Ministry of Defence

Synopsis of Causation

Lung Cancer

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

- 1.1. Malignant tumours of the lung generally arise from <u>epithelial</u> tissue and several discrete types of tumour are recognised depending on their site of origin within lung tissue and their <u>histological</u> nature. These tumours are commonly referred to collectively as lung cancer.
- 1.2. The World Health Organisation (WHO) classification of malignant lung tumours recognises four major histological types and also several minor types. The WHO classification also defines histological sub-forms of most of these types. The major histological types are:
 - Squamous cell carcinoma
 - Adenocarcinoma
 - Large-cell carcinoma
 - Small-cell carcinoma (also known as 'oat cell carcinoma')
- 1.3. The less common types of tumour include:
 - Adenosqaumous carcinoma
 - Adenoid cystic carcinoma
 - Mucoepidermoid carcinoma
 - Carcinoid tumour
- 1.4. Lung cancer is therefore not a homogeneous disease. Most lung cancers are of epithelial origin and because of variances in the clinical characteristics, most authorities now differentiate them into two main types. The presentation and prognosis of small-cell lung carcinoma (SCLC) differs significantly from the other main types and forms a group on its own. Squamous cell carcinoma, adenocarcinoma and large-cell carcinoma form the separate group of non-small-cell lung carcinomas (NSCLC).²
- 1.5. Lung cancer is now the most common malignant disease in the Western world and has shown the greatest absolute rise in mortality of any tumour in the UK over the past century.³ It accounts for 38,000 deaths in England and Wales per year with 80% of these being men. It is the most frequent cause of death from cancer in the USA in both men and women, having accounted for an estimated 171,600 new cases and 158,800 deaths in 1999.⁴ In the UK, the age-standardised incidence of lung cancer in men reached a peak in 1970 since when it started to fall. In women the rate continued to rise at a rate of 10% every five years up to 1980. Since then the incidence has continued to rise but the rate has slowed. In 2001 the incidence in men was 17% and in women it was 11%. In 2002 the mortality rate from lung cancer was 25% in men, whilst in women it overtook that of breast cancer with a mortality rate of 18% (breast cancer 17%).⁵
- 1.6. This has led to a major effort, aided by the rapid developments in molecular research, to increase the understanding of the processes leading to the development of lung cancer with the ultimate aim of providing new approaches to combat the disease.
- 1.7. The lungs are a common site for secondary spread from many other primary malignant tumours particularly those of breast, prostate, kidney, colon, stomach and testes. These

<u>metastases</u> have the aetiological and pathological features of the primary tumour and are not covered in this synopsis.

2. Clinical Features^{3,4}

- 2.1. Clinical presentation of lung cancer varies considerably depending on the type of tumour and its location within the structure of the lung. In most cases the tumour is well advanced by the time of diagnosis and the majority will have already metastasised by then. The overwhelming majority of cases are represented by the four main types as set out in section 1.2. From figures based on a study of a series of 59,620 cases collected between 1983 and 1987, 32% of lung cancers were adenocarcinoma, 30% were squamous cell carcinoma, 18% were large-cell tumours, 10% were small-cell tumours with other rarer types making up the remaining 10%.²
 - 2.1.1. **Squamous cell** tumours usually develop in a major bronchus and tend to obstruct the <u>bronchial lumen</u> leading to collapse and <u>pneumonitis</u> of the distal lobe or lobule. Some arise peripherally and this type accounts for around half of the superior sulcus or <u>Pancoast tumours</u> (see section 2.3.6).
 - 2.1.2. **Adenocarcinoma** tends to arise peripherally from bronchioalveolar epithelium forming a large diffuse mass which may be asymptomatic until the tumour has reached a large size. Such tumours invade blood and lymph vessels early in their development and frequently give rise to metastases before the primary lesion causes any symptoms. They frequently involve the pleura and metastasise to the scalene lymph nodes.
 - 2.1.3. **Large-cell** carcinoma can be central or peripheral and presentation varies with site of origin. Some large-cell tumours have some cell features of adenosquamous-type tumours and all bronchogenic carcinomas may exhibit cell types of several categories.
 - 2.1.4. Small-cell tumours (SCLC) usually originate from a bronchus and cause narrowing of the lumen without producing a discrete intrabronchial mass. These tumours metastasise early to hilar and mediastinal lymph nodes and readily invade blood vessels. There are subgroups of this type of tumour which have cell components similar to large-cell tumour. Pure small-cell tumours make up 90% of this group with only 1% being of the squamous cell or adenocarcinoma/SCLC mix.
- 2.2. Symptoms fall into three broad groups; those arising from the local effect of the tumour, those from its distant effects, and those causing general systemic effects in the body.
 - 2.2.1. **Local effects** are those caused by the tumour mass on surrounding tissue, such as obstruction of lung air passages, compression of structures within the lung itself or in the mediastinum, or erosion of surface tissue with bleeding and infection.
 - 2.2.2. **Distant effects** due to metastatic spread reflect the impairment of function of the organ involved or pressure and obstruction of structures surrounding that tissue. Lung cancer tends to metastasise to the bone, liver, lymph nodes, and brain. At presentation, up to 25% of patients may present with bone pain, 20% with hepatic involvement, 20% with lymphadenopathy and 5%-10% with neurological manifestation of cranial involvement.

