examination of numerous issues with respect to optimal performance of the procedure, integration into routine care alongside current diagnostic methods, and alternate indications for performance of EBUS-TBNA beyond staging of NSCLC.

Findings reported in this thesis confirm EBUS-TBNA may safely be performed under conscious intravenous sedation and such an approach is associated with very high patient satisfaction. Incidence of bacteraemia following EBUS-TBNA is comparable to that following routine flexible bronchoscopy. Performance of TBNA does not appear to measurably increase the risk of bacteraemia over that associated with insertion of the bronchoscope into the airway. Contamination of TBNA needle by oropharyngeal commensal bacteria is common however clinically significant infection following EBUS-TBNA appears rare. Based on current recommendations,[760] prophylactic antibiotics for prevention of endocarditis are not required. The risk of infection complicating EBUS-TBNA is based on lesion factors indicative of avascular tissue/spaces (eg. necrosis, cystic lesion). As contamination of the TBNA needle by oropharyngeal flora is common, caution should exercised when considering sampling of such lesions.

8.1.3.2 **Issues in the integration of EBUS-TBNA into routine care – comparison with current standards of care**

Decision tree analysis indicates that EBUS-TBNA is associated with significant cost-benefit in comparison to standard mediastinoscopy, across all clinically feasible parameters. Introduction of EBUS-TBNA to large centres in Australia is likely to be associated with significant cost benefit, despite the substantial capital cost in introduction of equipment. Introduction to health care settings beyond metropolitan tertiary hospitals is likely to be contingent on other factors, including work-load, and expertise available.
Inter-observer agreement is a measure of the degree of consensus among individuals examining the same specimen. For a field where answers are viewed as definitive, it is important for clinicians to be aware that while specific features may be used to determine the histologic origin of a tumour, the “gold-standard” is simply expert opinion. EBUS-TBNA specimens, obtained via a minimally invasive technique, are small volume and therefore usually processed as cytology specimens. They are therefore subject to increased interobserver variability in determination of NSCLC subtype than histologic specimens.[765] Findings from our study on interobserver agreement in assessment of NSCLC specimens acquired by EBUS-TBNA are significant in that they emphasize the difficulty in determining sub-type on morphologic criteria alone, and on ‘smear’ specimens alone. Findings dictate that all NSCLC specimens be subtyped only after immunohistochemical examination, as advised by the IASLC/ATS/ERS guidelines for classification of NSCLC in small biopsy/cytology specimens.[51]

Consistent performance in the staging of NSCLC has resulted in EBUS-TBNA becoming the procedure-of-choice for mediastinal staging. Less clear is its role in other indications, particularly the diagnosis of mediastinal lymphadenopathy of unknown aetiology. Lymphoma is frequently a postulated cause of this, raising the possibility that EBUS-TBNA may not be suitable for such patients, given the known difficulties of assessment of lymphoma on cytology specimens.[983, 984] Examination of the utility of EBUS-TBNA in assessment of suspected lymphoma revealed some interesting findings. Firstly, the likelihood of EBUS-TBNA obviating the need for more invasive procedures was 76%, and lymphoma was the final diagnosis in just 38% of patients. Sensitivity for detection of lymphoma at 76% was lower than sensitivity for staging of NSCLC but given the low pre-test probability of lymphoma and the high number of patients who avoided invasive surgery, use of EBUS-TBNA as the initial investigation in people with suspected lymphoma is justified.
Aim 4: What is the diagnostic significance of sarcoidal reactions demonstrated by EBUS-TBNA in regional lymph nodes of patients with non-small cell lung cancer; What is the prognostic significance of sarcoidal granulomas in regional lymph nodes of patients with non-small cell lung cancer

Sarcoidal reactions in malignancy are morphologically similar to epithelioid granulomas of systemic sarcoidosis but differ in pathogenesis and immune cell profile from sarcoidosis.[769] Their significance in patients undergoing staging of NSCLC was unclear both in the sense of how they may affect staging of the malignancy (and therefore determination of optimal therapy) and what impact they may have on subsequent clinical course.

