J R Coll Physicians Edinb 2011; 41:142–9
doi:10.4997/JRCPE.2011.219
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Advances in the prevention and treatment of lung cancer

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ABSTRACT Lung cancer remains the most common fatal malignancy in the Western world. Survival rates have only improved modestly over the past three decades and new approaches are urgently required. It is clear that a concerted effort to reduce cigarette smoking is required. However, about 10% of patients with lung cancer are never smokers, indicating genetic or other predisposition. Lung cancer screening programmes are being trialled to target high-risk populations. Genetic strategies will provide new methods for screening and predicting response to treatment. Current therapy for lung cancer has reached a plateau and novel agents have shown modest clinical efficacy. Understanding the mechanisms by which chronic inflammatory disorders such as chronic obstructive pulmonary disease contribute to lung cancer development will help to identify new biological targets and biomarkers of early disease. This review focuses on recent advances in lung cancer prevention and treatment.

KEYWORDS Biological therapy, genetics, inflammation, lung cancer, screening, smoking

DECLARATION OF INTERESTS No conflict of interests declared.

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INTRODUCTION

Lung cancer accounts for more than 30,000 deaths each year in the UK.[1] The most frequent histological type is non-small cell lung cancer (NSCLC), which includes adenocarcinoma and squamous cell carcinoma.[2,3] These tumours can present with locally confined disease and therefore curative surgery or radiotherapy, possibly in combination with chemotherapy, are the treatments of choice.[4,5] Depending on the stage, the survival rates for surgically resected NSCLC vary from 25% to 65% at five years.[6,7] In contrast, survival rates in advanced NSCLC are poor (5–10% at five years).[7] Fewer than one in three patients is suitable for radical surgery and therefore overall ten-year survival remains less than 10%.[1,7]

Despite advances in diagnosis and treatment, survival figures for lung cancer have only improved modestly in the past two decades.[7] This has led many clinicians to call for new research with the aim of developing novel and effective therapeutic strategies. Improved understanding of the molecular biology of lung cancer will lead to better therapy and the identification of new risk factors and early diagnostic markers. This review focuses on the recent advances in this field, with a specific focus on NSCLC.

LINK TO CIGARETTE SMOKE

A landmark case-control study by Doll and Hill published in 1950 investigated the link between tobacco smoke and lung cancer.[8] It recruited patients with carcinoma of the lung, stomach, colon or rectum admitted to 20 London hospitals. Patients were then interviewed with respect to smoking habits and, for each lung cancer case identified, a control from the same hospital of the same sex and similar age (within five years) but not suffering from cancer was also interviewed. The crucial result from this study was that cigarette smoking had a direct association with lung cancer and that smoking habits were formed before the onset of the disease, suggesting causality.[8] Subsequently cigarette smokers were shown to have about 20 times the risk of lung cancer as life-long non-smokers.[9,10] Passive exposure to cigarette smoke resulted in positive urine tests for carcinogens specific to tobacco and is associated with a higher cumulative risk of lung cancer.[11,12] The clear association between lung cancer and smoking indicates that trends in lung cancer epidemiology closely follow changes in tobacco consumption, with a lag time of 25–30 years.[13] Future trends in lung cancer will therefore be shaped by the increase in female smokers in the past few years and the higher prevalence of tobacco use in lower socioeconomic groups.[14]

Smoking cessation reduces lung cancer risk

Data from the past ten years demonstrated that people who quit smoking have a reduced risk of lung cancer compared with those with a continued smoking habit, although the risk does not return to that of life-long non-smokers, even after 30 years of abstinence.[15,16] A case-controlled study conducted between 1988 and 1993 showed that the risk of death from lung cancer in male ex-smokers was approximately 5%, compared with almost 16% in males of the same age who continued to smoke. This effect was strongest if smokers quit at the age of 30 but was still significant up to the age of 60.[16] A recent meta-analysis showed that continuation of smoking after diagnosis is associated with an increased risk of tumour recurrence and death (all causes) in early-stage lung cancer.[17] Targeting current smokers to actively promote smoking cessation is therefore central

to lung cancer prevention and to reducing the risk of recurrence after curative treatment.

