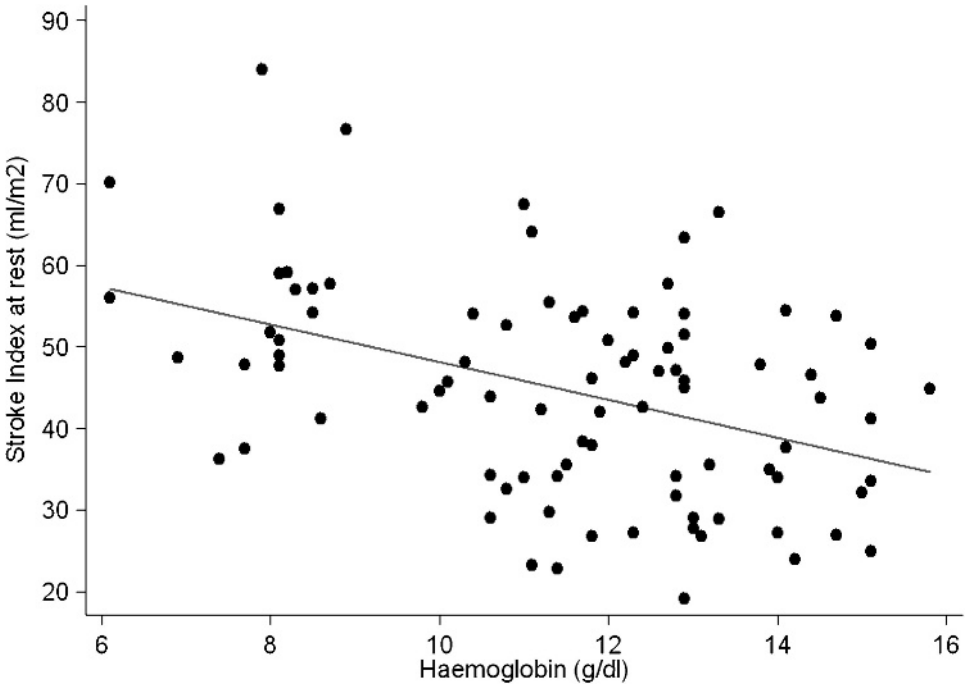

Abstract S33 Figure 1 Stroke index vs haemoglobin levels in 89 subjects ($r = -0.41$, $p<0.001$).

Lung cancer and mesothelioma: clinical trials and clinical practice

S34 AN EARLY EXERCISE INTERVENTION PREVENTS QUADRICEPS WEAKNESS AFTER THORACOTOMY FOR NON-SMALL CELL LUNG CANCER: RANDOMISED CONTROLLED TRIAL

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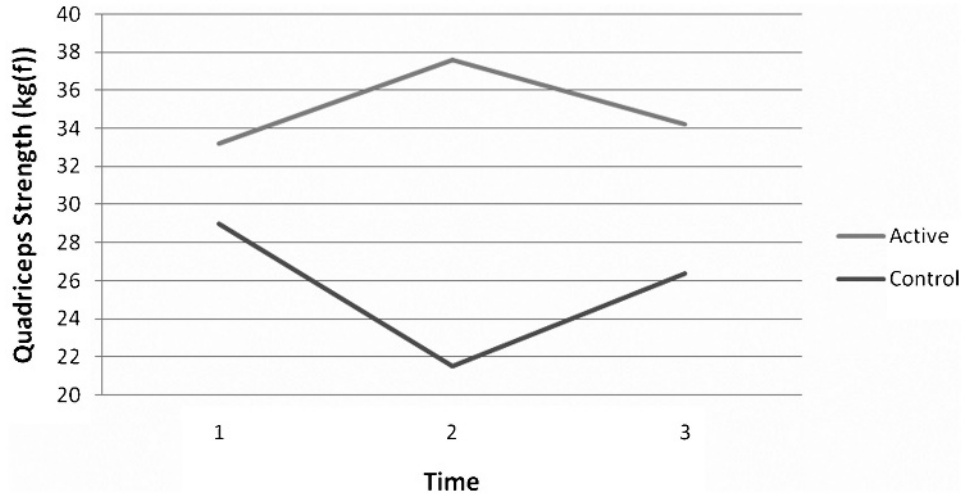
Deterioration in exercise tolerance and impairment in quality of life (QoL) are common consequences of lung resection. This study evaluates additional exercise and strength training after lung resection on QoL, exercise tolerance and muscle strength.

