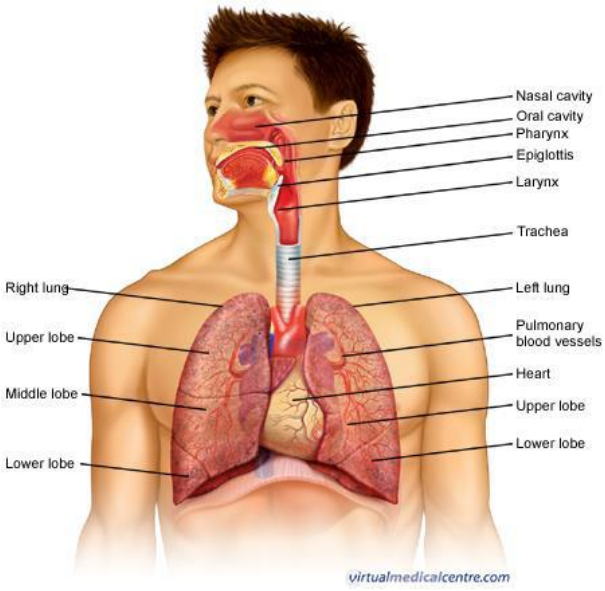
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet
on
Lung Cancer

Introduction

The chest contains two lungs, one lung on the right side of the chest, the other on the left side of the chest. Each lung is made up of sections called lobes – the right lung consists of three lobes and the left lung consists of two lobes. The lung is soft and protected by the ribcage. The purposes of the lungs are to absorb oxygen (O_2), into the bloodstream for distribution throughout the body and to remove carbon dioxide (CO_2), a waste product, from the body.



[Picture Credit – Anatomy of the Lungs]

Lung Cancer

Lung cancer is a disease characterised by uncontrolled cell growth in tissues of the lung. If left untreated, this growth can spread beyond the lung in a process called metastasis into nearby tissue and, eventually, into other parts of the body. Most cancers that start in lung, known as primary lung cancers, are carcinomas that derive from epithelial cells.

Incidence of Lung Cancer in South Africa

According to the National Cancer Registry (2012) the following number of lung cancer cases was histologically diagnosed in South Africa during 2012:

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Group - Males 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	1 743	1:79	4,72%
Asian males	85	1:57	10,14%
Black males	691	1:131	5,92%
Coloured males	355	1:34	8,19%
White males	6112	1:53	3,05%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	814	1:232	2,16%
Asian females	23	1:257	2,16%
Black females	234	1:558	1,42%
Coloured females	169	1:96	4,06%
White females	387	1:98	2,44%

The frequency of histologically diagnosed cases of lung cancer in South Africa for 2012 was as follows (National Cancer Registry, 2012):

Group - Males 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	1	6	15	142	485	571	389	117
Asian males	0	0	0	5	20	33	21	7
Black males	0	3	8	75	226	227	87	24
Coloured males	1	0	1	31	100	74	77	16
White males	0	0	5	39	62	203	139	47

Group - Females 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	1	3	15	55	213	249	199	75
Asian females	0	0	1	1	5	6	7	2
Black females	0	1	8	18	72	63	42	13
Coloured females	0	1	3	9	52	55	33	6
White females	1	1	3	19	75	111	105	48

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Types of Lung Cancer

There are two main types of lung cancer, non-small cell lung cancer and small cell lung cancer. These names refer to how the cancers look under a microscope to a pathologist. Most lung cancers are non-small cell. There are subtypes of non-small cell lung cancer.

Because different types of lung cancer are treated differently, an oncologist will determine exactly what treatment is best.

Non-Small Cell Lung Cancer (NSCLC)

NSCLC accounts for about 80% of lung cancers. There are different types of NSCLC, including:

- Squamous cell carcinoma (also called epidermoid carcinoma) - this is the most common type of NSCLC. It forms in the lining of the bronchial tubes and is the most common type of lung cancer in men.
- Adenocarcinoma - this cancer is found in the glands of the lungs that produce mucus. This is the most common type of lung cancer in women and also among people who have not smoked.
- Bronchio-alveolar carcinoma - this is a rare subset of adenocarcinoma. It forms near the lungs' air sacs. Recent clinical research has shown that this type of cancer responds more effectively to the newer targeted therapies.
- Large-cell undifferentiated carcinoma - this cancer forms near the surface, or outer edges, of the lungs. It can grow rapidly.

Small Cell Lung Cancer (SCLC)

SCLC accounts for about 20% of all lung cancers. Although the cells are small, they multiply quickly and form large tumours that can spread throughout the body. Smoking is almost always the cause of SCLC.

