Effectiveness Bulletin

Management of lung cancer

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Introduction

This paper summarises a series of interlinked systematic reviews carried out to inform guidance on commissioning cancer services published by the National Health Service (NHS) Executive.[1] These formed the basis of an *Effective Health Care* bulletin, Vol 4, No 3.[2] Information on the review process, including the specific questions considered, is given in *Improving outcomes in lung cancer: the research evidence.*[1]

Incidence and prognosis

Lung cancer (which includes cancer of the trachea and bronchi) is the third most common cause of death in England and Wales, with 30 803 deaths in 1996 (data provided on request from the Office for National Statistics, 1997). The prognosis is generally poor; about 80% of patients die within a year of diagnosis (unpublished data from Northern and Yorkshire Cancer Registry and Information Service, 1997) and a mere 5.5% survive 5 years.[3]

The disease tends to progress rapidly and many patients are both elderly and less fit than their contemporaries, often with other illnesses related to smoking. Fitter people with early stage cancers which can be treated by surgery have a much better prognosis; published reports suggest that two thirds of these patients may survive for 5 years.[4]

Causes and prevention

SMOKING

Ninety per cent of lung cancer deaths are estimated to be caused by smoking, 5% by radon, and 2% by asbestos.[5 6] Smoking prevention is the only measure that can be expected to have a substantial impact on the incidence and mortality of lung cancer. There is good evidence that interventions to help people stop smoking, provided at both local and national levels, can be highly cost effective.[7–9]

Effective interventions range from mass media campaigns to individual advice and support.[10] Rates of stopping achieved by selected interventions are given in the box.

Effective interventions to help people stop smoking

Type of intervention	*Stop rate (%)*
Brief advice from health professionals	2
Nicotine replacement plus advice, support or counselling	12
10 minutes (minimum) prenatal counselling for pregnant women, plus written material tailored to pregnancy	15

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Accepted for publication 20 July 1998

NUTRITION

There is an inverse association between consumption of fruit and vegetables and the incidence of lung cancer.[11–14] Supplements of vitamins thought to confer protection have not been shown to produce the same benefits; indeed, intervention trials have found increases in incidence and mortality of lung cancer in smokers who take β-carotene supplements.[15 16]

RADON

Radon is a naturally occurring odourless radioactive gas which emanates from some types of rock. People who live in houses in which radon concentrations are high are more likely to develop lung cancer.[6]

A meta-analysis of case-control studies which included 4263 lung cancer cases and 6612 controls found a significant dose related increase in the risk of lung cancer with increasing exposure to radon.[17] There is evidence of synergy between the effects of smoking and radon, such that cigarette smokers exposed to radon are at particularly high risk.[6 18]

Radon concentrations vary widely across Britain.[19] Indoor radon can be reduced by sealing buildings so that air cannot enter from the soil and by increasing ventilation to the lower levels of the building.[20] Such work is cost effective where radon concentrations are high: figures of $6100 and $35 000 per life-year saved have been calculated for homes with concentrations of >800 and >300 Bq/m^3, respectively (United States figures based on data from the mid-1980s).[21]

ASBESTOS AND OTHER ENVIRONMENTAL CARCINOGENS

Asbestos is the most common cause of lung cancer related to occupation; again, the risk increases with cumulative exposure.[22] Building workers, plumbers, and gas fitters, carpenters, electricians, and metal plate workers and fitters form the largest high risk groups.[23]

Other substances known or thought to cause lung cancer include acetaldehyde, acrylonitrile, arsenic, beryllium, bis (chloromethyl) ether, cadmium, chromium, formaldehyde, nickel, polycyclic aromatic compounds (in diesel exhaust), silica, synthetic fibres, vinyl chloride, and welding fumes.[24]

Information and communication

Dealing with lung cancer can involve difficult choices for patients and clinicians. Effective communication is essential to ensure that patients who wish to make informed choices are able to do so, and that their views are respected.