53 (28 male) patients attending thoracotomy for lung cancer, mean age 64 years (range 32–82); mean pack years (SD) 31.9 (26.8); body mass index 25.6 (4.2); forced expiratory volume in 1 s (FEV_1) 2.0 (0.7) litres, were randomised to control (usual care) or intervention (twice daily training plus usual care). After discharge the intervention group received monthly home visits and weekly telephone calls; the control group received monthly telephone calls up to 12 weeks. Assessment preoperatively, 5 days and 12 weeks postoperatively consisted of quadriceps strength using magnetic stimulation, 6 minute walking distance (6MWD) and QoL-EORTC-QLC-C3.

QoL was unchanged over 12 weeks; 6MWD showed significant deterioration at 5 days postoperatively compared with



Abstract S34 Figure 1 Estimated marginal means of quadriceps strength. Repeated measures of assessment time (1 = preoperative; 2 = 5 days postoperative; 3 = 12 weeks postoperative) against quadriceps strength (kg(f)).

preoperatively, mean difference (SD) −131.6 (101.8) m and −128.0 (90.7) m in active and control groups, respectively (p = 0.89 between groups), which returned to preoperative levels by 12 weeks in both groups. Quadriceps strength over the 5 day inpatient period showed a decrease of −8.3 (11.3) kg in the control group compared with an increase of 4.0 (21.2) kg in the intervention group (p = 0.04 between groups).

Strength and mobility training provided after thoracotomy successfully prevented the sarcopenia seen in a control group; however, there was no effect on 6MWD or QoL. 6MWD returned to preoperative levels by 12 weeks regardless of additional support offered.

S35 EARLY DETECTION OF LUNG CANCER: A SOCIAL MARKETING EVALUATION

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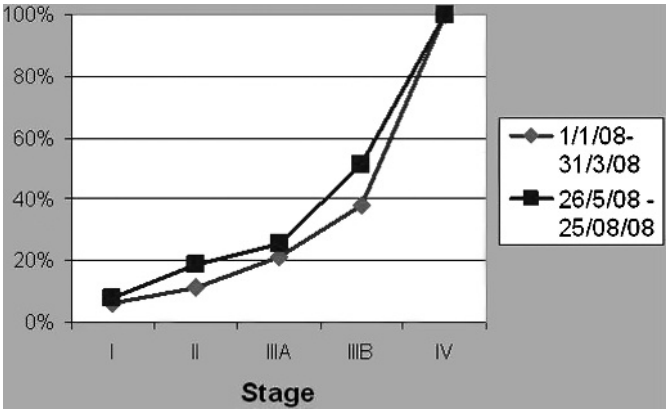
Introduction and Objectives The lateness of diagnosis of lung cancer in its natural history may prejudice outcomes. This project aimed to overcome barriers to early diagnosis, by promoting symptom-reporting behaviour and by modifying the response of health services, using a mixed method, social marketing campaign, developed using insight from qualitative research and local audit.

Methods The intervention was conducted in six localities. Changes before and after the campaign were assessed and compared with control localities. Three outcomes were investigated: a telephone survey of >800 members of the general public, to measure public awareness of lung cancer symptoms and intention to seek healthcare; the impact on chest *x* ray referral rates; and the incidence and stage of disease at diagnosis. A logistic regression model with covariates was fitted (sex, age group, socioeconomic group and smoking status).