There are two types of SCLC. The cancer cells of each type grow and spread in different ways. The types of small cell lung cancer are named for the kinds of cells found in the cancer and how the cells look when viewed under a microscope:

- Small cell carcinoma (oat cell cancer)
- Combined small cell carcinoma

(LungCancer.Org; Mayo Clinic; National Cancer Institute).

Causes of Lung Cancer

Lung cancer has always been – and still is – more common in men. As more women have started smoking, the number of women developing lung cancer has been on the increase.

People who do not smoke can also develop lung cancer. Approximately 10–15% of people who get lung cancer have never smoked.

Other risk factors include the effects of past cancer treatment and exposure to asbestos, radon gas and – in very rare cases – substances such as uranium, chromium and nickel. Lung cancer is not infectious and can't be passed on to other people.

Smoking - The more one smokes, the greater the risk of developing lung cancer. It is also more likely to develop in people who start smoking at a young age. If someone stops smoking, their risk of developing lung cancer falls quite quickly. After about 15 years, the chance of developing the disease is similar to that of a non-smoker.

This section on smoking includes the use of:

- Hookah
- e-Hookah

In the event of someone quitting to smoke, positive health benefits can immediately be experienced. The following indicates the health benefits that can be expected upon quitting the habit of smoking:

Within:

- 20 minutes - the blood pressure, pulse rate and the temperature of one's hands and feet have returned to normal
- 8 hours – the remaining nicotine in one's bloodstream will have fallen to 6.25% of normal peak daily levels, a 93.75% reduction
- 12 hours - blood oxygen level will have increased to normal and carbon monoxide levels will have dropped to normal
- 72 hours – One's entire body will test 100% nicotine-free and over 90% of all nicotine metabolites (the chemicals it breaks down into) will now have passed from the body via one's urine. Symptoms of chemical withdrawal have peaked in intensity, including restlessness. The number of cue induced crave episodes experienced during any quitting day will peak for the 'average' ex-user. Lung bronchial tubes leading to air sacs (alveoli) are beginning to relax in recovering smokers. Breathing is becoming easier and the lung's functional abilities are starting to increase
- 5 - 8 days - the 'average' ex-smoker will encounter an 'average' of three cue induced crave episodes per day. Although we may not be 'average' and although serious cessation time distortion can make minutes feel like hours, it is unlikely that any single episode will last longer than 3 minutes. Keep a clock handy and time them.
- 2 to 4 weeks - cessation related anger, anxiety, difficulty concentrating, impatience, insomnia, restlessness and depression have ended. If still experiencing any of these symptoms get seen and evaluated by your physician
- 8 weeks - insulin resistance has normalised despite average weight gain of 2.7 kg (1997 study).
- 1 year - the excess risk of coronary heart disease, heart attack and stroke have dropped to less than half that of a smoker
- 5 years - the risk of a subarachnoid haemorrhage has declined to 59% of previous risk while still smoking (2012 study). In a female ex-smoker, the risk of developing diabetes is now that of a non-smoker (2001 study)
- 5 to 15 years - the risk of stroke has declined to that of a non-smoker
- 10 years - the risk of being diagnosed with lung cancer is between 30% and 50% of that for a continuing smoker (2005 study). Risk of death from lung cancer has declined by almost half for an average smoker (one pack per day). Risk of cancer of the mouth, throat, oesophagus and pancreas have also declined. Risk of developing diabetes for both men and women is now similar to that of someone who never smoked (2001 study)
- 15 years - the risk of coronary heart disease is now that of a person who has never smoked. The risk of pancreatic cancer has declined to that of someone who never smoked (2011 study (WhyQuit).

In a recent study by Alexandrov, *et al*., (2016) their analysis shows a direct link between the number of cigarettes smoked in a lifetime and the number of mutations in tumour DNA.

The researchers found that, on average, smoking a packet of cigarettes a day led to:

- 150 mutations in each lung cell every year
- 97 in the larynx or voice box
- 23 in the mouth
- 18 in the bladder
- six in the liver

According to the researchers, the more mutations there are, the higher the chance that these will occur in the key genes that are called cancer genes, which convert a normal cell into a cancer cell.

Passive smoking- breathing in other people's cigarette smoke (passive smoking) increases the risk of lung disease and cancer

Pipes and cigars - although pipe and cigar smokers have a lower risk of lung cancer than cigarette smokers, they are still at a much greater risk for lung cancer than non-smokers with an increased risk of cancer of the lip

Cannabis - Cannabis smoke contains a similar profile of carcinogenic (cancer causing) chemicals as tobacco smoke and is inhaled more deeply. Although cannabis smoke is known to contain similar harmful and carcinogenic substances to tobacco smoke, relatively little is still currently understood regarding the respiratory health effects from cannabis smoking (Gates, *et al*.).