The most common complaint by cancer patients is that they are given too little information.[25] Almost all want accurate information about diagnosis and treatment; such information reduces anxiety even when the news is bad.[26–29]

Some of the most effective types of treatment, in terms of life expectancy, can cause severe adverse effects. While some patients place great value on the hope of increased survival time, others are more concerned about the quality of their remaining life.[30]

To make appropriate choices, patients need accurate information about anticipated effects, both good and bad, of each treatment option. This has additional benefits. Patients who are given information on what they are likely to experience before they undergo treatment are less anxious and express greater satisfaction.[31 32] Psychoeducational interventions which include information can reduce some adverse effects of treatment.[33 34]

Diagnosis

SCREENING AND EARLY DIAGNOSIS

Systematic reviews of screening with radiography (*x* ray films) and sputum cytology (examination of cells in sputum produced by coughing) for asymptomatic men at high risk of lung cancer have concluded that it is not effective.[35 36] Three randomised controlled trials (RCTs) including 30 000 male smokers over the age of 45, controlled prospective studies, and case-control studies found no evidence to suggest that early diagnosis achieved through screening can reduce mortality from lung cancer. Although more tumours which can be removed by surgery and lower case fatality rates are found with more frequent screening,[37] this is likely to be due to lead time and duration biases.

DIAGNOSTIC METHODS

The aim of diagnosis is both to identify the presence and extensiveness of lung cancer and to determine the tumour type. This information is essential for decision making about management.

Lung cancer is broadly differentiated into two types, which respond differently to different types of treatment: small cell lung cancer and non-small cell lung cancer. About 80% of patients have non-small cell tumours, and 20% small cell.

Most symptomatic tumours can be seen on *x* ray films. Histological information is usually obtained by bronchoscopy, but this can have adverse effects (mortality 0.2%) and can be unpleasant for patients.[38 39] Although tumour type can sometimes be identified from sputum cytology, this method cannot be used to exclude lung cancer because it has a high false negative rate.[40]

STAGING

In non-small cell lung cancer, accurate staging is particularly important for decision-making about surgery. Tumour stage can be assessed by computed tomography (CT) or sampling lymph nodes around the bronchial tubes (mediastinum). A randomised controlled trial which compared staging by CT with CT plus routine mediastinoscopy (surgical investigation of the mediastinum) showed that mediastinoscopy did not improve outcomes if the lymph nodes seen on the scan appeared normal.[41]

In small cell lung cancer, CT is useful to assess the extent of the disease when thoracic radiotherapy (see later) is being considered, as this treatment is only appropriate for patients who have limited disease (tumour confined to one side of the chest).[42]

Meta-analysis of 25 published studies shows that metastatic lung cancer (non-small cell lung cancer or small cell lung cancer) can be excluded by careful clinical examination using predefined criteria and blood tests; routine CT is not normally necessary.[43]

Treatment of non-small cell lung cancer

First line treatment for non-small cell lung cancer is normally surgery or radiotherapy, depending on the condition of the patient and the stage of the disease.

SURGERY

Surgery is regarded as the only treatment that offers the hope of cure in non-small cell lung cancer. The most effective types of surgery involve opening the chest (thoracotomy) and removing a lung (pneumonectomy) or a lobe of a lung (lobectomy).[44]

Surgery is only appropriate for patients who are relatively fit, who have adequate respiratory capacity, and who have early stage, histologically confirmed, non-small cell lung cancer. There is no evidence that selection should be based on the patient's age.[45] It seems that these conditions are often not met in the United Kingdom; in particular, a survey carried out in 1990 suggests that many surgeons fail to ensure that patients are adequately staged.[46]

A trial in 1963[47] found that surgery was more effective than radiotherapy but there are no recent reliable estimates of the increase in survival which may be attributed to surgery. Observational evidence from a United States study suggests that 5 year survival for patients with stage I disease who undergo surgery is 70%, compared with 10% for those who do not.[48] However, outcomes for patients who undergo surgery in NHS hospitals are poorer than this, if only because most have later stage tumours; audit data from Yorkshire suggest that the overall 5 year survival rate is 27% (unpublished data from Northern and Yorkshire Cancer Registry and Information Service, 1997).