Results After adjustment for covariates, the likelihood of target area group respondents, postintervention compared with preintervention, visiting their general practitioner (GP) with a persistent cough and asking for an *x* ray was 1.97 times (95% CI, 1.18 to 3.31, p = 0.003) that of control group responders (absolute difference 74% vs 70%). Chest *x* ray referrals increased by 9% in non-targeted practices and by 27% in targeted practices. There was a significant, 60% increase in the number of cases diagnosed after the campaign, compared with the same month in the previous year (from 32 to 54). The stage at diagnosis also improved significantly: before the campaign 9 (11%) cases were diagnosed at stages I and II, rising to 14 (19%) (p<0.02); see fig 1 showing the cumulative stage distribution before and after intervention.



Abstract S35 Figure 1.

Conclusions This is encouraging, early evidence for an impact of an awareness and early diagnosis initiative for lung cancer, aimed at both the general public and primary care. A longer term evaluation is required to understand fully the impact of such an intervention, with more robust outcomes, including disease-specific and overall mortality.

S36 ROLE OF CT HEAD IN LUNG CANCER STAGING IN PATIENTS WITH NO NEUROLOGICAL SYMPTOMS

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Background The brain is one of the most common extrathoracic sites of metastasis in patients with lung cancer. One necropsy study concluded that the incidence of brain metastasis is 30–50% in patients with lung cancer. The current National Institute for Health and Clinical Excellence (NICE) guideline does not recommend routine CT scan of the brain (CTB) when patients undergo investigations for suspected lung cancer in the absence of neurological symptoms or signs. From February 2008 our local lung cancer CT staging protocol was revised and started including CTB when there is an obvious mass lesion in chest radiograph (CXR) or when an abnormality suspicious of malignancy was seen when the patient is undergoing a CT scan of the chest (CT chest).

Methods We retrospectively analysed the results of these patients who had CTB done at the same time as CT chest (February 2008–March 2009). We excluded the patients who had any neurological symptoms or signs suggestive of cerebral metastasis. Patients were identified from our Radiology database as well as our lung cancer database.

Results 160 patients were identified and the mean age was 70 years (males 50%). 96% of the patients had a CXR abnormality suspicious of malignancy. The mean size of the mass lesion when one was found in CT chest was 4 cm. The 116 (72.5%) diagnoses of malignancies made and the presence of cerebral, adrenal and liver metastasis are listed in table 1. Seventeen patients (11%) had evidence of cerebral metastasis; the primary site was exclusively the lung. Only 6% of the patients were found to have adrenal and liver metastasis. The mean size of the primary lesion was 4 cm in both patients with and without cerebral metastasis. 62% of the patients with cerebral metastasis had at least N2 disease.

Conclusion Cerebral metastasis is more common in lung cancer. Early detection of cerebral metastasis would alter the patient

Abstract S36 Table 1 Malignancies diagnosed in 160 patients

Diagnosis	Total number	Cerebral metastasis	Adrenal metastasis	Liver metastasis
Small cell carcinoma	13	2 (15%)	1 (8%)	3 (23%)
Squamous cell carcinoma	28	4 (14%)	3 (11%)	2 (7%)
Non-small cell carcinoma	25	3 (12%)	3 (12%)	1 (4%)
Clinical diagnosis of NSCLC	21	5 (20%)	1 (5%)	1 (5%)
Adenocarcinoma	18	3 (17%)	1 (5%)	2 (11%)
Mesothelioma	3	0	0	0
Lymphoma	2	0	0	0
Carcinoma of bowel	1	0	0	0
Carcinoma of oesophagus	1	0	0	0
Metastatic carcinoma of unknown primary	2	0	0	0
Breast carcinoma	1	0	0	0
Ovarian carcinoma	1	0	0	1 (100%)
Total	116	17	9	10

Data are presented as numbers and percentage.
NSCLC, non-small cell lung carcinoma.

pathway significantly when being investigated for lung malignancy. We recommend that we include CTB in the lung cancer staging protocol when an abnormality suspicious of malignancy is found either in CXR or CT chest even in the absence of any neurological signs or symptoms.

S37 MESOTHELIOMA AS A METASTATIC DISEASE: A POSTMORTEM STUDY

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Background Mesothelioma is often perceived as a locally aggressive cancer. The ability of mesothelioma to metastasise and how mesothelioma causes death are unclear. We studied mesothelioma cases from Western Australia (WA) where crocidolite mining has led to significant exposure of the population to asbestos.