- 2.2.3. Systemic effects may be metabolic, endocrine or neurological and are either due to the effect of metastases on other organs or to the effects of the tumour itself producing substances that mimic the effect of hormones produced by the normal endocrine system. Manifestations may include abnormal production of vasopressin leading to overhydration, or production of adrenocorticotrophic substances that cause thirst, polydypsia, oedema, and abnormal pigmentation as in Cushing's syndrome. Other effects such as gynaecomastia, hypercalcaemia and hyperthyroidism may appear from production of substances that mimic the effect of oestrogens and parathyroid hormones. Carcinomatous neuromyopathies may also occur.
- 2.2.4. Around 5% of cases of lung tumour are discovered coincidentally on chest radiographs taken for other purposes.
- 2.3. Common presenting symptoms are cough, often described as 'brassy' in nature, haemoptysis, wheeze, stridor or dyspnoea. As cough is a common symptom of other respiratory diseases, the significance may be overlooked by those with other respiratory problems and by smokers who may well have a chronic persistent cough. Any change in the nature of the cough or cough history should be investigated in smokers or those with other chronic chest conditions, such as chronic obstructive pulmonary disease.
 - 2.3.1. Haemoptysis may be the sole presenting symptom in around 5% of cases and appears at some stage of the disease in around 50% of cases.
 - 2.3.2. Wheeze may occur as a presenting symptom in some cases although it is common in other chest diseases particularly chronic obstructive pulmonary disease associated with smoking. Coarse wheeze, not cleared by coughing, may be a feature of local obstruction of a larger airway.
 - 2.3.3. Stridor is a harsh noise often mistaken for wheeze but which arises from marked narrowing of the <u>glottis</u>, <u>trachea</u> or major <u>bronchi</u> and is usually more marked on inspiration than expiration.
 - 2.3.4. Dyspnoea is unlikely to be a presenting feature except in a small number of cases. It may be present as part of a concurrent lung or heart disorder but only tends to be a feature of lung tumour when progression of the tumour replaces or distorts lung tissue to a degree sufficient to impair relative lung function. Progressive dyspnoea from secondary pleural disease with effusion or superior vena cava obstruction may also be observed.
 - 2.3.5. Chest discomfort is a feature of around 40% of cases at presentation. This is often a vague and non-specific ache arising from within the chest but difficult to localise. More specific <u>pleuritic pain</u> may present from local invasion or metastases of the chest wall or visceral pleura.
 - 2.3.6. General symptoms such as lack of energy, chills, night sweats and malaise may occur. There may also be a variety of symptoms and signs relating to disruption of specific structures within the thorax including <u>dysphagia</u> from invasion of the oesophagus, effects of pressure on the recurrent laryngeal nerve causing hoarse voice due to vocal cord paralysis, and obstruction of large central blood vessels. Involvement of the sympathetic nerve trunk may produce Horner's syndrome. A tumour arising in the superior pulmonary sulcus (Pancoast tumour) can produce

- effects on the brachial plexus, pain in the shoulder, upper anterior chest, weakness and atrophy of the muscles of the hand as well as Horner's syndrome, laryngeal paralysis and spinal cord compression.³
- 2.3.7. Symptoms associated with metastatic spread are those caused by dysfunction of the organ involved and may be the initial presenting complaint. Spread to the anterior <u>scalene nodes</u> may be early and these can be palpated in the <u>supraclavicular</u> area.