Advances in smoking cessation

Cigarette smoke-related cancer remains a significant health burden, despite changes in government policy and public health campaigns. This is in part due to nicotine addiction promoting continued smoking and thus exposure to inhaled carcinogens.[18] Until recently, smoking cessation therapy has focused on counselling, nicotine replacement and bupropion. Unfortunately, long-term cessation rates are poor (approximately twice placebo).[19]

Recent work has advanced our knowledge of nicotine addiction and produced targeted drug therapy to promote smoking cessation. In 2006, a clinical trial compared varenicline, a partial agonist at the $\alpha 2$-$\beta 4$ nicotinic receptor, with sustained release bupropion or placebo. Importantly, 12 weeks of varenicline therapy produced significantly greater continuous abstinence rates compared with the other two interventions.[20] An additional study demonstrated that prolonged therapy with varenicline (24 weeks) improved abstinence rates compared with placebo, even when the drug was stopped,[21,22] although long-term quit rates remained low. These studies resulted in the approval of varenicline for use in smoking cessation. It is also important to note the key role of smoking cessation services in coordinating cessation therapy and improving quit rates.[23]

It is clear that further research is required into the mechanisms of nicotine addiction. A new report highlights a nicotine addiction locus on chromosome 15q24-25, which includes the $\alpha 5$-$\alpha 3$-$\beta 4$ nicotinic receptor gene cluster.[24] A polymorphism, which alters an amino acid in this nicotinic receptor, is associated with lung cancer and chronic obstructive pulmonary disease (COPD).[24] It is hoped that this kind of research will identify novel genes that promote nicotine addiction and thus reveal new targets for drug therapy. The future may involve assessing 'addiction' genes in smokers to allow individualised therapy.

GENETIC RISK FACTORS

Approximately 10% of lung cancers arise in life-long non-smokers.[25] This group accounts for nearly 3,000 deaths each year in the UK.[25] The development of lung cancer in non-smokers cannot be solely attributed to passive smoking or atmospheric pollution, suggesting the existence of genetic and/or other risk factors. This hypothesis is supported by the observation that smokers who have a first-degree relative diagnosed with lung cancer before 50 years of age have a higher risk of developing lung cancer than those with no family history.[26]

Bailey-Wilson and colleagues' linkage analysis of 52 families with three or more individuals affected by respiratory tract malignancy showed that susceptibility to lung cancer maps to a locus on chromosome 6q23-25.[27] Detailed mapping of this region revealed a potential candidate gene, although its function is unknown.[28] Genome-wide association studies have also identified loci on chromosomes 5p15, 6p21 and 15q25 that are associated with lung cancer.[29,30] Of particular interest, 15q25 contains three cholinergic nicotine receptor genes and variations in these genes may contribute to lung cancer risk independent of effect on nicotine addiction.[31] These loci only account for 10% of familial lung cancer risk and stratification of current and ex-smokers by number of risk variants shows that smoking is the predominant risk factor.[32]

Other approaches to identify genetic factors associated with lung cancer have focused on differential gene expression profiles from airway epithelium of current and never smokers and the sequencing of lung cancer genomes.[33,34] It is anticipated that research of this type will identify at-risk populations for screening, define markers of early disease and suggest novel targets to prevent the carcinogenic effects of tobacco smoke.

LUNG CANCER SCREENING

Screening for lung cancer is an attractive option. Symptoms caused by lung cancer occur at a late stage as the tumour invades local structures or spreads to distant sites. Thus, the majority of patients present with advanced disease.[1] Early-stage lung cancer has a better survival rate, primarily as a result of response to treatment and therefore identification of small lung tumours before symptoms are present may greatly affect lung cancer survival.[7] Several challenges need to be addressed before a successful lung cancer screening programme can be established: defining a screening method, determining the population for screening and developing a pathway for follow-up of pulmonary nodules.