Methods Postmortem records of all mesothelioma patients who underwent an autopsy were identified from the mesothelioma database (~1600) of the WA Cancer Registry.

Results Of the 253 postmortem records identified, 208 were complete, including 190 cases of pleural and 18 peritoneal mesothelioma. Patients with pleural mesothelioma were predominantly (90%) males and 55% had right-sided tumour. Median survival was significantly longer in epithelioid mesothelioma over biphasic and sarcomatoid subtypes (262 vs 214 vs 127 days, respectively; $p = 0.0017$). Extrapleural metastases were extremely common, affecting 75.6% of patients; 55.2% had metastases in the contralateral hemithorax and 68.5% outside the thoracic cavity. Lung was the most common site of spread, followed by pericardium (56.6%), liver (42.8%), adrenals (22.8%), kidney (21.3%), bone (19.8%), thyroid (10.1%), skin (5%) and brain (4%). On average, each patient had metastases to three extrapleural organs. Metastatic spread was more common in the epithelioid subtype (table 1). The cause of death could be determined from the postmortem in 30% of cases. Pulmonary emboli were present in 11.5%, were considered large in 4.7% and to contribute to death in 5.6%. Pneumonia was present in 81 (38.9%). Pericardial effusion was noted in 52 (27.4%), with three dying from cardiac tamponade. Great vessel invasion was recorded in 12 (7.4%), but none caused death. In the peritoneal group, 16 (88.9%) had liver metastases, 10 had ascites, 5 had direct gastrointestinal tract invasion, 8 had pneumonia and 3 had bowel obstruction.

Conclusion Metastases from direct, lymphatic and haematological spread are very common in mesothelioma. Sarcomatoid subtype is associated with a lower incidence of metastasis, but confers a worse prognosis. Pneumonia is a common mode of death in this population, but pulmonary embolism is less so. No anatomical cause of death was seen in a significant portion of patients, suggesting metabolic or physiological causes may play a role.

Abstract S37 Table 1 Metastatic spread of mesothelioma by histological subtype

	Epithelioid	Biphasic	Sarcomatoid	p Value
n (%)	59 (31.1)	62 (32.6)	33 (17.4)	
Any extrathoracic spread	36/48 (75.0)	41/50 (82.0)	18/29 (62.1)	0.144
Any lymph node	46/51 (90.2)	41/50 (82.0)	16/33 (48.9)	<0.001
Contralateral pleura	35/57 (61.4)	25/60 (41.7)	9/32 (28.1)	0.012
Contralateral parenchyma	36/57 (63.2)	25/60 (41.7)	5/33 (15.2)	<0.001
Direct chest wall invasion	19/59 (32.2)	29/62 (46.8)	18/33 (54.5)	0.126
Peritoneal	14/47 (30.0)	16/51 (31.4)	2/29 (6.9)	0.035

S38 THE INCIDENCE AND DISTRIBUTION OF METASTASES FROM PLEURAL MALIGNANT MESOTHELIOMA AT POSTMORTEM IN THE BRISTOL AREA (2005–2008)

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Introduction Traditionally, malignant mesothelioma has been regarded as a locally aggressive disease, unlikely to cause distant metastases. Currently, death is usually the result of infection or respiratory failure, along with systemic symptoms associated with progressive malignancy. If survival improves with future novel treatments, symptoms from metastatic disease will become more clinically relevant and important to recognise for optimal patient management.

Objectives To identify all deaths with malignant mesothelioma reported to the Coroners Office in the Bristol region, and to identify the incidence and site of metastatic spread.

Methods The Coroners Office in Bristol collects data from four strategic health authorities;

- Bath and North East Somerset
- Bristol
- North Somerset
- South Gloucester

The database was searched for all records including mesothelioma on the death certificates between 1 January 2005 and 31 December 2008. The corresponding paper files, including the death certificate and postmortem result, were examined. Demographic details, histological subtype and site of metastases were recorded.

Results 149 cases of malignant pleural mesothelioma were reported to have died between January 2005 and 31 December 2008. Cases were predominantly male (87.2%), and right sided (55%), with a median age of death of 73 years (47–92).

