

# Abstracts: Lung cancer symposium

**ABBREVIATIONS** chemo/radiotherapy (CIRT), chemotherapy (CT), computerised tomography (CT), epidermal growth factor receptor (EGFR), fine needle aspiration (FNA), ground glass attenuation (GGA), International Association for the Study of Lung Cancer (IASLC), non small cell lung cancer (NSCLC), non-calcified nodules (NCNs), positron emission tomography (PET), radiotherapy (RT), systematic nodal dissection (SND), tyrosine kinase (TKI), vascular endothelial growth factor (VEGF)

## SESSION I THE SCALE OF THE PROBLEM AND CAN THAT BE CHANGED?

Chairman: Dr R Milroy, Consultant Physician in Respiratory Medicine, Stobhill General Hospital, Glasgow, Scotland

### Epidemiology of lung cancer

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**Abstract** Lung cancer is a major public health concern worldwide. Every year in Scotland, over 4,300 people are diagnosed with lung cancer; and just under 4,000 die from the disease. While tobacco smoking has been established as the main cause of lung cancer for decades, a substantial reduction in risk following smoking cessation before middle age has only been confirmed more recently.<sup>1</sup> Consistent with historic trends in smoking prevalence, age-standardised incidence rates have been falling in Scotland since the late 1970s in men, and have begun to plateau in women. In common with several other countries, incidence rates of adenocarcinoma have increased over time, perhaps associated with changes in cigarette design, although squamous cell carcinoma remains the predominant type of lung cancer among men in Scotland.<sup>2</sup> For decades, Scotland has had one of the highest rates of lung cancer in the world. However, mortality rates among men are now higher in some Eastern European countries, and rates in Danish women are approaching those in Scottish women. It has been shown that per cigarette smoked, the risk of developing lung cancer is higher in the west of Scotland than in some other countries.<sup>3</sup> Survival from lung cancer is poor, although there is some evidence of a recent slight improvement. Low socio-economic status is associated with higher incidence and worse survival. Clinical audit data from the mid-1990s suggest low rates of active treatment in Scotland,<sup>4</sup> but more recent cancer registry data suggest that an increased proportion of cases now receive chemotherapy.

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**Key words** aetiology, incidence, lung cancer, mortality, survival, trends

**Sponsors** None.

**Declaration** No conflict of interest declared.

### The politics of smoking cessation

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**Abstract** Not available at the time of going to press.

## JOHN HAMILTON BROWN LECTURE

Chairman: Professor N Douglas, President, Royal College of Physicians of Edinburgh, Edinburgh, Scotland

### Screening

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### Abstract

#### Pro Screening

In 2006, it is projected that there will be approximately 170,000 new cases of lung cancer in the US and only 15% of those individuals will survive five years.<sup>1</sup> The five-year survival has been relatively static for the past few decades. One of the major limitations to improving five-year survival is the fact that over 50% of patients present to their physicians with advanced stage disease. In the past

decade, there has been increasing interest in the role of low-dose spiral CT scan screening for early detection of lung cancer.<sup>2-9</sup>

In three of these CT screening trials investigators obtained chest radiographs within three months of the screening CT scans. The chest X-ray missed 70–80% of the lung cancers detected by the CT.<sup>2,3,5</sup> The average size of the cancer detected by CT was 15 mm vs 30 mm for screening chest X-ray detected cancer.<sup>9,10</sup> Thus, it is clear that screening with CT will detect smaller size lung cancers.

Computerised tomography screening trials have reported a high rate of early stage cancers. Henschke *et al.* noted that 22 of 27 lung cancers (81%) were stage IA.<sup>5</sup> Similarly, Nana *et al.* detected 78% stage IA<sup>7</sup> and Sobue *et al.* observed 69% stage IA.<sup>10</sup> For prevalence and incidence lung cancers, Swensen *et al.* reported stage IA disease in 69% and 59% respectively.<sup>9</sup> In the US the percentage of all newly diagnosed cancers with stage IA in the general population is approximately 25% (SEER Database).