Findings indicated that sarcoidal reactions may result in false up-staging on FDG-PET (non-invasive staging). They were observed to occur in 4.3% of all patients undergoing surgical resection of NSCLC. More significantly, their presence was isolated to those with stage I disease. The pathogenesis of sarcoidal reactions remains unclear. The immune modulating (evading) ability of cancer is well recognized. Sarcoidal reactions may be effective cell-mediated anti-tumour immune responses which occur in a small proportion of patients in early phases of the establishment of metastases, prior to the acquisition of the ability to evade immune system detection and attack.

Further study on the pathogenesis of tumour-related sarcoidal reactions is required. Dendritic cell activation has been used in the treatment of multiple solid organ malignancies.[976, 977] The ability of EBUS-TBNA to evaluate immune profiles in a minimally invasive fashion is also an area for further work.
8.2 FUTURE DIRECTIONS

EBUS has steadily become a standard fixture in the bronchoscopy suite of all hospitals where it is available. The utility in diagnosing and staging mediastinal/hilar lymphadenopathy is firmly established. Having confirmed its place in the clinical evaluation of patients with PPL or mediastinal/hilar lymphadenopathy, there remain a number of potential avenues for further development of EBUS in the assessment of such patients.

Radial EBUS is largely used at present as a tool to locate peripheral lesions to allow accurate sampling. Future work will examine the ability of radial EBUS to guide therapeutic interventions such as photodynamic therapy,[985] brachytherapy,[986] or placement of fiducial markers to aid stereotactic radiotherapy.[987] Electromagnetic navigation bronchoscopy is a newer bronchoscopic technique allowing not just localization of a peripheral lesion, but guidance/navigation through the bronchial tree to direct bronchoscopic sampling of peripheral pulmonary lesions.[988] Diagnostic yield is variable and appears to be greatest when used in combination with radial EBUS.[688]

The advent of biologic and targeted therapies has emphasized the importance of detailed molecular analysis of NSCLC specimens. Initial identification and characterization of these mutations was performed on surgical tissue specimens. However such mutations are clinically relevant to the majority of patients with systemic metastases, for whom surgery is inappropriate. The value to undertake molecular/genetic assessment of disease in such patients on samples obtained by minimally invasive means is widely recognized, and has been proven possible through proof-of-concept studies.[725, 728] Development of this possibility into routine clinical care will further enhance individual-specific care of patients with advanced NSCLC.

Finally, other bronchoscopic techniques may be developed further to aid in the assessment of patients at high risk of lung cancer. The role of autofluorescence
bronchoscopy and narrow band imaging in assessment of preinvasive central airway lesions remains to be established and similarly, *in vivo* histologic and subcellular imaging with optical coherence tomography may allow assessment of peribronchial lesions or even parenchymal abnormalities.[989] Such tools, following demonstration of their clinical possibilities, will need to proceed through thorough assessment of how they should be incorporated into current care both in terms of integration with existing techniques and also following a cost-effectiveness assessment as advances in technology are likely to be associated with increasing costs.

With increasing, and increasingly complex, bronchoscopic techniques becoming available the field of bronchoscopy (or interventional pulmonology) is likely to become more specialized and specific training and accreditation programs will be required to ensure that those performing such procedures are adequately trained and competent to do so. Competency assessment may include simulated bronchoscopy or clinical tools to assess performance,[990-992] however further work is required to validate such tools, and cross-discipline agreement will need to be reached to determine what constitutes ‘competency’ and how this is best achieved and maintained to ensure optimal performance of these valuable techniques.
8.3 CONCLUSION

Advances in minimally invasive assessment made possible by endobronchial ultrasound (both radial and linear) of intrathoracic lesions have allowed more accurate pre-operative assessment than previously available. In addition, the techniques have been demonstrated in this thesis to be cost-effective in all clinical scenarios for linear EBUS, and in selected scenarios for radial EBUS. This thesis has examined issues regarding optimal performance of each of these techniques and undertaken extensive evaluation against current standards-of-care to better define the role of endobronchial ultrasound in the routine care of patients with suspected or known lung cancer.
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