Radiation therapy to the Chest - cancer survivors who had radiation therapy to the chest are at higher risk of lung cancer. Patients at highest risk include those treated for Hodgkin disease and women with breast cancer treated with radiation after a mastectomy (but not a lumpectomy)

Radon gas – radon is a colourless, odourless radioactive gas that forms from the decay of radioactive elements such as uranium. The radon gas given off by soil and rock can enter homes and buildings through cracks in floors and walls, pipe, wires and pumps. Radon concentrations are usually highest in basements or in underground mining environments. It can also be released from underground water supplies in small amounts. Exposure can also occur from building materials made from radon containing substances. Exposure to high concentrations of radon can increase the risk for developing lung cancer. It is believed that approximately 9% of lung cancers may be caused by exposure to radon. Smoking, radon, and secondhand smoke are the leading causes of lung cancer. Radon is the number one cause of lung cancer among non-smokers, according to Environmental Protection Agency (EPA) estimates. Overall, radon is the second leading cause of lung cancer

Age - like most types of cancer, lung cancer is more common in older people. About 80% of lung cancers are diagnosed in people over 60. Lung cancer rarely affects people under 40

Genetic risk - some people with a close relative who has had lung cancer may be at an increased risk of it themselves, although the increase in risk is very small. The risk is slightly greater if a relative is a non-smoker and developed lung cancer at an early age, or if more than one relative on the same side of the family developed lung cancer

If concerned about a family history of lung cancer, it helpful to read our more detailed information about genetic risk or talk to a medical practitioner or health professional

Asbestos - people who have been in prolonged or close contact with asbestos have a higher risk of developing lung cancer, especially smokers. Asbestos and tobacco smoke act together to increase the risk. Many people have been in contact with asbestos during their working lives. Low-level exposure increases the risk of lung cancer only slightly (compared to the risk from smoking), while heavy exposure may result in a much higher risk.

If a person has worked with asbestos and develop lung cancer, he/she may be able to claim compensation or be paid Industrial Injuries Disablement Benefit. More advice can be obtained from a treating doctor, a cancer support organisations or by calling our cancer support specialists.

Asbestos exposure also increases the risk of mesothelioma, a cancer of the membranes which cover the lungs.

Industrial exposure - several industrial carcinogens, for example, arsenic and polycyclic hydrocarbons as well as some occupations including non-ferrous metal production and painting, have been linked to lung cancer

Exposure to Diesel Exhaust Fumes - diesel exhaust was classified as a cause of lung cancer by the International Agency for Research on Cancer (IARC) in June 2012, following a review of evidence mainly from highly-exposed workers. IARC cited a study of diesel exhaust exposure in miners, which showed risk of lung cancer was increased approximately three times in those most heavily exposed

Exposure to herbicides and insecticides - the large American Prospective Agricultural Health Study Exposure suggests that exposure to herbicides and insecticides increases lung cancer risk

Occupational exposure to silica - silica exposure can result in silicosis with an increased risk for lung cancer, but without silicosis there is no increased risk. The body of evidence supports an increased risk of lung cancer with exposure to asbestos in non-smokers and that risks are especially high in those who smoke, who also have past exposure to asbestos

Family History - a family history of lung cancer in a first-degree relative is associated with a two-fold (double) increased risk, independent of smoking. If both cancers are diagnosed before the age of 60, the risk ratio is almost five-fold. The association between family history and risk may be stronger in black individuals than white

Past cancer treatment - people who have been treated for some types of cancer may have a slightly increased risk of developing lung cancer many years later. Women who were treated with radiotherapy for breast cancer and who smoke may have an increased risk of lung cancer. People who have been treated for some types of lymphoma using radiotherapy to the chest area as well as men who have been treated for testicular cancer using radiotherapy to the chest area, have a slightly increased risk of lung cancer, especially if they smoke. However, the risk of developing lung cancer is far outweighed by the benefits of the initial treatment

Diet - scientists are studying many different foods and dietary supplements to see whether they increase the risk of getting lung cancer. It is known that smokers who take beta-carotene supplements have increased risk of lung cancer.

Beta-carotene is an antioxidant. It protects the body from damaging molecules called free radicals. Free radicals damage cells through a process known as oxidation. Over time, this damage can lead to a number of chronic illnesses. There is good evidence that eating more antioxidants foods helps boost your immune system, protect against free radicals, and may lower your risk of heart disease and cancer. But the issue is a little more complicated when it comes to taking antioxidant supplements.