While there is some debate about size of cancer and the prognosis, a number of publications have demonstrated better survival for stage IA lung cancers <2 cm in maximum diameter versus those that are 2–3 cm in size.<sup>11,12</sup>

To date there are no reported large Phase III randomised screening trials of CT vs chest radiographs or observation alone. The National Lung Cancer Screening Trial is such a randomised trial of 50,000 participants that will attempt to answer this question. Other randomised screening trials are underway in The Netherlands (NELSON trial) and France (DepiScan). The endpoints of these trials will be to determine if screening with CT vs the control arm decreases lung cancer mortality.

### Con Screening

Screening with CT has detected a high rate of NCNs. The Mayo Clinic trial detected NCN in 51% of participants at baseline<sup>4</sup> and 73% of participants after five annual CT scans.<sup>9</sup> A study from Germany observed NCN in 43% of participants<sup>6</sup> and a Canadian study observed 46% of participants with NCNs.<sup>8</sup> In the Mayo Clinic trial 61% of NCN were <4 mm in size and 34% were 4–7 mm. Only 6% of NCN were 8 mm or greater and required further investigation immediately. All NCN (7 mm and smaller) require some follow-up CT evaluation even if it is at yearly intervals. Our recommended follow-up interval is 1 year for nodules  $\leq$  4 mm and 6 months for 5–7 mm.

In some participants the presence of NCN results in further diagnostic testing. In a report by Pinsky *et al.*, 12% of participants with an abnormal screening CT scan underwent biopsy and only a little over half of these turned out to be cancer.<sup>14</sup> Crestanello and colleagues reviewed the number of thoracic surgery procedures performed in the Mayo Clinic CT screening trial and

noted that 10 of 55 surgeries (18%) were performed for benign disease.<sup>15</sup>

Interval lung cancers are cancers that develop between annual screening CT scans. These are usually due to rapidly growing cancer and are frequently small cell lung cancer. In the Mayo Clinic series 3 of 66 patients with lung cancer presented as interval cancers.<sup>9</sup> Diederich *et al.* noted that 5 of 15 lung cancers in their study were interval cancers presenting with symptoms. Interval cancers are almost always advanced and incurable.<sup>16</sup>

Not all screen detected cancers are curable. Swensen *et al.* reported 49 total deaths in their screening trial and 12 of these were from lung cancer.<sup>9</sup> Some of the lung cancers detected by CT screening were stage III at the time of diagnosis. German investigators reported six deaths due to lung cancer in their screening trial.<sup>16</sup> It is unrealistic to think that screening is going to prevent 80–90% of lung cancer deaths.

Most controversial of all is the cost of screening for lung cancer. Cost effective studies can only be determined after efficacy is proven and to date that has not been established. Cost effective estimates in the literature range from \$2,500 to over \$200,000 per year of life saved.<sup>17, 18, 19</sup> This wide variation is based on different assumptions in the models employed. It is probably fair to say that we do not have a good estimate of costs associated with CT screening. This is an important aspect of the NLST trial that will be evaluated.<sup>13</sup>

While there are both proponents and opponents of CT screening for lung cancer, there are currently no completed randomised control trials that clearly evaluate the capability of screening to decrease lung cancer mortality. These trials are in progress and the results are anxiously awaited.

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**Key words** cost effective estimates, chest X-ray, five-year survival, interval lung cancers, low-dose spiral CT scan screening, National Lung Cancer Screening Trial, non-calcified nodules,

**Sponsors** None.

**Declaration** No conflict of interest declared.

## SESSION 2 MAKING AND MANAGING THE DIAGNOSIS

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### The medical view

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### Abstract

**Background** Lung cancer is the most common cause of cancer death worldwide and, even in the best centres, less than 15% of patients will survive to five years. One of the major reasons why the prognosis is so poor is that many

patients have locally advanced or metastatic disease by the time they reach specialist care. There is also wide variation in survival rates between different centres and this variation may result, in part, from differences in management strategies.<sup>1</sup>

### Theme

Screening for lung cancer is currently the subject of intense research activity but is not yet proven to improve outcomes. A high level of clinical awareness is required, especially in high risk patient groups, of early symptoms together with a low threshold for requesting a plain chest X-ray. Rapid referral to a specialist team is then essential in order to both make the diagnosis and to assess the individual in terms of the stage of disease and their fitness for radical therapy. More recent additions to the more well known tools in this process include ultrasound FNA biopsy of occult deep cervical lymph nodes,<sup>2</sup> endobronchial ultrasound biopsy of mediastinal lymph nodes<sup>3</sup> and PET scanning.<sup>4</sup> The care pathway is often complex and to provide a rapid and sensitive service the whole process needs careful pre-planning.