Surgery for lung cancer carries a 5% overall risk of operative mortality and causes significant morbidity. Ten per cent of patients have major life threatening complications, and 50% have persistent incisional pain for 1–4 years.[49] Quality of life is temporarily impaired, returning to preoperative baseline after 6 months.[50]

Almost 11% of thoracotomies in the United Kingdom are open and close: the chest is cut open but the tumour is not removed (D Watson, personal communication, 1997). This usually occurs when the disease is too extensive to be treated by surgery—that is, the stage of

the tumour has not been accurately assessed—and implies avoidable morbidity and wasted resources.[51] Considerably lower rates can be achieved; for example, a rate of 4% was reported in a Canadian trial.[41]

RADIOTHERAPY

Patients who are less fit, or whose tumour is too extensive for surgery but do not have distant metastases, are likely to benefit from radical radiotherapy. Medium term survival seems to be improved by higher doses of radiotherapy but the risk of serious adverse effects also increases.[42]

The radiotherapy schedule most often used for radical treatment (60 Gy in 30 fractions) continues for 6 weeks. This type of conventional radiotherapy has been compared in an randomised controlled trial with CHART (continuous hyperfractionated accelerated radiation therapy), in which a similar total dose is given in small fractions three times daily for 12 consecutive days. CHART was found to reduce mortality (hazard ratio 0.76; 95% confidence interval (95% CI) 0.63 to 0.92; p=0.004). After 2 years, 29% of patients treated with CHART were alive, versus 20% of those treated conventionally.[52 53]

Adjuvant radiotherapy, given before or after surgery, has not been shown to improve outcomes; indeed, it may be harmful.[54 55] A meta-analysis of data from randomised controlled trials of postoperative radiotherapy found that it led to a 7% reduction in survival at 2 years (p<0.0003).[56]

CHEMOTHERAPY

A meta-analysis of outcomes for 9387 patients in 52 randomised controlled trials shows that modern cisplatin based chemotherapy leads to slight improvements in survival, compared with no chemotherapy.[57] In early non-small cell lung cancer, adjuvant chemotherapy offers an absolute survival benefit of 4% (95% CI: 1% to 7%) at 2 years and 2% (95% CI: 1% to 4%) at 5 years.

The value of chemotherapy before surgery is uncertain, although two small randomised controlled trials have suggested that it may improve survival.[58–60] This issue is being considered in a major United Kingdom trial.[61]

Various new generation drugs have been developed which seem promising and may improve outcomes. However, there is as yet no clear evidence from published randomised controlled trials that these drugs are more effective than established platinum based combinations.[62 63]

Treatment of small cell lung cancer

The first line treatment for small cell lung cancer is normally chemotherapy. Radiotherapy may be used as well as chemotherapy, but a randomised controlled trial showed no improvement in outcomes after surgery.[64]

CHEMOTHERAPY

Before the introduction of combination chemotherapy, most patients with small cell lung cancer survived for 2–4 months. Since 1980, median survival times reported in trials have been around 12 months.[65 66] Outside the context of trials, patients treated with chemotherapy in England live for a median of about 7 months (unpublished data from Northern and Yorkshire Cancer Registry and Information Service, 1997).

Combination chemotherapy leads to better outcomes than single agent treatment.[65] In particular, oral etoposide leads to more toxicity and worse survival than standard combination chemotherapy.[67 68]

The combination most often studied is cyclophosphamide/doxorubicin/vincristine (CAV), which can induce responses and temporary remission from symptoms in 80%–90% of patients. Cisplatin/etoposide (PE) produces similar benefits.[69] Three to six cycles of chemotherapy may be given.[70–72] In general, more effective regimens tend to be more toxic, so the greatest improvements in survival time are likely to be accompanied by worse adverse effects; but there is marked individual variability in the impact of chemotherapy.[70 73–77]

No published randomised controlled trials compare CAV or EP with new generation agents such as gemcitabine, taxanes, vinorelbine, or navelbine, alone or in combination. Reports of uncontrolled phase II trials do not provide reliable evidence of effectiveness.