3. Aetiology

- 3.1. Neoplastic change in tissue occurs when the genetic structure of the cells becomes changed (gene mutation) and the normal equilibrium between stimulation and inhibition of cell growth becomes disordered. This results in mutated cells reproducing at a greater rate than normal. Two important gene types play a part in triggering malignant change. Proto-oncogenes encourage cell reproduction and growth, and suppressor genes inhibit cell growth. Mutation of proto-oncogenes produces carcinogenic oncogenes which drive excessive cell reproduction. Various factors can influence the mutation of normal genes to carcinogenic oncogenes. These include a variety of environmental factors that damage the genetic material of tissue cells and certain hereditary genetic manifestations of polymorphism that can occur, resulting in the cells being more prone to malignant mutation.
 - 3.1.1. The specific mechanism of the cause of lung cancer is not known, whichever histological type is involved. It appears to be due to the effects of environmental factors coming together in a genetically susceptible individual. There is usually a long latent period of at least 20 years following initial exposure to a carcinogen before lung cancer develops. It is therefore predominantly a disease of middle to old age with 90% of cases occurring between ages 40 and 80 years. Lung cancers in younger age groups show a predominance of adenocarcinomas with a greater frequency in women. ²
- 3.2. **Genetic factors** have been implicated in causation of lung cancer. Epidemiological studies have shown a familial predisposition to lung cancer that is independent of tobacco smoke exposure. This seems to be due to an <u>autosomal recessive gene</u>, which may confer a high relative risk of lung cancer for the individual. The identification of specific genes that cause lung cancer is hampered by familial risk being obscured by environmental factors. Several chromosomal loci and genes that are frequently found to be modified in lung cancer have been identified. The ras family of oncogenes was the first to be described in association with lung cancer. Ras gene mutations occur in 20%-40% of non-small-cell lung cancer, especially adenocarcinomas, and the presence of K-ras mutations is linked with significantly shortened survival.⁴
 - 3.2.1. Lung tissue appears to contain enzymes that can detoxify the effect of potential carcinogens including the polycyclic hydrocarbons and nitrosamines that are found in tobacco smoke and residue. Changes to the genetic structure of certain genes may alter the effect of these enzymes and such changes may cause greater absorption, accumulation and distribution of carcinogens in lung tissue, with resulting increase in cancer susceptibility.³
- 3.3. **Environmental factors** that have been considered to be linked to causation in cancer of the lung are; tobacco smoke, ionising radiation, industrial hydrocarbons, minerals such as asbestos and silica. Air pollution from modern industrial processes and transport has also been considered as a potential factor in the increase of the disease over the past century. The role of these agents is examined in detail in sections 3.4 to 3.6.
- 3.4. **Tobacco smoke.** There is an overwhelming link between development of certain types of lung cancer and exposure to tobacco smoke. This and tobacco tar residue contain a variety of potential and established carcinogens including complex hydrocarbons. Early suspicions of this link were initially confirmed by a series of three studies in the USA

and one in the UK. ^{7,8,9,10} These studies also showed that the increased risk from tobacco smoke is dose related and associated with the amount and duration of smoking and the method of smoking used (cigarette, cigar or pipe-smoking). A further prospective study of the health effects of smoking by Doll et al., based on a cohort of over 30,000 British doctors, was started in 1954 and has now progressed over 50 years. As well as the other health risks of smoking such as chronic chest disease, heart and vascular disease, the causal link between smoking and lung cancer has been firmly established. ^{11,12} This and other continuing work has also demonstrated that quitting smoking reduces the risk of lung cancer and that after twenty years, the risk falls to the same level as for those who have never smoked. ¹³

- 3.4.1. Around 80-85% of cases of lung cancer are associated with a history of smoking with a twenty-fold increase in relative risk between current smokers and non-smokers. However less than 20% of smokers develop lung cancer suggesting that other individual constitutional factors are also at play.⁴
- 3.4.2. **Passive smoking.** 15-20% of cases of lung cancer develop in non-smokers. The effect of passive smoking from exposure to an environment where tobacco is smoked is increasingly considered to be a factor in causation of lung cancer. 14,15,16 However, it is probable that only 5-10% of the cases that develop in non-smokers can be attributed to passive smoking.³ One study into the risk of lung cancer in life-long non-smokers compared the risks of lung cancer in nonsmoking partners living with a smoker with the risk for those living with a nonsmoker. This concluded that there is compelling evidence to confirm that breathing other people's tobacco smoke is a cause of lung cancer. The risk of developing lung cancer in a partner who had never smoked was estimated to be 24% greater if living with a smoker, with a dose-response relationship between the non-smoker's risk and the number of cigarettes smoked by the partner as well as the duration of exposure to the tobacco smoke.¹⁷ Some have challenged this link including one study based on a re-analysis of epidemiological evidence which cited publication bias as a possible confounding factor in estimating this risk. However, while this concluded that there was evidence of bias which resulted in an overstatement of the relative risk, it did not exclude a significant risk to non-smokers from environmental tobacco smoke. 18 The effects of passive smoking in the workplace are less defined, as the problems in estimating exposure and other confounding factors make assessment of risk less reliable.
- 3.4.3. Men who smoke are more likely to develop the squamous cell and small-cell tumour <u>histiotypes</u> whereas women and non-smokers are more likely to develop adenocarcinoma or large-cell carcinoma.²
- 3.4.4. A large proportion of cases of lung cancer could be prevented by the avoidance of tobacco smoke and programmes aimed at preventing and stopping smoking are in place in many European countries and in the USA to try to reduce the incidence of this disease.
- 3.5. **Radiation.** Ionising radiation can penetrate living tissue and damage DNA and can theoretically produce cancer in most tissues. Everyone is exposed to background radiation from naturally occurring sources including cosmic radiation, and this varies depending on geographic location. Some of this will be linked to cancers in the population as a whole. The rate of emission from a radioactive source is measured in