Chest X-ray and computed tomography screening

Initial screening programmes in lung cancer using chest radiographs and/or cytological analysis of sputum in male smokers have produced disappointing results.[35] Computed tomography (CT) screening may be a better technique as it is able to detect lung parenchymal changes before they are apparent clinically or on chest X-ray. Several lung cancer screening trials using low-dose CT showed that malignant tumours can be detected at an earlier stage than by clinical assessment.[35–39] However, these trials were not controlled in design and therefore effect on mortality is difficult to determine. In addition, these studies showed high false positive rates and low rates of detection of incident cases of lung cancer.[35] To address these issues, randomised controlled trials of low-dose CT in lung cancer screening are being conducted. Designed to compare the effect of screening with low-dose CT or chest X-ray on lung cancer

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mortality, the largest of these studies recruited more than 50,000 patients in the US between 2002 and 2004. The last round of screening was carried out in 2007 and an overview report has been published this year.[39] Smaller European studies have reported preliminary results on prevalence of lung cancer at baseline screening but have yet to complete.[40,41]

Screening programmes are not without inherent difficulties, some of which are specific to lung cancer. Many of the reported screening studies show that uptake by the 'at-risk' population is low and methods for recruitment are inefficient.[42] In addition, the prevalence of pulmonary nodules detected by CT is high in the 'at-risk' population.[43] However, the majority of nodules are benign, even in smokers, raising concerns about over-investigation of potential malignancy.[44] Finally, although some screening studies have suggested improvements in lung cancer mortality in the screened population, other investigators have suggested that this may simply be due to detection of cancer earlier within its natural history or so-called 'lead-time' bias.[45]

UK lung screening trial

To address these issues Baldwin et al. have recently described the UK lung screening trial (UKLS).[46] This will recruit 28,000 patients from seven centres in the UK with ≥5% lung cancer risk within five years, determined using a well-established model of lung cancer risk (Liverpool Lung Project risk model). Patients will be randomised to either low-dose CT screening or no screening with a ten-year follow-up. The study will employ a single-screen design with a nodule management protocol based on volumetric analysis and nodule characteristics, which determines referral to the multidisciplinary team or CT follow-up. It also defines a new protocol for the follow-up of pulmonary nodules. It is hoped that this study will not have the problems of long-term compliance as it employs a single screen technique and may prove to be cost-effective as it targets a high-risk population. It is highly likely that routine CT screening in the UK will wait until the results of this trial.

ADVANCES IN THE STAGING OF NSCLC

The primary influence on lung cancer treatment decisions by the multidisciplinary team is the stage of the tumour at diagnosis. The Tumour Node Metastasis (TNM) classification of NSCLC, which originated in 1974, has recently been revised. For the first time, this revision (the seventh edition) is based on analysis and validation of outcome data from a large international database of lung cancer cases.[47] There have been several important alterations in the descriptions of the T and M groupings to reflect differences in patient prognosis, which are summarised in Table 1. Following careful analysis, the N descriptor has remained unchanged (N0–3). Although these new TNM subgroups have resulted in a more complex definition of the stage groups (I–IV), the seventh edition classification is widely accepted as a more evidence-based system for the basis of treatment decisions.

TABLE 1 Summary of important changes in the seventh edition of the Tumor Node Metastasis (TNM) classification

T descriptor
A size cut-off of 2 cm divides T1 tumours into 'a' and 'b' subcategories.
A size cut-off of 5 cm divides T2 tumours into 'a' and 'b' subcategories.
Tumours with additional tumour nodules in the same lobe as the primary tumour are now designated T3 rather than T4.
Additional tumour nodules in other ipsilateral lobe(s) are reclassified from M1 to T4.
M descriptor
Tumours associated with additional tumour nodules in the contralateral lung are classified as M1a.
M1a category now includes lung tumours with malignant effusion involving the pleural or pericardium (reclassified from T4).
M1b subcategory includes those tumours with distant/extra-thoracic metastases.