Studies that look at big groups of people suggest that those who eat 4 or more daily servings of fruits and vegetables rich in beta-carotene may reduce their risk of developing heart disease or cancer. Foods rich in beta-carotene include those that are orange or yellow, such as peppers, squashes, and carrots.

A few studies have found that people who take beta-carotene supplements may have a higher risk for conditions such as cancer and heart disease. Researchers think that may be because the total of all the nutrients you eat in a healthy, balanced diet gives more protection than just beta-carotene supplements alone.
There is also some evidence that when smokers and people who are exposed to asbestos take beta-carotene supplements, their risk of lung cancer goes up. For now, smokers should not take beta-carotene supplements (University of Maryland Medical Center).

HIV and Aids - significant increases in risk of lung cancer have been reported in research studies conducted among people with HIV and Aids even after accounting for smoking, although one study showed an association in men only

Chlamydia Pneumoniae - people with antibodies to Chlamydia pneumoniae have show an increase in risk for lung cancer. Chlamydia pneumoniae is an infectious bacteria associated with a number of diseases including pneumonia

Systemic Lupus Erythematosus - an increased risk of lung cancer has been shown in people with systemic Lupus Erythematosus

Klinefelter syndrome – Klinefelter syndrome has been shown to be a risk factor although the risk is less than two-fold

Tuberculosis - a systematic review of published studies showed that the risk for lung cancer is almost doubled for people with a previous diagnosis of tuberculosis (TB), after taking into account smoking history. The risk increase persisted for more than 20 years after TB diagnosis
(MacMillan Cancer Support; WebMD; Centers for Disease Control and Prevention; Cancer Research UK; United States Environmental Protection Agency).

Signs and Symptoms of Lung Cancer
Lung cancer typically doesn't cause signs and symptoms in its earliest stages. Signs and symptoms of lung cancer typically occur only when the disease is advanced. Signs and symptoms of lung cancer may include:

- a new cough that doesn't go away
- changes in a chronic cough or ‘smoker's cough’
- a cough that gets worse or does not go away
- coughing up blood, even a small amount
- shortness of breath or wheezing
- constant chest pain – especially when coughing
- frequent chest infections, such as pneumonia, or an infection that does not go away
- wheezing
- hoarseness
- swelling of the neck and face
- fatigue (feeling very tired all the time)

- loss of appetite
- losing weight without trying
- bone pain
- headache

(Mayo Clinic; Canadian Cancer Society; NIH Senior Health).

Diagnosis of Lung Cancer

The following are used to diagnosed cancer of the lung:

Medical history - to find out if lung cancer may be present, the doctor evaluates a person's medical history, smoking history, his/her exposure to environmental and occupational substances, and family history of cancer.

Physical examination - the doctor also performs a physical exam and may order a test to take an image of the chest or other tests. Seeing a spot on an image is usually how a doctor first suspects that lung cancer may be present.

Sputum cytology - if lung cancer is suspected, the doctor may order a test called a sputum cytology. This is a simple test where a doctor examines a sample of mucous cells coughed up from the lungs under a microscope to see if cancer is present.

Biopsy - but to confirm the presence of lung cancer, the doctor must examine fluid or tissue from the lung. This is done through a biopsy - the removal of a small sample of fluid or tissue for examination under a microscope by a pathologist to confirm the presence of lung cancer.

Bronchoscopy – a procedure to collect cells or small samples of tissues from the airways and lungs. The doctor inserts a bronchoscope, a thin, lighted tube, into the mouth or nose and down through the windpipe to look into the airways to collect any samples of tissue cells if needed.

Needle aspiration - the doctor numbs the chest area and inserts a thin needle through the chest wall into the tumour to remove a sample of tissue.

Thoracentesis - using a needle, the doctor removes a sample of the fluid that surrounds the lungs to check for cancer cells.

Thoracotomy - surgery to open the chest is sometimes needed to diagnose lung cancer. This procedure is a major operation performed in a hospital.

Imaging tests - doctors use imaging methods such as a spiral Computerised Tomography (CT) scan also commonly known as helical C) or a Positron Emission Tomography (PET) scan to look for signs of cancer. A CT scan is a series of detailed pictures of areas inside the body. A PET scan is a computerised image of the metabolic activity of body tissues.
Other tests - this includes removal of lymph nodes for examination under a microscope to check for cancer cells. Lymph nodes are small, bean-shaped structures found throughout the body that filter substances in a fluid called lymph and help fight infection and disease.
(NIH Senior Health; WebMD).

Staging of Lung Cancer
Staging is the process of finding out how far a cancer has spread. This is important because treatment options and outlook for recovery and survival depend on the cancer's stage.