Dose-intensification, achieved either by increasing doses or by reducing the time-interval between cycles of chemotherapy, does not offer any benefit.[65 78] Meta-analysis of results of 60 published studies shows little correlation between dose-intensity and survival.[79]

Up to 10% of patients in some trials have died after chemotherapy, usually 1–2 weeks after treatment began.[80–82] Patients at particularly high risk of early death have poor performance, extensive disease, white blood cell count >10 000/mm^3 and high alkaline phosphatase, high blood urea or low serum albumin.[81] Age does not seem to be a significant independent risk factor.[83]

Nausea and vomiting peaks for about 3 days with each cycle of chemotherapy and can cause marked impairment of quality of life.[71 73 76 84–86] A meta-analysis of 30 randomised controlled trials shows that 5-HT$_3$ receptor antagonists are significantly more effective than conventional anti-emetics for prophylaxis of acute vomiting caused by cytotoxic chemotherapy, whether or not this includes particularly emetogenic drugs such as cisplatin.[87]

RADIOTHERAPY

Patients with small cell lung cancer who respond to chemotherapy may also benefit from radiotherapy. This can be given both to the chest, to improve local tumour control, and to the brain, to reduce the risk of brain metastases (prophylactic cranial irradiation).

Two meta-analyses of randomised controlled trials have confirmed that the addition of thoracic radiotherapy to chemotherapy can increase survival time in patients with limited small cell lung cancer.[88 89] One, using individual data from 2140 patients in 13 randomised controlled trials, found that the relative risk of death in patients who had combined radiotherapy and chemotherapy, compared with those who had

chemotherapy only, was 0.86 (95% CI 0.78 to 0.94; p=0.001). This represents an absolute overall survival benefit of 5.4% ± 1.4%; about 10% of patients alive after 3 years with chemotherapy alone, versus 15% after combined treatment. There was no evidence of benefit for patients >70 years old but the 95% CIs are wide (relative risk 1.07; 95% CI 0.70 to 1.64).[88] Thoracic radiotherapy leads to better tumour control within the chest but more early deaths (odds ratio 2.54; 95% CI 1.90 to 3.18; p<0.01).[89] These early deaths are counterbalanced by improved longer term survival.[88 89]

Prophylactic cranial irradiation can significantly enhance survival and reduce the risk of brain metastases without compromising quality of life.[90 91] A meta-analysis of individual data from randomised controlled trials found that prophylactic cranial irradiation for patients in complete remission after chemotherapy reduced the risk of death, relative to those who did not have it, to 0.84 (95% CI 0.73 to 0.97; p=0.01). This represents a 5.4% absolute improvement in the 3 year survival rate (21% *v* 15%). Radiotherapy doses ranged from 8 Gy in one fraction to 40 Gy in 20 fractions and there seems to be a dose-response relation.[92]

Management of advanced disease

Advanced lung cancer causes many distressing symptoms. Over three quarters of patients have breathlessness and cough, which can be severe and disabling. Weight loss, weakness and malaise, chest and bone pain, haemoptysis (coughing up blood), and anxiety are also common. Palliation—reducing the severity of symptoms—is the main aim of treatment for most patients, and should be an integral part of care for all patients with lung cancer.[93–96]

RADIOTHERAPY

Radiotherapy can palliate symptoms in 70% of patients with advanced lung cancer.[97] It is appropriate for patients with advanced non-small cell lung cancer and may relieve symptoms in patients with small cell lung cancer for whom chemotherapy is unacceptable or inappropriate.