units of Becquerel (Bq) where one Bq represents one event of radiation emission per second. This is an extremely small amount of radiation and multiple units of 1000 Bq (1kBq), 1000 kBq (1MBq) and 1000MBq (1GBq) are frequently used. The amount of radiation energy absorbed by unit weight of a body organ is expressed in units of Gray (Gy). Radiation equivalent dose is measured in units of Sieverts (Sv) The Sievert represents a high dose of radiation and measurements are usually given in millisieverts (mSv). The equivalent dose in Sieverts reflects the differing sensitivity of different tissues and different types of radiation which produce different relative amounts of tissue damage. The equivalent dose is determined by multiplying the absorbed dose in Gy by a weighting factor that reflects both tissue sensitivity and radiation type. The units of Becquerels, Grays and Sieverts are new units which replaced Curies (Ci), rads and rems respectively. Background radiation in the UK is on average 2mSv per annum, being up to 8 mSv in some areas associated with a natural occurrence of radioactive radon gas (see section 3.5.7).

- 3.5.1. Adverse effects of ionising radiation can be considered as either early (deterministic) or late (stochastic/probabilistic). Early effects arise shortly after exposure usually within hours or weeks. There is a threshold dose below which no effect is evident. This threshold is high, being several hundred times the normal background level and severity of reaction is proportional to dose. Duration of exposure is important and a short acute exposure to a dose is more harmful than exposure to the same dose over a longer period of time. Late effects arise some 2-40 years following exposure and risks are probably dose related. There is no threshold level of exposure for late effects. Any exposure carries a finite risk although not all individuals exposed to the same level of radiation will suffer adverse effects. The main late adverse effects of exposure to ionising radiation are induction of malignancies and hereditary defects. Conditions which can be induced by radiation can also be induced by other life factors such as smoking, diet, alcohol and occupational exposure to toxins. Tumours related to other causes are indistinguishable from those associated with radiation exposure. Total body doses up to 10 mSv are not likely to produce an adverse effect, but 1000mSv (1Sv) is likely to cause radiation sickness A total equivalent dose of 10,000 mSv (10Sv) is likely to be lethal (early effects).
- 3.5.2. Long-term exposure to lower doses of ionising radiation in excess of background levels has been implicated in causation of many malignant diseases (late effect). However, UK overall cancer rates are higher than expected for the generally low background radiation levels indicating that factors other than radiation are involved in causation of malignancies. Limits of annual radiation exposure are set for those working with ionising radiation. From 1 January 2000 these are 20 mSv per annum for classified workers and 6 mSv per annum for unclassified workers. The recommended dose limit for the general public is 1mSv per annum above background levels.
- 3.5.3. Studies of the effects of radiation exposure such as in nuclear accidents and the atomic bomb detonations in Japan have shown an increased incidence of many cancers including lung cancer among survivors. It has been estimated that atom bomb survivors were exposed to levels of radiation at around 150 times the expected background radiation. A higher risk of lung cancer from radiation appears to be a factor particularly at higher doses (above 200mSv) but a small effect has been identified at levels above 50 mSv. Those exposed in the first and

second decade of life showed a higher risk relative to dose. ¹⁹ The risk of lung cancer at the low doses of radiation experienced in the general population and by recent radiation workers, who are subject to dose limitation, has not been clearly established but is not considered to be significant. ²⁰ This is supported by studies by the National Radiological Protection Board of occupational exposure of radiation workers. These have found levels of mortality from solid tumours including lung cancer to be less than the national rate. ²¹

- 3.5.4. **UK Nuclear Tests.** During the 1950s, the UK carried out a series of 21 atmospheric tests of nuclear weapons in Australia and the Pacific. Concern has been expressed by service personnel and other participants who were involved in these tests or serving in the vicinity that this had lead to an increased risk of ill health and malignancies. An independent epidemiological study to examine this was commissioned by the Ministry of Defence in 1983. The study was carried out by the National Radiation Protection Board and the International Cancer Research Fund. It involved an historical cohort study which compared mortality and incidence of cancer in over 20,000 test participants, representative of the group as a whole, with that of a well defined control group of other service personnel who had not taken part in the tests but were otherwise as similar as possible. Three reports have been published.
- The main conclusions of the first NRPB report were that presence at the nuclear weapons test sites had not had a detectable effect on life expectancy or overall risk of developing cancers but there was a possible increased the risk of multiple myeloma and leukaemia (other than chronic lymphatic leukaemia) compared with service controls. However, this was not considered to be due to ionising radiation exposure. There was a particularly low rate of these two conditions in the control group, and those subgroups actually present at detonations or otherwise where the possibility of radiation exposure was greatest did not show the highest standardised mortality rates or relative risk for these disorders. Apart from this, the findings did not identify any detectable effect on life expectancy of participants or any overall risk of malignancy.²² The study was extended to the end of 1990 with special scrutiny to ensure that the low rates in the first study did not reflect incomplete follow-up. The second report published in 1993 confirmed the original findings that there was no effect on life expectancy and no increased risk of malignancy in participants but also did not confirm the original finding in relation to myeloma and leukaemia.²³
- 3.5.6. The most recent study in this series in which the follow-up period had been extended to 1998 was published in 2003. This study concluded that in the further seven years of follow-up, the overall levels of mortality in the UK nuclear weapons test participants had continued to be similar to those in a matched control group and overall mortality from all causes was lower in both groups than expected from national rates. Notwithstanding subsequent debate, the validity of the extended findings is accepted by the scientific community. Current evidence therefore does not support a causal link between lung cancer and participation in the UK nuclear testing programme.²⁴
- 3.5.7. **Radon.** This is a radioactive gaseous element formed by radioactive decay of uranium. It produces a series of 'daughter' isotopes from successive radioactive decay. Radon isotope decay produces alpha particles which are highly ionising but which have low penetration of body tissue. However, inhalation of radon