Staging of lung cancer uses a system created by the American Joint Committee on Cancer (AJCC).

The TNM system
The *TNM system* for staging contains 3 key pieces of information:

- **T** describes the size of the primary tumour, measured in centimetres (cm), and whether the cancer has spread to organs next to the tumour
- **N** describes the extent of spread to nearby (regional) lymph nodes
- **M** indicates whether the cancer has metastasised (spread) to other organs of the body

Numbers or letters appear after ***T***, ***N***, and ***M*** to provide more details about each of these factors:

- the numbers 0 through 4 indicate increasing severity
- the letter X means 'cannot be assessed' because the information is not available
- the letters 'is' mean 'carcinoma *in situ'*, which means the tumour is contained within the top layer of anal tissue and has not yet reached deeper layers of tissue

TX primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0 no evidence of primary tumour
Tis carcinoma *in situ*
T1 tumour 3cm or less in greatest dimesion, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus
T2 tumour with any of the following features of size or extent:
  - more than 3cm in greatest dimension
  - involving main bronchus, 2cm or more distal to the carina
  - invading the visceral pleura
  - associated with atelectasis or obstructive pneumonitis that extends to the hilar region (area between the two lungs) but does not involve the entire lung

T3 tumour of any size that:
  - directly invades the chest wall (including superior sulcus tumours), diaphragm, mediastinal or parietal pericardium
  - is located in the main bronchus less than 2cm distal to the carina but without involvement of the carina
  - is associated with atelectasis or obstructive penumonitis of the entire lung

T4 tumour of any size that:
  - invades the mediastinum, heart, great vessels, trachea,oesophagus, vertebral body or carina
  - is associated with a malignant pleural effusion

Regional Lymph Nodes (N)
NX regional lymph nodes cannot be assessed

N0 no regional lymph nodes metastasis
N1 metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, including direct extension
N2 metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3 metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)

Distant Metastases (M)
MX presence of distant metastasis cannot be assessed
M0 no distant metastasis
M1 distant metastasis

Stage Grouping

Occult	TX	N0	M0
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T1	N1	M0
	T2	N1	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV (CTSN)	Any T	Any N	M1

Where Lung Cancer May Spread to in the Body
In the event of lung cancer spreading to other parts of the body, it may spread as indicated in the **bold section** below:

Cancer Type:	**Main Sites of Metastasis (Spread)**
Bladder	Bone, liver, lung
Breast	Bone, brain, liver, lung
Colon	Liver, lung
Colorectal	Liver, lung, peritoneum (lining of abdomen)
Kidney	Adrenal gland, bone, brain, liver, lung
Lung	**Adrenal gland, bone, brain, liver, other lung**
Melanoma	Bone, brain, liver, lung, skin, muscle
Ovary	Liver, lung, peritoneum (lining of abdomen)

Pancreas	Liver lung, peritoneum (lining of abdomen)
Prostate	Adrenal gland, bone, liver, lung
Stomach	Liver, lung, peritoneum (lining of abdomen), ovaries
Thyroid	Bone, liver, lung
Uterus	Boner, liver, lung, peritoneum (lining of abdomen), vagina
Non-melanoma skin cancer	Very rare: lymph nodes, lung, bone (if in head/neck region)

(National Cancer Institute)

Treatment of Lung Cancer

The type of treatment a patient will receive for lung cancer depends on several factors, including:

- the type of lung cancer (non-small cell or small cell)
- the size and position of the cancer
- how far advanced the cancer is (the stage)
- patient's overall health

Deciding what treatment is best can be difficult. The cancer team will make recommendations, but the final decision will be that of the patient.

Treatment options include:

- surgery
- radiotherapy
- chemotherapy

Small Cell Lung Cancer (SCLC)

For most patients with small cell lung cancer, current treatments do not cure the cancer. Regardless of stage, the current prognosis for patients with SCLC is poor despite improvements in diagnosis and therapy made during the past 25 years. Without treatment, SCLC has the most aggressive clinical course of any type of pulmonary tumour, with median survival from diagnosis of only 2 to 4 months. About 10% of the total population of SCLC patients remains free of disease during the 2 years from the start of therapy, which is the time period during which most relapses occur. Even these patients, however, are at risk of dying from lung cancer (both small and non-small cell types).] The overall survival at 5 years is 5% to 10%.

(NHS Choices; National Cancer Institute)

Non-Small Cell Lung Cancer

Nine types of standard treatment are used:

<u>Surgery</u>

Five types of surgery are used to treat lung cancer:

- Wedge resection – removal of a tumour and some of the normal tissue around it. When a slightly larger amount of tissue is taken, it is called a segmental resection.