Full assessment of every patient by a Multi-disciplinary team which includes expert representatives from all the sub-specialties is essential to ensure that patients are given the best chance of the most aggressive therapy appropriate to their particular clinical status. This is particularly true because many of the patients are elderly and there is a high incidence of smoking-related co-morbidities.

Communicating the diagnosis and management options sensitively, allowing for informed patient choice, is also a major part of high quality care and nurse specialists have contributed greatly to improvements in this area.

### Conclusions

Although lung cancer remains a difficult clinical problem, well-organised specialist diagnostic and assessment services can have a major impact on outcomes for patients both in terms of survival and quality of life.

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**Key words** Breaking bad news, early diagnosis, lung cancer, screening, multi-disciplinary team working, PET scanning, staging.

**Sponsors** None.

**Declaration** No conflict of interest declared.

### Lung cancer nursing, where are we, where are we going?

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#### Abstract

**Background** Lung Cancer Specialist nursing is a relatively new nursing specialty. Many posts developed as a result of local identified need or special interest. As a result the job role has developed differently and in various directions from acute care, community care, palliative settings or a combination of all of these.

In an attempt to scope the numbers of specialist nurses, their job role and level of activity, a collaborative national audit was conducted by The British Thoracic Society, The National Lung Cancer Forum for Nurses, The Royal college of Nursing and The Scottish Nurses Lung Cancer Interest Group.

**Methods or Theme** A postal questionnaire was sent to all specialist nurses registered as members of the The National Lung Cancer Forum for Nurses, The Roy Castle foundation Nurse Specialist register and the Scottish Lung Cancer Nurses Interest group. The questionnaire gathered information relating to numbers of nurses in post, the clinical activities and non-clinical activities they fulfil as part of their role.

Many nurses work independently and isolated with little or no support. Where teams of lung cancer nurses exist, the level of services provided and nursing research appeared greater.

**Conclusions** Single-handed nurses have a significant case load, often with minimal support. Recommendation of a maximum number of nurses to patient to be decided. Secretarial support required. NICE guidance in relation to nurses should be adhered to. Audit will help in developing future job roles for lung Cancer Specialist Nurses.

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**Key words** Lung cancer, lung cancer specialist nurses, nursing activities, postal questionnaire.

**Sponsors** British Thoracic Society.

**Declaration** No conflict of interest declared.

### The patient's perspective

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**Abstract** The Roy Castle Lung Cancer Foundation has developed a Lung Cancer Patients Charter,<sup>1</sup> based on the views of many patients and carers. The Charter highlights the following key areas:

#### 1. Access to best treatment and care

In particular, patients need access to quality information. What is available in your clinic area? Is it up to date? Were patients consulted in its development? Do you have a list of suitable websites?

There is a genuine concern that due to financial constraints, lung cancer patients are being denied access to new treatments

#### 2. Raised public awareness of lung cancer

The multiple and non-specific nature of many of the symptoms, make it difficult for patients to spot. Patients report symptoms for months and sometimes years prior to seeking medical attention.<sup>2</sup>

General public awareness is poor. A US analysis of cancer stories showed a significant media under-reporting of lung cancer.<sup>3</sup> Seventeen percent of stories were on lung cancer, with half addressing tobacco issues.

Several awareness raising initiatives are underway – eg, The Roy Castle Lung Cancer Foundation and Macmillan campaign,<sup>4</sup> also the UK Lung Cancer Coalition.

#### 3. More lung cancer research

The NCRN reported that only 3% of site specific research carried out by its members was in lung cancer. A tiny proportion, given the enormous burden of this disease.