and its isotopes can produce significant accumulated doses of radiation in lung tissue. Radon occurs naturally in most geological areas but occurs in greater amounts in areas where granite predominates such as Devon, Cornwall, Somerset, Northamptonshire and Derbyshire. Abnormal levels of radon gas can occur within the atmosphere in buildings sited in these particular areas. The risk of lung cancer has been recognised for some time and there is an agreed "action level" of 200 Becquerels/cubic metre (Bg/m³) at which it is recommended that measures are taken to reduce radon levels. Mining of pitchblende or other ores found in granite-rich rock also results in exposure to radon isotopes and carries a significant risk of lung cancer. Recent estimates of the risk of lung cancer from radon have concluded that the risk of lung cancer increased by 16% (95% confidence interval 5%-31%) per 100Bq/m³ increase in usual radon concentration in the atmosphere. There was a linear dose response relationship with no threshold, and the risk remained significant although lower at radon levels below the 200Bg/m³ action level. The absolute risk of lung cancer by age 75 years at radon concentrations of 0, 100, and 400 Bg/m3 would be 0.4%, 0.5% and 0.7% respectively. A substantial increase in this risk for lifelong smokers has been estimated to be around 25-times greater than for nonsmokers.²⁵

Depleted uranium (DU). This has been used in recent years for military purposes as a component of armour plating and armour-piercing munitions. The use of weapons that incorporate DU in recent conflicts has raised concern about the long-term effects on the health of participants and combatants from the residue of such weapons. There have been persistent speculative reports on the health risks of exposure to DU and concern expressed about the use of radioactive and chemically toxic munitions. The risk of developing lung cancer has been a particular concern because of the known effects of inhalation of uranium isotopes in uranium mining and the effect of environmental radon. In response to this, the Royal Society set up an independent expert working group to review the present state of knowledge of the hazards of DU and to identify areas where further research should be undertaken. The group took a scientific approach and did not attempt to take a position on the merits of using such munitions or to assess a possible link with illness from the first Gulf War. They assessed the exposure to DU which personnel were likely to have experienced, and to relate these exposures to the known health risks of DU, the likely health risks, and the potential longer-term consequences. The report was presented in two parts. The first part concluded that apart from extreme circumstances the risk of developing fatal cancers from battlefield exposure to DU is so small that it would not be detectable above the normal risk in the general population. Such extreme circumstances would include, for example, the radiation dose absorbed by a survivor from a vehicle struck by penetrating DU munitions. In such cases the risk of developing lung cancer would be no more than twice that of the general population. In addition to its radiobiological effects, DU is a heavy metal with potential toxic effects on the kidneys, and the second part of the report addressed possible effects on kidney function and other longer-term consequences. This concluded that any potential risk of kidney damage or damage to other organs in both soldiers and others living in the environment was likely to be very low. However the report did conclude that in extreme circumstances and under worst case assumptions, soldiers who receive large intakes of DU theoretically could suffer adverse effects on the kidney and lung. 26,27 Evidence from studies of 16 US veterans of the 1990/91 Gulf War who have embedded shrapnel from DU munitions has shown no increased risk of cancer or any other adverse health effect. No UK personnel who took part in that war have embedded DU in their bodies. A study of cancer incidence in UK participants in the Gulf War 1990/91 concluded that there is no current excess risk of cancer overall nor of site specific cancers in Gulf War veterans. There is an ongoing follow-up on mortality for participants in the 1990/91 Gulf conflict with results published twice a year.