Extrapleural metastases were extremely common, occurring in 85.2% of cases. A total of 444 sites of metastatic spread occurred in 127 cases of pleural malignant mesothelioma, averaging 3.5 metastatic sites per case. Nodal metastases occurred in 38.3% and extrathoracic metastases in 49%. The most common site of intrathoracic metastatic spread was to lung (45.6%), followed by pericardium (35.6%). The most commont extrathoracic site of spread was to liver (24.8%), followed by peritoneum (23.5%), spleen (6.7%) and bone (6.7%). Pulmonary embolus was identified at postmortem in 8 cases (5.4%). Sarcomatoid subtype had a lower metastatic rate to lymph nodes than epithelioid or biphasic subtypes. However, there was no significant difference in the rates of extrathoracic or total metastases.

Conclusions Metastatic spread in pleural malignant mesothelioma is common (85.2% of cases). Pulmonary embolus was identified in 5% of cases and sarcomatoid subtype metastasised to lymph nodes less commonly than epithelioid mesothelioma.

Abstract S38 Table Rates of metastatic spread according to histological subtype

Mesothelioma type, n (%)	Any lymph node metastases, n (%)	Extrathoracic metastases, n (%)	Any metastases, n (%)
Unknown 50 (33.6%)	17 (34)	21 (42)	42 (84)
Epithelioid 43 (28.9%)	23 (53.5)	25 (58.1)	38 (88.4)
Sarcomatoid 31 (20.8%)	7 (22.6)	15 (48.4)	25 (80.6)
Biphasic 24 (16.1%)	10 (41.7)	11 (45.8)	21 (87.5)
Anaplastic 1 (0.7%)	0 (0)	1 (100)	1 (100)
Total 149	**57 (38.3)**	**73 (49)**	**127 (85.2)**
p Value (excluding "unknown" and "anaplastic")	**0.028**	**NS**	**NS**

S39 SYSTEMIC BIOCHEMICAL MARKERS ARE IMPORTANT IN MORTALITY PREDICTION IN MESOTHELIOMA: A NOVEL PREDICTION MODEL

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doi:10.1136/thx.2009.127068m

Introduction Malignant pleural mesothelioma is frequently considered clinically to be localised to the chest, although it may often have significant systemic manifestations in advanced disease. Classification and Regression Tree (CART) analysis is able to create decision trees and classify risk groups by analysing the interaction between different variables and an outcome measure. We analysed clinical and laboratory data to identify prognostic factors for 1-year mortality in patients with mesothelioma in Portsmouth, UK, a dockyard city with high previous asbestos usage.

Methods Data from 323 histologically confirmed mesothelioma cases were retrospectively analysed using electronic demographic records, laboratory result databases and case note review. 24 routinely collected variables at the time of diagnosis (including histology, haematological, serum and pleural fluid biochemical results, co-morbidity and presenting symptoms) were analysed using CART modelling (utilising the V-fold cross validation technique) to establish prognostic indices for 1-year mortality.

Results Of the 323 cases, 273 (84%) were male, mean (±SD) age at the time of diagnosis was 68 (±10) years and mean body mass index (BMI) was 24.01 (±4.1) kg/m^2; at the time of data collection 265 (82%) of the cohort were dead. Overall median survival was 7.0 (interquartile range (IQR) 3–12) months. 72 (22%) patients had chemotherapy, and no patients were referred for trimodality therapy. CART identified six risk groups using five variables to best fit a prediction model with a C-statistic of 0.63. The best prognostic group had a serum albumin >37.5 g/l and urea <5.0 mmol/l (1-year mortality 25.0%); the highest risk group had a serum albumin ⩽37.5 g/l, alkaline phosphatase >100.0 IU/l, phosphate ⩽1.14 mmol/l and did not receive chemotherapy (1-year mortality 80.0%); a full breakdown of risk group parameters is provided in table 1.