Staging techniques for lung cancer have also advanced in the past decade, including more sophisticated imaging such as 18F-deoxyglucose positron emission tomography (FDG-PET). This technique is now widely available to cancer centres and has been shown to accurately stage lung cancer and prevent unnecessary radical treatment.[48] However, its applicability is limited by false positive and negative results[48] and confirmation by histology is often necessary.

Minimally invasive staging techniques have progressed significantly, particularly in the field of endobronchial ultrasound (EBUS). Endobronchial ultrasound allows almost complete staging of mediastinal lymph nodes, can be carried out as a day case and has a high sensitivity and specificity.[49] It is now often the first-choice diagnostic and staging technique for suspected NSCLC with an involvement of the mediastinal nodes on imaging (CT or FDG-PET) and can prevent unnecessary thoracotomy.[50] Endobronchial ultrasound is, however, limited to fine needle aspirate (FNA) samples, which may not be sufficient for the assessment of biomarkers of treatment response. This issue is being addressed by research on ribonucleic acid extracted from EBUS-FNA samples.[51]

ADVANCES IN CHEMO- AND RADIOTHERAPY

Adjuvant therapy

Surgical resection remains the recommended treatment modality for patients with early stage (I–II) disease, as it produces the best survival outcome.[52] Radical radiotherapy should be considered for patients who have potentially resectable disease but cannot undergo surgery for other reasons.[53] Despite radical surgery, five-

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year survival rates are suboptimal, often due to tumour recurrence at untreated sites. This has led to considerable research into the effectiveness of adjuvant therapy for resected NSCLC. In an analysis of the five largest trials of adjuvant cisplatin-based chemotherapy using individual patient data, Pignon et al. showed an absolute survival benefit of approximately 5% at five years with platinum-based chemotherapy, irrespective of the second drug in the regime.[54] They also concluded that the benefit was greater for those with stage II or III disease. As a result, the National Institute for Health and Clinical Excellence (NICE) guidelines now suggest considering post-operative chemotherapy for patients after complete resection.[55]

In contrast, post-operative radiotherapy (PORT) remains controversial. Analysis of randomised controlled trials and national databases has not suggested an overall survival benefit with PORT, although some data suggest a prognostic benefit in those patients with N2 disease.[56–58] The ongoing Lung Adjuvant Radiation Trial aims to assess PORT in patients with resected N2 NSCLC.[59] Post-operative radiotherapy may also be of possible benefit in patients with N0 disease with incomplete resection margins.[60,61] Combined post-operative chemo- and radiotherapy has also been trialled, with no statistically significant survival benefit and increased side effect profile.[62,63] In the light of these studies, the NICE guidelines suggest that PORT be considered in patients with incomplete resection.[56] One of the next challenges for adjuvant therapy trials will be the definition of tumour biomarkers that predict response to treatment to allow oncologists to develop individualised management strategies for patients.

Advanced NSCLC

Recent advances have been made in the treatment of unresected stage III NSCLC. Analysis of earlier studies showed that the combination of radical radiotherapy and chemotherapy provides a significant benefit in survival compared with either treatment modality alone.[64] An up-to-date meta-analysis of 19 randomised trials confirmed that combination therapy significantly reduces overall risk of death compared with radiotherapy alone at an increased risk of toxicity.[65] Furthermore, this publication demonstrated that concurrent chemoradiation provided a significant survival advantage compared with chemotherapy followed by radiation, with an absolute survival benefit at two years of approximately 10%.[65] It is likely that advances in this field will come with the development of novel radiation techniques and trials of new chemotherapy agents.