- Segmental resection of the lung - part of the lung lobe containing the cancer and a slightly larger amount of healthy tissue around it is removed than in the case of a wedge resection

- Lobectomy – removal of a whole lobe (section) of the lung

- Pneumonectomy – removal of the whole lung

- Sleeve resection – remove of part of the bronchus

Even if the doctor removes all the cancer that can be seen at the time of the surgery, some patients may be given chemotherapy or radiation therapy after surgery to kill any remaining cancer cells. Treatment given after the surgery to lower the risk of recurrence, is called adjuvant therapy.

Radiation therapy - radiation therapy is a cancer treatment that uses high-energy x-rays or other types of radiation to kill cancer cells or keep them from growing. There are two types of radiation therapy. External radiation therapy uses a machine outside the body to send radiation toward the cancer. Internal radiation therapy uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer.

Radiosurgery - is a method of delivering radiation directly to the tumour with little damage to healthy tissue. It does not involve surgery and may be used to treat certain tumours in patients who cannot have surgery.

The way the radiation therapy is given depends on the type and stage of the cancer being treated. It also depends on where the cancer is found. For tumours in the airways, radiation is given directly to the tumour through an endoscope.

Chemotherapy - chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the cerebrospinal fluid, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). The way the chemotherapy is given depends on the type and stage of the cancer being treated.

Targeted therapy - targeted therapy is a type of treatment that uses drugs or other substances to identify and attack specific cancer cells without harming normal cells. Monoclonal antibodies and tyrosine kinase inhibitors are two types of targeted therapy being used in the treatment of non-small cell lung cancer.

Monoclonal antibody therapy - is a cancer treatment that uses antibodies made in the laboratory from a single type of immune system cell. These antibodies can identify substances on cancer cells or normal substances that may help cancer cells grow. The antibodies attach to the substances and kill the cancer cells, blocking its growth, or keeping it from spreading. Monoclonal antibodies are given by infusion. It may be used alone or to carry drugs, toxins, or radioactive material directly to cancer cells.

Monoclonal antibodies used to treat non-small cell lung cancer include bevacizumab and cetuximab. Bevacizumab binds to vascular endothelial growth factor (VEGF) and may

prevent the growth of new blood vessels that tumours need to grow. Cetuximab binds to epidermal growth factor receptor (EGFR) and works to stop cancer cells from growing and dividing.

Tyrosine kinase inhibitors - are targeted therapy drugs that block signals needed for tumours to grow. Tyrosine kinase inhibitors may be used with other anticancer drugs as adjuvant therapy.

Tyrosine kinase inhibitors are used to treat non-small cell lung cancer and include erlotinib and gefitinib. They are types of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. Crizotinib is a type of tyrosine kinase inhibitor that is used to treat non-small cell lung cancer with certain gene changes.

Immunotherapy - The US Food and Drug Administration has approval the anti–PD-1 immunotherapy pembrolizumab (Keytruda), in combination with pemetrexed and carboplatin, for patients with untreated metastatic non-squamous non–small-cell lung cancer (NSCLC).

The approval was based on results of a cohort from KEYNOTE-021, an open-label, multi-cohort trial. The study compared 4 cycles of pemetrexed and carboplatin in 63 patients vs pemetrexed/carboplatin plus 200 mg pembrolizumab intravenously every 3 weeks in 60 patients until progression or unacceptable toxicity. Eligible participants had locally advanced or metastatic non-squamous NSCLC and had not previously received any systemic therapy. Patients in either arm could also receive pemetrexed as maintenance therapy at the investigator's discretion. Patients were randomized by PD-L1 tumour expression (tumour proportion score [TPS] < 1% vs TPS ≥ 1%).

Patients who received pembrolizumab had improved overall response rates and progression-free survival. The overall response rate was 55% in patients who received pembrolizumab plus chemotherapy vs 29% in those who received chemotherapy alone (*P* = .0032). The median progression-free survival was 13 months with pembrolizumab vs 8.9 months for chemotherapy alone for a hazard ratio of 0.53 (95% CI, 0.31–0.91; *P* = .0205).

The overall response rate among patients with TPS < 1% was 57% in the pembrolizumab-treated group vs 13% in the chemotherapy-alone group. In patients with TPS ≥ 1%, the overall response rate was 54% in the pembrolizumab-treated group vs 38% in the chemotherapy-alone arm

Serious adverse events in the pembrolizumab arm occurred in 41% of patients vs 28% in those who only received chemotherapy.

The most common adverse events of any grade among patients who received pembrolizumab were constipation (51%), fatigue (71%), and nausea (68%). Grade 3/4 adverse events included dyspnoea and fatigue (3.4% each), and diarrhoea, nausea, rash, and vomiting (1.7% each).