#### 4. Be free of Stigma and Blame

Patients are often blamed for having inflicted the disease upon themselves. A MORI Poll showed that 7 out of 10 people felt that people with lung cancer had brought the disease on themselves.<sup>3</sup> The stigma caused by a tobacco-related disease can create hardship and feelings of guilt.<sup>4</sup>

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**Key words** General public awareness, stigma of a tobacco-related disease, under-reporting of lung cancer.

**Sponsors** None.

**Declaration** No conflict of interest declared.

### The Surgeon

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**Abstract** In patients who are sufficiently robust to withstand surgery, resection remains the most effective treatment for NSCLC which is confined to the chest and which can be completely resected. The British Thoracic Society<sup>1</sup> has set out guidelines for assessment of fitness. For suitable tumours in stage I, II and selected stage IIIA cases lobectomy is the minimum amount of lung to be resected.<sup>2</sup> Re-staging at thoracotomy should include the examination of lymph nodes in the hilum and mediastinum. The International Association for the Study of Lung Cancer has recognised a standardised term for this evaluation and set minimum acceptable standards. This technique, SND,<sup>3</sup> has been shown to improve operative staging with resultant improvement in stage-specific survival,<sup>4</sup> and may lead to improved overall survival.<sup>5</sup>

There is increasing evidence that size criteria, other than 3 cms, affect the prognosis in NSCLC. Tumours < 2 cms have a better prognosis than most T2 cases. Certain pathological sub-groups of adenocarcinoma are reliably node-negative and have an excellent prognosis with surgery.<sup>6</sup> The growing interest in CT screening for lung cancer has led to many small cancers being identified. Tumours in which the proportion of GGA is > 50% of the total tumour size have a similarly good prognosis.<sup>7</sup> These factors suggest that sub-lobar resection may be appropriate in selected cases. However, we must be wary of compromising the prospects for cure in such patients by this, or other, novel treatments without evidence from controlled studies.

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**Key words** Ground glass attenuation, lobectomy, resection for NSCLC, stage-specific survival, systematic nodal dissection.

**Sponsors** None.

**Declaration** No conflict of interest declared.

## SESSION 3 THE MANAGEMENT OF EARLY LUNG CANCER: WHOSE DOMAIN?

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### The Clinical Oncologist

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**Abstract** Even for early stage lung cancer, both non small cell and limited disease small cell, the survival figures are disappointing. The key to improving management is decision making by multidisciplinary teams of lung cancer professionals. The clinical oncologist offers the option of high dose radiation treatment alone or in combination with chemotherapy.

This paper will address the evidence for the use of high dose radiation treatment in early stage disease. It will also examine the emerging new options for treatment such as concurrent chemo-radiation, altered fractionation schedules for radiotherapy and new techniques in delivery of radiation treatment. There will be a focus on current clinical trials.

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**Key words** Chemoradiation, fractionation schedules, multidisciplinary team, radical radiotherapy.

**Sponsors** None.

**Declaration** No conflict of interest declared.

### Management of early lung cancer

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**Abstract** There have been considerable advances in the treatment of lung cancer over the past few years, mainly in NSCLC.

#### Operable NSCLC Stage III

There is now firm evidence for platinum based chemotherapy following resection in stage I-III NSCLC. The most recent trials indicate a five year survival benefit of 4–15%.<sup>1, 2</sup> Neoadjuvant, pre-operative chemotherapy still requires a definitive trial to prove its value. Furthermore the recent adjuvant results have rendered a surgery alone comparison inadequate.

Two trials in N2 patients, with somewhat different designs investigated the value of surgery compared to RT following initial concurrent CRT or response to CT. Neither trial conclusively proved an overall survival benefit for surgery.<sup>3, 4</sup>

#### Advanced inoperable Stage III NSCLC

The sequencing of RT with CT in selected patients with unresectable stage III disease is in favour of concurrent CRT using standard international (60–65 Gy) RT fractionation. In some UK areas standard concurrent CRT remains logistically difficult.

#### Small cell lung cancer

In good performance status, limited stage patients, platinum based CT and RT is now standard.<sup>5</sup>

#### Conclusion

The advent of targeted agents heralds a new approach in NSCLC therapy. Further developments in combined modality treatment are expected and engender enthusiasm for increased clinical trial development.