The standard treatment for patients of good performance status with advanced NSCLC (stage IIIB–IV) remains two-agent platinum-based chemotherapy.[66,67] Recent data from a phase III trial suggest that cisplatin plus pemetrexed has a survival advantage over cisplatin plus gemcitabine for NSCLC with non-squamous histology.[68]

Second-line chemotherapy is increasingly used for patients of good performance status. Phase III trials have demonstrated the efficacy, in terms of survival and quality of life, of single-agent docetaxol or pemetrexed, compared with supportive care, for patients with recurrent or progressive disease.[69–71] In addition, two phase III trials indicated that patients treated with maintenance docetaxol or pemetrexed following four cycles of platinum-based chemotherapy had improved progression-free survival in comparison with those on best supportive care.[72,73] Maintenance pemetrexed also improved overall survival.[73] Despite these advances, five-year survival in stage IIIB–IV NSCLC remains very poor, and novel targeted agents are being sought.

GROWTH FACTOR PATHWAYS IN NSCLC

A major event in malignant transformation is the development of uncontrolled cellular proliferation. A wide range of polypeptide growth factors regulate cell division by binding to receptors that possess intrinsic tyrosine kinase activity.[74] Mutations in these growth factor signalling pathways have been identified in many cancers and have been the focus for the development of novel therapies.[75] The best studied of these in lung cancer are the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF).

Epidermal growth factor receptor

The EGFR family (HER1–4) is a group of transmembrane receptors that play a critical role in the pathogenesis of many cancers.[76] Epidermal growth factor receptor expression is observed in up to 80% of NSCLC tumours and has been shown in some studies to predict poorer prognosis.[77] Two groups of agents targeting EGFR have been trialled in lung cancer: monoclonal antibodies blocking ligand-receptor interaction (cetuximab) and inhibitors of the EGFR tyrosine kinase activity (gefitinib and erlotinib). In phase II trials cetuximab was generally well tolerated and could confer survival advantage either as single therapy in patients with previously treated advanced NSCLC or in combination with standard chemotherapy regimes as first-line treatment for advanced NSCLC.[78] In a phase III trial of EGFR-positive advanced NSCLC (FLEX), cetuximab added to cisplatin and vinorelbine produced a modest survival advantage (1.2 months), compared with chemotherapy alone.[79] A recent meta-analysis of four trials concluded that the combination of cetuximab and standard chemotherapy as first-line treatment in advanced NSCLC can improve survival and response rate compared with chemotherapy alone, although the cost-effectiveness has been questioned.[80,81]

Gefitinib and erlotinib have been the primary focus of clinical trials as they can be orally administered. Several phase II studies in advanced NSCLC demonstrated good tolerability, encouraging objective response rates and

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improved quality of life scores with gefitinib.[82–84] However, several large phase III trials in previously treated and in chemotherapy-naive advanced NSCLC have failed to show an overall survival advantage with gefitinib.[85–88] This is in contrast to a phase III trial comparing erlotinib with placebo in previously treated stage IIIB/IV NSCLC that indicated a significant survival advantage with erlotinib,[89] which was subsequently approved as second-line therapy for advanced stage NSCLC.

The results with gefitinib have been disappointing. However, certain patient groups (e.g. adenocarcinoma, female gender, non-smokers) may exhibit better responses to anti-EGFR therapy.[90] Interestingly, these individuals have the highest rate of EGFR tyrosine kinase mutation.[91] Several small phase II studies of gefitinib in patients with EGFR mutations have shown encouraging progression-free survival times.[92] The IRESSA Pan-Asia Study (IPASS) trial investigated the effectiveness of first-line gefitinib compared with standard chemotherapy in a patient group (n=1,217) from East Asia with advanced NSCLC (adenocarcinoma histology) and a history of light or no smoking.[93] A total of 437 patients had an evaluation of EGFR mutation. Importantly, the mutation-positive group (n=261) had a significantly better response to gefitinib compared with chemotherapy, whereas this was not the case in the mutation-negative group. This suggests that the assessment of EGFR mutations may be an important biomarker in NSCLC for predicting response to anti-EGFR tyrosine kinase inhibitors.[93]

Another important factor that determines response to these agents is the presence or development of drug resistance. Recognised resistance mechanisms in NSCLC include mutations in KRAS, activation of other additional signalling pathways (e.g. mesenchymal epithelial transition factor) and EGFR mutations (e.g. T790M).[94] Defining new resistance factors and the design of second-generation inhibitors of EGFR will be the focus of future research.