- 3.5.9. **Medical exposure.** Medical exposure to radiation for both diagnostic and therapeutic purposes forms the largest proportion of overall background radiation experienced by the population at large. The risks of such exposure must be balanced against the clinical benefits. Most diagnostic exposures produce doses of between 3-30 mSv and one estimate gave the risk for all types of cancer from diagnostic exposures as 0.6% for the UK, resulting potentially in 700 additional cancer cases per year. 30,31 Radiotherapy results in exposures which are significantly higher than in diagnostic use of radiation, particularly within the areas of the treated fields. Studies of mortality rates in patients treated with radiotherapy for non-malignant conditions such as ankylosing spondylitis have shown a significant increase in relative risk of mortality from cancer. In one study where the estimated mean total body dose of radiation for individuals was 2.64Gy there was a relative risk of 1.30 with a significantly increased incidence of several tumours including tumours of the lung.³² Over recent years policies to reduce the overall medical exposure to ionising radiation have come into place. The most recent of these were the Ionising Radiation (Medical Exposure) Regulations (IRMER) of 2000 which defined the responsibilities of all involved in delivery of medical procedures involving ionising radiation. The regulations defined the responsibilities of those who requested, authorised and carried out radiation-based procedures as well as the employers' responsibility for maintenance of equipment, provision of training and monitoring of practices. The regulations apply the principle that exposure should be as low as reasonably practicable (ALARP) taking into account the risks and benefits of the procedure. The intention is that no exposure should be carried out unless it can be fully justified bearing in mind the nature of the procedure, the dose involved and the condition of the subject and the benefits to be gained. With this level of control, exposures such as those mentioned above which produced a significant risk of adverse effect are no longer acceptable. Policies to reduce medical radiation exposure have been in place for more than thirty years although no evidence to confirm a change in risk has been found. Current procedures appear to produce doses which form only a part of the overall background radiation exposure and produce minimal risks compared with the overall lifetime risk of 1:4 for individuals developing cancer from all causes.
- 3.5.10. **Electromagnetic radiation.** It has been claimed that cancers in general may be related to exposure to both low frequency and radiofrequency radiation but results of studies have been conflicting and confusing. The National Radiation Protection Board (NRPB) has not identified any specific risk of cancer from exposure to electromagnetic radiation with a frequency of up to 300GHz (which includes microwaves). Neither does the NRPB identify any specific risks of cancer from laser radiation. The basic low energy nature of these types of radiation is inconsistent with cell mutation and there is no reliable evidence to link lung cancer causally with exposure to electromagnetic radiation.

- 3.6. **Occupational and other environmental causes.** Several carcinogenic toxins encountered in industry are now accepted as causally linked to lung cancer.
 - Minerals such as asbestos and silica have been implicated in causation of malignant lung tumours. The association of asbestos with epithelioid lung cancer is now firmly established as is it is with mesothelioma. Studies have shown that there is between 4-7 times greater risk of developing lung cancer in those exposed to asbestos.³ This risk is related to level and duration of exposure to the mineral, and lung cancer due to asbestos is accepted under certain conditions as a prescribed industrial disease by the Department for Work and Pensions in the UK. A recent report from the Industrial Injuries Advisory Council (IIAC) points to evidence that an excess risk of lung cancer in the presence of asbestosis is undisputed with in some cases a greater than 5-fold increase in risk being observed. The evidence also shows that the risk of lung cancer is doubled, even in the absence of asbestosis or pleural thickening, where there has been substantial occupational exposure to asbestos. Lung cancer in association with silicosis is also a prescribed industrial disease and is a particular risk for those employed in quarrying, mining, pottery manufacture and other defined jobs where exposure to silica dust is accepted.
 - 3.6.2. **Coke ovens and coal gas production**. Heating and distilling fossil fuel produces a variety of polycyclic aromatic hydrocarbons (PAH) and these substances occur widely as industrial pollutants. Work in gas and coke ovens and foundry work involves exposure to a complex mix of particles and vapours containing known carcinogens, and has been linked to an increased risk of lung cancer. A relative risk of lung cancer of 1.2 above the population risk has been demonstrated in workers exposed to an average concentration of emissions of 1.5 micrograms of PAH per cubic metre.³⁴
 - 3.6.3. **Other occupations** implicated in causation of lung cancer include nickel refining and chromate manufacture. ³⁵ Those working with arsenicals or bis(chloromethyl) ether are exposed to a higher risk of lung cancer. Other substances which are suspected to have a link with lung cancer are acrylonitrile, beryllium, vinyl chloride, iron ore and some wood dusts. ³
 - 3.6.4. **Air pollution.** The effect of increasing air pollution from combustion engine exhaust fumes and industrial emissions has been mooted as a possible cause of the epidemic rise in lung cancer in the 20th century. The more recent decline in incidence of lung cancer in the UK compared with USA and Germany is not clearly related to a reduction in smoking habit suggesting that other factors have been at play. A possible link to air pollution is the subject of ongoing investigation but difficulties in excluding other confounding factors such as smoking habit and the widespread nature of other potential carcinogens have made assessment of this effect problematical. Control of industrial and motor vehicle emissions over the past thirty years should have reduced any associated risk and there is no compelling evidence that changes in environmental pollution have had any significant affect on the incidence of lung cancer. ^{3,36}
 - 3.6.5. **Interaction.** Most of the environmental risks appear to be compounded by the effects of more than one factor. The risk of lung cancer in an asbestos worker is almost one hundred times greater for a smoker than a non-smoker. A similar

effect is found in coke oven and foundry workers. Some carcinogenic agents may therefore act in combination to increase the risk and multiple exposures from environmental factors may confound any studies looking at the specific risk of one substance.