Ten percent of patients discontinued pembrolizumab due to adverse events, with acute kidney injury (3.4%) as the most common cause.

Pembrolizumab can also cause immune-mediated toxicities including colitis, endocrinopathies, hepatitis, nephritis, and pneumonitis. Based on the severity, pembrolizumab should be either discontinued or withheld, and patients should be given corticosteroids if needed.

The recommended dose of pembrolizumab for NSCLC is 200 mg IV every 3 weeks until progression, unacceptable toxicity, or for 2 years in patients without disease progression.

Laser therapy - laser therapy is a cancer treatment that uses a laser beam (a narrow beam of intense light) to kill cancer cells.

Photodynamic therapy (PDT) - is a treatment that uses a drug, called a photosensitiser or photosensitising agent, and a particular type of light. When photosensitisers are exposed to a specific wavelength of light, they produce a form of oxygen that kills nearby cells.

Each photosensitiser is activated by light of a specific wavelength. This wavelength determines how far the light can travel into the body. Thus, doctors use specific photosensitisers and wavelengths of light to treat different areas of the body with PDT.

Photodynamic therapy causes little damage to healthy tissue. It is used mainly to treat tumours on or just under the skin or in the lining of internal organs. When the tumour is in the airways, PDT is given directly to the tumour through an endoscope.

Cryosurgery - cryosurgery is a treatment that uses an instrument to freeze and destroy abnormal tissue, such as carcinoma *in situ*. This type of treatment is also called cryotherapy. For tumours in the airways, cryosurgery is done through an endoscope.

Electrocautery - electrocautery is a treatment that uses a probe or needle heated by an electric current to destroy abnormal tissue. For tumours in the airways, electrocautery is done through an endoscope.

Watchful waiting - watchful waiting is closely monitoring a patient's condition without giving any treatment until symptoms appear or change. This may be done in certain rare cases of non-small cell lung cancer.
(National Cancer Institute; Medline Plus; CancerNetwork).

(Revised 4/2015)

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Non-Small Cell Lung Cancer (NSCLC)

Note: All recommendations are Category 2A unless otherwise indicated.

Chemotherapy Regimens For Neoadjuvant and Adjuvant Therapy[1]

REGIMEN	DOSING
Cisplatin +	**Days 1 and 8:** Cisplatin 50mg/m^2 IV **plus**

vinorelbine[2–4]	**Days 1, 8, 15 and 22:** Vinorelbine 25mg/m^2 IV. Repeat cycle every 4 weeks for 4 cycles. **OR** **Day 1:** Cisplatin 100mg/m^2 IV **plus** **Days 1, 8, 15 and 22:** Vinorelbine 30mg/m^2 IV. Repeat cycle every 4 weeks for 4 cycles. **OR** **Day 1:** Cisplatin 75–80mg/m^2 **plus** **Days 1 + 8:** Vinorelbine 25–30mg/m^2. Repeat every 3 weeks for 4 cycles.
Cisplatin + etoposide[3]	**Day 1:** Cisplatin 100mg/m^2 IV **plus** **Days 1–3:** Etoposide 100mg/m^2 IV. Repeat cycle every 4 weeks for 4 cycles.
Cisplatin + vinblastine[3]	**Days 1, 22, 43, 64:** Cisplatin 80mg/m^2 IV. **Days 1, 8, 15, 22, 29, and then every 2 weeks after day 43:**Vinblastine 4 mg/m^2. Repeat every 3 weeks for 4 cycles.
Cisplatin + gemcitabine[5]	**Day 1:** Cisplatin 75mg/m^2 IV **plus** **Days 1 and 8:** Gemcitabine 1,250mg/m^2 IV. Repeat cycle every 3 weeks.
Cisplatin + docetaxel[6]	**Day 1:** Docetaxel 75mg/m^2 IV + cisplatin 75mg/m^2 IV. Repeat every 3 weeks for 4 cycles.
Cisplatin + pemetrexed[7,8]	**Day 1:** Cisplatin 75mg/m^2 IV + pemetrexed 500mg/m^2 IV.* Repeat every 3 weeks for 4 cycles.
For patients with comorbidities or patients not able to tolerate cisplatin[1]	
Paclitaxel + carboplatin[9]	**Day 1:** Paclitaxel 200mg/m^2 IV + carboplatin AUC=6 IV. Repeat cycle every 3 weeks for 4 cycles.
Concurrent Chemotherapy/Radiotherapy (RT)[1]	
Cisplatin + etoposide[10,†](preferred regimen)	**Days 1, 8, 29 and 36:** Cisplatin 50mg/m^2 IV **plus** **Days 1–5 and 29–33:** Etoposide 50mg/m^2 IV **plus** Concurrent thoracic radiotherapy 1.8Gy/day for 5 days/week (total dose, 61Gy).
Cisplatin + vinblastine (preferred regimen)[11]	**Days 1 and 29:** Cisplatin 100mg/m^2 IV **plus** **Days 1, 8, 15, 22 and 29:** Vinblastine 5mg/m^2 IV with concurrent thoracic radiotherapy (total dose, 60Gy).
Carboplatin + pemetrexed (nonsquamous)[12]	**Day 1:** Carboplatin AUC 5 IV **plus** **Day 1:** Pemetrexed 500 mg/m^2 IV with concurrent thoracic radiotherapy. Repeat every 3 weeks for 4 cycles.
Cisplatin + pemetrexed (nonsquamous)[7,8]	**Day 1:** Cisplatin 75 mg/m^2 IV. **Day 1:** Pemetrexed 500 mg/m^2 IV with concurrent thoracic radiotherapy. Repeat every 3 weeks for 3 cycles.
Sequential Chemotherapy/Radiotherapy (RT)[1]	
Cisplatin + vinblastine[11]	**Days 1 and 29:** Cisplatin 100mg/m^2 IV. **Days 1, 8, 15, 22 and 29:** Vinblastine 5mg/m^2 IV; **followed by**thoracic radiotherapy with 60Gy in 30 fractions beginning on Day 50.