Chest symptoms may be relieved with minimal adverse effects with a single fraction of radiotherapy.[98] A series of linked randomised controlled trials comparing the effectiveness of four radiotherapy schedules found few differences in outcomes. Although a higher dose (39 Gy) may improve survival slightly in patients with a better prognosis, symptoms are controlled less rapidly and adverse effects are greater.[98–100]

Radiotherapy offers substantial relief for over 40% of patients with pain due to bone metastases. Meta-analysis of results of randomised controlled trials show little discernible difference in effectiveness between different fractionation schedules or doses.[101]

CHEMOTHERAPY

Chemotherapy can reduce the severity of many symptoms concurrently in patients who respond. It is appropriate as first line treatment for patients who present with extensive small cell lung cancer. Its role in the treatment of advanced non-small cell lung cancer is less clear; although it produces an increase of around 6 weeks in life expectancy (an absolute improvement in survival of 10% (95% CI 5% to 15%) at 1 year),[57] the overall balance of benefits to adverse effects, and the cost effectiveness, is not clear. This issue is currently being considered in the big lung trial.[61]

Quality of life in patients undergoing chemotherapy for advanced non-small cell lung cancer tends to be overestimated because it is based on data from the healthier subgroup who survive for longer.[102 103] Most reports lack detail and none includes patients' assessments or measures day to day changes.[104] Studies which report control of symptoms usually include only clinicians' reports, which may not accurately reflect patients' experience.[105] The symptoms assessed may not be those that cause the greatest distress; fatigue, one of the most common symptoms of lung cancer, is rarely considered.[93 102 106 107]

Nevertheless, it seems that chemotherapy can offer at least partial relief from some symptoms.[108–113] The median duration of palliation associated with three treatment cycles ranges from 10 to 24 weeks but the balance between palliation of symptoms and adverse effects varies widely between people.[114] Any benefits are usually apparent after the first cycle of chemotherapy and almost always by the third course.[111]

MANAGEMENT OF BREATHLESSNESS

Breathlessness due to lung cancer can be life limiting and sometimes, life threatening. Uncontrolled breathlessness can be costly to the health service; a study of 122 lung cancer patients presenting with breathlessness at the emergency department of a cancer centre found that 60% were admitted to hospital.[115] Various approaches to treatment are used, ranging from behavioural interventions, through drug treatment, to interventions to physically remove tumour from the airways.

Counselling and breathing retraining by nurses can reduce anxiety and enhance patients' ability to cope with the effects of breathlessness. Two randomised controlled trials, one published[116] and one unpublished (Bredin M, Krishnasamy M, Corner J, *et al. Multicentre evaluation of a nursing clinic for breathlessness in patients with lung cancer*) have shown that this approach can significantly reduce distress ratings and improve physical functioning in patients with lung cancer. These results are consistent with many publications that show that psychoeducational interventions can improve both physical and psychological wellbeing of cancer patients.[33]

Pharmacological interventions for breathlessness include opioids, anxiolytics, and anaesthetics, but evidence for their effectiveness is poor.[117–121]

Breathlessness due to pleural effusion is treated by surgery but there is no clear evidence on the most effective method of management.[122–132]

When breathlessness is caused by obstruction of the main airways, it is normally treated with external beam radiotherapy. If this is not possible, intraluminal brachytherapy, which involves placing radioactive material directly on, or near to, the tumour, may be used. Published evidence suggests that intraluminal brachytherapy should not be used for patients who can tolerate conventional radiotherapy.[133] Intraluminal brachytherapy can control cough, haemoptysis, and breathlessness in about 75% of patients but it can also cause serious adverse effects, including fatal haemoptysis in perhaps 20% of patients.[134–143]

Other methods of opening the airways include laser treatment, cryotherapy, and stent insertion. All have been reported to produce rapid improvements but there have been no comparative trials.