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**Key words** Chemotherapy early stage lung cancer, concurrent chemo/radiotherapy, non small cell lung cancer, platinum based chemotherapy, radiotherapy.

**Sponsors** None.

**Declaration** No conflict of interest declared.

#### Emerging novel therapeutic targets from basic research

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**Abstract** Following standard therapeutic management a clear plateau in patient survival has now been reached. New and innovative treatment approaches are urgently needed.

Novel therapies are currently being developed to block oncogenic transformation or restore these mechanisms to their prior normal and unaltered state. Specific targeted agents generally show improved toxicity profiles in comparison to conventional cytotoxic agents.

All cancers show serum independent growth as a result of the following mechanisms:

- Autocrine and paracrine growth factor loops.
- Oncogenic transformation of growth factor receptors.
- Oncogenic transformation of mitogenic intracellular signal transduction pathways.

Therefore growth factor receptor inhibitors e.g. Neuropeptide inhibitors (in SCLC or Epidermal Growth

Factor Inhibitors or signal transduction inhibitors e.g. tyrosine kinase inhibitors have been used to block serum independent growth.

Lung Cancers show resistance to chemotherapy and radiation induced apoptosis. This may be acquired from the local tumour microenvironments e.g. as a result of integrin-mediated cell adhesion or genetic as a result of over-expression of anti-apoptotic genes e.g. Bcl2.

Cancers all require new blood vessel formation for continued growth. High vessel density is a negative prognostic factor for overall survival and associated with higher incidence of lymph and distant metastases. Vascular endothelial growth factor is a growth factor that plays a major role in the development of tumour vasculature and hence is responsible for the growth and metastatic spread of different cancers. Thus inhibition of angiogenesis by VEGF inhibitors is a potential novel therapeutic strategy.

In addition, pharmacogenomics allows tailoring of conventional chemotherapy regimens to the individual patient according to the genetic characteristics/mutational status of the tumour.

**Key words** Epidermal growth factor inhibitors, growth factor receptor inhibitors, growth factor receptors, mitogenic intracellular signal transduction pathways, pharmacogenomics, tyrosine kinase inhibitors, vascular endothelial growth factor.

**Sponsors** None.

**Declaration** No conflict of interest declared.

### **New armaments against lung cancer**

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#### **Abstract**

**Background** Lung cancer is the most common cause of cancer death worldwide, with most patients dying with metastatic disease. Although the availability of platinum-based chemotherapy has resulted in increased survival of several groups of patients with NSCLC, the prognosis of the majority of them remains poor. It is evident that advances in the treatment will require new approaches and recent research has focused on molecular-targeted therapies.

**Methods or Theme** One of the most explored targets is the EGFR. Epidermal growth factor receptor is a member of the ErbB family of transmembrane tyrosine kinase receptors and several retrospective studies have identified the expression of EGFR as a negative prognostic factor in patients with resected early NSCLC. Two main categories

of EGFR inhibitors have been identified: monoclonal antibodies to the extracellular domain of the EGFR, and small molecules that are inhibitors of the intracellular TKI domain by interfering with autophosphorylation by ATP.

Significant clinical experience has been gained with gefitinib and erlotinib, two small-molecule TKIs with activity in NSCLC. The recent discovery of the association between mutations in the EGFR domain and sensitivity to TKIs has evoked intensive discussions on the selective prescription of TKIs and prospective translational studies will hopefully soon solve this matter.

Another promising therapeutic strategy is inhibition of the specific processes essential for tumor vascular development. The target is the proangiogenic VEGF. A large comparative study with or without bevacizumab, a humanised monoclonal antibody that binds VEGF, in selected patients with advanced NSCLC has shown a positive result and several other new antiangiogenic agents are in development.

**Conclusions** The identification of gefitinib, erlotinib and bevacizumab as active agents in NSCLC marks the beginning of a new therapeutic period for patients with NSCLC. Until recently a major limitation of these therapies have been the inability to identify those patients most likely to benefit. The discovery of molecular correlates of response holds the promise that we will soon have tools to tailor therapy according to the profile of the patient.

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## **SESSION 4 THE FUTURE**

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