Conclusions Simple, objective, biochemical markers taken at the time of diagnosis may provide important prognostic information for mortality from mesothelioma. These indices are likely to be reflective of underlying systemic and nutritional health. An awareness of these parameters may augment clinical and multidisciplinary team decisions, although the accuracy of the model precludes its use alone to inform treatment decisions.

Abstract S39 Table 1 Stratification of different risk groups to predict 1-year mortality in mesothelioma patients

	High risk		Medium risk			Low risk
	Risk 1	Risk 2	Risk 3	Risk 4	Risk 5	Risk 6
n/N (%: mortality)	16/20 (80.0%)	25/35 (71.4%)	86/133 (64.7%)	45/71 (63.4%)	16/40 (40.0%)	6/24 (25.0%)
Parameter						
Albumin (g/l)	⩽37.5	>37.5	⩽37.5	⩽37.5	⩽37.5	>37.5
Alkaline phosphatase (IU/l)	>100.0	–	>100.0	⩽100.0	>100.0	–
Urea (mmol/l)	–	>5.0	–	–	–	<5.0
Phosphate (mmol/l)	⩽1.14	–	>1.14	–	⩽1.14	–
Chemotherapy	No	–	–	–	Yes	–

n, number of deaths within a category; N, total numbers within a category.

Clinical studies into the pathogenesis of acute lung injury

S40 LIPOPOLYSACCHARIDE INHALATION DRIVES PULMONARY INFLAMMATION AND CAUSES ALVEOLAR EPITHELIAL AND ENDOTHELIAL ACTIVATION/INJURY IN AN IN VIVO HUMAN MODEL OF ACUTE LUNG INJURY

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Acute lung injury (ALI) is an inflammatory process characterised by damage to the alveolar epithelial–capillary endothelial barrier leading to alveolar flooding. The objective of this study was to determine if lipopolysaccharide (LPS) inhalation, as an in vivo human model of ALI, causes alveolar epithelial and endothelial activation/injury.

Ten healthy subjects, enrolled in the placebo arm of a clinical trial,[1] who inhaled 50 μg of LPS, and 5 healthy controls were recruited. Bronchoalveolar lavage (BAL) was performed at 6 h and plasma sampling at 24 h after LPS inhalation. Surfactant protein-D (SP-D), an alveolar type 2 epithelial cell biomarker, von Willebrand factor (vWF), an endothelial cell biomarker, and calgranulin C reflecting neutrophil and/or macrophage activation were measured by ELISA. Cytokines were measured by cytometric bead array. The protein permeability index (PPI) (BAL protein/plasma protein ratio) was calculated as a marker of barrier integrity. Data are mean (±SD) or median (interquartile range).

LPS inhalation induced a significant increase in BAL SP-D (fig 1a) and BAL vWF (fig 1b). There was a significant increase in plasma SP-D (ng/ml) (107.3 (69.2–132.2) vs 35.4 (28.8–61.5), $p = 0.005$) but no change in plasma vWF levels. BAL calgranulin C (pg/ml) was also increased (176.8 (90.1) vs 5.1 (3), $p<0.001$). There was an associated increase in BAL interleukin-6 (IL-6) (pg/ml) (509.8 (264.0) vs (1.6 (0.5) $p = 0.001$), IL-8 (pg/ml) (389.4 (93.6) vs (28.8 (12.67) $p<0.0001$) and (monocyte chemoattractant protein-1 (MCP-1) (pg/ml) (562.4 (257.3) vs (13.7 (7.3) $p = 0.0004$). In contrast, only MCP-1 was detectable in plasma after LPS inhalation but was not increased compared with normal volunteers. PPI was significantly elevated after LPS inhalation compared with normal volunteers ($p<0.05$).

This is the first study to demonstrate alveolar epithelial and endothelial activation/injury due to LPS inhalation in vivo. It is likely that the proinflammatory response characterised by the local pulmonary release of inflammatory mediators induced by LPS inhalation causes the epithelial and endothelial activation/injury. This model of ALI shows an increase in a range of biomarkers implicated in ALI and is a valuable tool in early phase clinical trials of potential pharmacological therapies for ALI.

1. **Shyamsundar M** *et al*. *AJRCCM*, 2009;**179**:1107–1114.