Angiogenesis and vascular endothelial growth factor

For a tumour to grow and remain viable, new blood vessel formation is essential. This process, named angiogenesis, is regulated by VEGF and its receptor tyrosine kinases.[95] High VEGF levels in NSCLC are associated with a poor prognosis, making this signalling pathway an attractive target in NSCLC.[96] Bevacizumab is a humanised monoclonal antibody that binds and neutralises VEGF. Two phase III trials in advanced NSCLC confirmed that bevacizumab in combination with standard chemotherapy improves objective responses and progression-free survival time compared with chemotherapy alone.[97,98] However, a significant increase in pulmonary haemorrhage has been observed with bevacizumab.

Several small molecule tyrosine kinase inhibitors have been developed recently that target VEGF and other growth factor signalling receptors, including EGFR and platelet-derived growth factor. Initial phase II trial results have shown some efficacy with these agents in advanced NSCLC.[99,100] The results of ongoing phase III trials are awaited.

Growth factor receptor signalling remains an active area of research interest in NSCLC. It is likely that with increased knowledge of these pathways, their activating mutations and downstream components, novel targeted therapies will be developed in the next ten years. Defining markers of treatment response will remain the challenge for the future and will hopefully lead to individualised cancer therapy.

LUNG CANCER AND INFLAMMATION

The role of inflammation in lung cancer development has been much better understood in the past five years. It is now clear that COPD, even in the absence of cigarette smoking, increases the risk of lung cancer up to five-fold and that treating airways inflammation in COPD with inhaled corticosteroids may reduce the risk of lung cancer.[101,102] Pulmonary fibrosis is also associated with an increased risk of lung cancer.[103] In addition, C-reactive protein, a marker of the systemic inflammatory response, has been shown to predict lung cancer risk.[104] Furthermore, microbial colonisation and associated inflammation in patients with COPD, including ex-smokers, may increase the risk of lung cancer. In vivo, infecting the mouse lung with *Haemophilus influenzae* can produce bronchial inflammation with a pattern similar to COPD and promote lung cancer development.[105]

There is now a growing body of evidence that the processes involved in chronic lung inflammation are shared by those early on in lung cancer development and may in fact promote the growth of established tumours.[106,107] In studies of lung cancer resections, the tumour infiltrating stroma consisted of a complex reaction of immune cells, fibroblasts, blood vessels and extracellular matrix, with similar features to a chronic wound.[108] Certain cell types in this infiltrate correlated with patient prognosis, including macrophages and lymphocytes, suggesting an important role in lung cancer pathogenesis.[109] In a syngeneic mouse model, lung cancer growth was reduced by restricting 'alternative' macrophage activation.[110] Research defining pathways that regulate lung cancer inflammation may reveal new targets for therapy.

The next ten years will hopefully see a clear understanding of the inflammatory signals involved in early cancer development. This may reveal new markers for lung cancer screening and define targets to prevent or reverse the carcinogenic effects of tobacco smoke. The impact of these advances on lung cancer survival are unlikely to be felt for two to three decades and therefore research into lung cancer screening and treatment must continue.

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CONCLUSION

Lung cancer continues to cause early death and, despite advances in standard treatment, mortality rates have seen only a modest improvement in the past 20 years. We now need strategies for reducing smoking, preventing the carcinogenic effects of tobacco smoke and detecting lung cancers early in the disease course by targeting at-risk populations. Furthermore, new treatments for lung cancer are required to improve survival after 'curative' radical surgery and in locally advanced/metastatic disease. In parallel, novel molecular markers of disease progression and response to therapy must be defined through the assessment of tumour genetic signatures. We believe that significant advances will be made through research into the role of chronic inflammation in the early development, growth and spread of lung cancer and that this should be a major focus for the next decade. Ultimately, it is hoped that lung cancer will become, for the majority of patients, a disease with extended periods of remission or even cure after therapy.

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