3.7. **Systemic disease.** Tumour-types such as adenocarcinomas, which predominantly occur in the lung periphery, may be associated with a history of chronic inflammatory interstitial lung disease. Systemic diseases such as <u>sarcoidosis</u> and <u>scleroderma</u> can be involved, as can tuberculosis or chronic pulmonary fibrosis from mineral dust. The mechanism of this is not known but may relate to a reaction to long-term insult to the tissues. 4,37,38

4. Prognosis^{3,4}

- 4.1. In most cases of lung cancer the tumour has progressed significantly before it has become symptomatic, although some are found incidentally by chest x-rays done for other clinical reasons. Around 90% of patients will have developed symptoms at the time of diagnosis. The different histological types also progress at different rates.
 - 4.1.1. **Squamous cell tumour** is relatively slow growing, doubling its volume in around 90 days and has the lowest incidence of distant metastasis.
 - 4.1.2. **Small-cell tumours** have a rapid growth rate, doubling volume in around 30 days, with early metastasis by both lymphatic and blood-borne spread. At diagnosis, more than 90% will probably have metastasised. This type of tumour is now considered to be pathologically and clinically distinct from the other forms and, with extensive disseminated disease being present in more than 50% of patients at diagnosis, it carries the worst prognosis.
 - 4.1.3. **Large-cell tumours and adenocarcinomas** grow at a rate somewhere between the above types and both can exhibit a spectrum of cell types.
 - 4.1.4. Other rarer types of tumour have a variable rate of progression and dissemination from low grade with a good prognosis to more aggressive disease.
- 4.2. Prognosis depends on the histological type of the tumour, the stage the disease has reached at diagnosis, and the overall age and condition of the patient. All of these may help to determine the type of treatment offered. For purposes of staging the non-small-cell types are differentiated from small-cell tumours.
- 4.3. **Non-small-cell tumours.** Staging of disease due to NSCLC is based on the TNM (Tumour, Nodes, Metastases) method which relates disease progression to the degree of local infiltration by the tumour, the degree and area of spread to lymph nodes, and the presence or absence of distant metastases. The stage the disease has reached not only helps with determination of the method of treatment but also has value in indicating likely prognosis. Investigations to determine staging vary according to the clinical presentation, the age and condition of the patient. These may be invasive or non-invasive with a variety of methods from cytology of sputum, chest radiography, computed tomography (CT), magnetic resonance imaging (MRI), and bronchoscopy with biopsy. Biopsy may also be percutaneous with the aid of an imaging procedure. Positron emission tomography (PET) scanning is a more recent development which shows promise in identifying the nature of solitary nodules or assessing intrathoracic spread. Lung function testing is essential in establishing fitness for surgical resection of the tumour.
 - 4.3.1. Treatment can be by surgery, radiotherapy or chemotherapy, or a combination of any of these.
 - 4.3.2. **Surgical resection** is most likely to be curative in non-small-cell lung cancer but the rapid progression of the disease in small-cell lung cancer normally renders the condition inoperable. Patients at up to stage T2 where tumour is localised to lung and visceral pleura with no nodal involvement may be suitable

for resection. Small peripheral lesions do best and squamous cell types have higher 5- and 10-year survival rates. Around 20% of patients with non-small-cell tumours come to surgical resection, with the rest excluded because of the presence of metastatic spread or poor general condition of the patient.

- 4.3.3. **Radiotherapy** is probably the most common choice for those who are excluded from surgery. It may be used as an alternative to surgery in those who may be technically suitable for resection but who are too unwell for the procedure. It may also be used as an adjunct to surgery either pre- or post-operatively in borderline cases, although there is no reliable evidence that postoperative radiotherapy adds value in survival times. Radiation for palliative treatment is useful in moderating some symptoms, particularly haemoptysis, cough and dyspnoea from bronchial obstruction. It is also helpful in treating pain from bone secondary spread.
- 4.3.4. **Chemotherapy** has some success in non-small-cell tumours, and combination therapy using several <u>cytotoxic</u> agents can achieve partial responses in up to 50% of patients so treated.
- 4.3.5. For non-small-cell tumours the 5-year survival time varies from around 60% for the lower stages to 4.9% for those at the highest stage. The median survival times vary for the same range from 60 months to 11 months. For those treated surgically, the figures for 5-year survival vary from 68.5% to 28.8% respectively and median survival varies between 60 months and 22 months.
- 4.4. **Small-cell tumours** are considered separately from the other tumours from the point of treatment and prognosis because the nature of their rapid growth and metastasis makes it difficult to apply the normal TNM staging process. Surgical resection is possible only in rare cases where the disease is still localised at presentation. Radiotherapy is important in palliation and there is a small benefit in about 15% of patients with limited disease. Small-cell tumours are much more sensitive to chemotherapy with much higher response rate. With modern treatment regimens median survival times have increased to 14-18 months for limited disease and 9-12 months for extensive disease. Such regimens would now be expected to produce a complete response in 40-50% of cases and partial response in a further 40%.³
- 4.5. Palliative treatment of symptoms arising from metastases and complications of treatment, and general care aimed at improving quality of life, form an essential part of the management of patients with lung cancer.