PAIN CONTROL

In a recent study of 695 cancer patients referred to specialist palliative home care services in England and Ireland, 71% of those with lung cancer experienced pain at referral.[144] Pain due to lung cancer can be relieved with drugs (particularly opioids) and radiotherapy; psychoeducational and physical interventions may also be helpful.[145]

Clinicians often fail to recognise that pain is inadequately managed[146] and suboptimal pain control is common in advanced cancer patients.[147 148] This is largely avoidable; effective pain relief can be achieved for 80%–90% of patients with cancer with the World Health Organisation three step analgesic ladder.[149 150]

PALLIATIVE CARE

A prospective study of patients treated for lung cancer in Yorkshire suggests that many patients obtain inadequate palliation.[94] Among patients requiring supportive care, few receive initial hospice or palliative care referral.[97] Patients dying of cancer with no specific palliative care may have severe unrelieved symptoms, particularly pain; they may have unmet practical, social, and emotional needs; and they may have both because of poor coordination of services and because health professionals seem to be unwilling to share information.[151–162] In hospital, staff have been found to withdraw from patients when curative interventions were no longer being given, and to pay little attention to their symptoms, emotional needs, or needs for care.[155]

Specialist palliative care can improve symptom control, patient and carer satisfaction with care, and involvement in the process of care. However, a specialist symptom control team was not found to be adequate for controlling breathlessness.[151]

Most cancer patients prefer to be cared for at home, but fewer than one third actually die at home.[163–165] An American randomised controlled trial that compared home nursing care with conventional physician led care found that lung cancer patients who were nursed at home had less distress and maintained greater independence than those who received physician led care.[166] Outside the context of trials, poor control of symptoms often means that people with cancer are unable to spend their remaining life at home; currently in the United Kingdom, only half receive support from a palliative care team or specialist nurse.[167]

Provision of specialist palliative care can enable patients to spend more time at home and less time in acute hospital beds, which can reduce costs. However, while home care enables patients to remain independent and out of hospital for longer, there is some evidence that inpatient palliative care may offer better pain control.[167]

Palliative care in the community can be very fragmented; up to 25 different paid carers may visit a person's home during the course of a terminal illness.[167] Nurse coordinators can improve patients' access to appropriate services so that fewer inpatient days and nurse home visits are required; this can reduce NHS costs.[168]

Cost effectiveness

There is little reliable information on the cost effectiveness of management options for patients with lung cancer. Although there is considerable concern about the potential for large increases in cost of treatment, particularly with increasing use of chemotherapy for non-small cell lung cancer, most published studies of cost-effectiveness are based on assumptions which may not be generalisable to the United Kingdom.[169–176] There is, however, information derived from a United Kingdom based randomised controlled trial on the comparison between conventional radical radiotherapy and CHART (already mentioned).

CHART

Data from the CHART trial suggest that it can be highly cost effective. Cost data were collected for 248 representative patients with lung cancer and included radiotherapy, hospital services (inpatient admissions and outpatient visits), hospital transport, community services, and patient travel. The overall costs per patient were £2484 for CHART and £1786 for conventional treatment, a difference of £698 (95% CI £392–£1003; $p<0.001$).[177]

The additional cost of CHART has been estimated at about £2500 (£1100–£3250) per disease free life-year. This calculation, based on interim results, assumed a 2 year survival differential of 10% (25% *v* 15%) and a cost differential of £900 (D Coyle, personal communication, 1998). The actual 2 year survival differential of 9% (29% *v* 20%)[53] and cost differential of £700 would suggest a slightly lower cost per life-year.[177]

Conclusions

The greatest reduction in morbidity and mortality from lung cancer is likely to be achieved through improved prevention. Cigarette smoking is by far the most important cause of the disease and interventions to help smokers to give up can be highly cost effective.

The prognosis for most patients is poor and palliative care is usually required from the time of diagnosis. A range of interventions can be used to control symptoms and improve quality of life. These include not only anticancer treat-

ments such as radiotherapy and chemotherapy, but also pain relief and psychoeducational interventions—such as breathing retraining.

We acknowledge invaluable assistance given by members of the National Cancer Guidance Group, in particular Bob Haward, Mike Richards and Fergus Macbeth. Evidence reviews on which this work was based were carried out by Jessica Corner, Irene Higginson, Julie Hearn, Fergus Macbeth, and staff at the NHS Centre for Reviews and Dissemination, University of York.

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