5. Summary

- 5.1. Malignant tumours of the lung generally arise from the epithelial tissue and are known collectively as lung cancer. This group of tumours presents one of the most significant health problems of modern times resulting in many cases worldwide and a significant burden on health-care provision. Incidence has been increasing significantly over the past 60 years although in the UK this has fallen slightly over the past 10 years.
- 5.2. The carcinogenic effect of tobacco smoke constitutes the predominant cause of lung cancer but other known carcinogens such as asbestos, ionising radiation, polycyclic aromatic hydrocarbons and a variety of other chemicals add to the incidence of the condition. Genetic factors also play a part with epidemiological evidence showing a familial tendency to the disease.
- 5.3. Most cases of lung cancer are well advanced before symptoms present and overall survival is still relatively poor despite continued advances in treatment regimens.

6. Related Synopses

Mesothelioma

Chronic Obstructive Pulmonary Disease

Asthma

7. Glossary

adrenocorticotrophic An effect produced by hormones secreted by the adrenal

glands.

autosomal recessive Requires that two affected parents have the trait

(characteristic) in order to pass it to the offspring.

bronchus (-i) The main large air tube leading to the various lobes of the

lung. Hence: bronchial – pertaining to the bronchi; bronchial

lumen – the hollow part of the bronchial tube.

bronchoscopy An investigation for examining the bronchi by passing an

imaging instrument into the bronchial passages via the

windpipe.

Curies (Ci), rads, rems Superseded units for radiation emission and absorption.

1 Curie = 3.7 times 10^{10} Becquerels; 1 rad (Radiation absorbed dose) = 0.01 Gy; 1 rem (Roentgen equivalent man)

= 0.01 Sv.

cytotoxic Literally 'poisonous to cells' – a drug used to kill susceptible

malignant cells.

dysphagia Difficulty or discomfort on swallowing.

dyspnoea Difficulty in breathing or laboured breathing –

breathlessness.

epithelial Pertaining to the epithelium – in this case the cellular lining

of the air passages.

glottis Part of the larynx (voice box) that is associated with voice

production.

gynaecomastia Abnormal breast development in males.

haemoptysis Coughing-up of blood or blood-stained sputum.

hilar Pertaining to the part of the lung where major blood vessels

and air passages enter the lung from the midline.

histiotypes Of a particular cell type – having similar appearance and

structure to others.

histological Characterisation by the microscopic structure of a cell.

intrabronchial Developing within the cavity of a bronchial air tube.

lymphadenopathy Enlargement of lymph glands usually from infection or

malignant disease.

mediastinal Pertaining to the mediastinum – the central area of the chest

that lies between the lungs and contains the heart, major

blood vessels and air passages.

mesothelioma A malignant tumour arising from the lining of the lungs,

heart or abdominal cavity.

metastasis (-es) Secondary disease arising from spread of a malignant tumour

to a distant site in the body. Hence: *metastasise* – to spread

to other parts of the body.

neoplastic Pertaining to neoplasia – literally the formation of new tissue

and by custom referring to the pathological process of

tumour formation.

pitchblende A dark, heavy mineral that forms the ore from which

uranium is obtained.

pleuritic pain A sharp, stabbing pain on breathing – usually due to

inflammation of the lining of the chest wall.

pneumonitis An inflammation of the air sacs of the lung often caused by

infection.

polydypsia Excessive need to drink fluids – often a symptom of diabetes

mellitus (due to insulin lack) and diabetes insipidus (due to

abnormalities of the pituitary gland).

sarcoidosis An inflammatory disease that can affect many parts of the

body but which predominantly affects the lungs.

scalene node A lymph node within a group situated near the scalene

muscles of the neck.

scleroderma A disseminated connective tissue disease that causes

thickening and scarring of various tissues of the body

including the skin.

stridor A harsh sound during breathing due to air passing through

obstructed air passages – usually the larger tubes or the voice

box.

superior vena cava One of the large veins draining the areas of the upper limbs

and head into the heart.

supraclavicular area The indented area of skin above the collar bone.

trachea The main air passage from the mouth and throat to the lungs

- the 'windpipe'.

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