Paclitaxel + carboplatin[13]	**Day 1:** Paclitaxel 200mg/m^2 IV over 3 hours + carboplatin AUC=6 IV over 1 hour. Repeat every 3 weeks for 2 cycles; **followed by** thoracic radiotherapy 63Gy beginning on Day 42.
Concurrent Chemotherapy/Radiotherapy (RT) Followed by Chemotherapy[1]	
Paclitaxel + carboplatin[13]	**Day 1 (weekly):** Paclitaxel 45–50mg/m^2 IV and carboplatin AUC=2 IV. Concurrent thoracic radiotherapy; **followed by** two additional cycles of paclitaxel 200mg/m^2 IV and carboplatin AUC=6 IV.
Cisplatin + etoposide[10]	**Days 1, 8, 29, and 36:** Cisplatin 50mg/m^2 IV. **Days 1–5, 29–33:** Etoposide 50mg/m^2 IV with concurrent thoracic radiotherapy; **followed by** two additional cycles of cisplatin 50mg/m^2 IV and etoposide 50mg/m^2 IV.

Systemic Therapy for Advanced Disease[1]

• The drug regimen with the highest likelihood of benefit, with toxicity deemed acceptable to both the physician and the patient, should be given as initial therapy for advanced lung cancer.
• Stage, weight loss, performance status (PS), and gender predict survival.
• Platinum-based chemotherapy prolongs survival, improves symptom control, and yields superior quality of life compared to best supportive care.
• Histology of NSCLC is important in the selection of systemic therapy.
• New agent/platinum combinations have generated a plateau in overall response rate (25%–35%), time to progression (4–6 months), median survival (8–10 months), 1-year survival rate (30%–40%), and 2-year survival rate (10%–15%) in fit patients.
• Unfit patients of any age (PS 3–4) do not benefit from cytotoxic treatment, except erlotinib for those who are epidermal growth factor receptor (EGFR) mutation-positive.

Principals of Maintenance Therapy[1]

Continuation maintenance refers to the use of at least one of the agents given in first line, beyond 4 to 6 cycles, in the absence of disease progression. Switch maintenance refers to the initiation of a different agent, not included as part of the first-line regimen, in the absence of disease progression, after 4 to 6 cycles of initial therapy.
• Continuation Maintenance: Bevacizumab and cetuximab given in combination with chemotherapy should be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials supporting their use.
• Continuation of bevacizumab after 4–6 cycles of platinum-doublet chemotherapy and bevacizumab (category 1).
• Continuation of cetuximab after 4–6 cycles of cisplatin, vinorelbine, and cetuximab (category 1).
• Continuation of pemetrexed after 4–6 cycles of cisplatin and pemetrexed chemotherapy, for patients with histologies other than squamous cell carcinoma (category 1).
• Continuation of bevacizumab + pemetrexed after 4–6 cycles of bevacizumab, pemetrexed, cisplatin/carboplatin, for patients with histologies other than squamous cell carcinoma.
• Continuation of gemcitabine after 4–6 cycles of platinum-doublet chemotherapy (category 2B).
• Switch Maintenance: Two studies have shown a benefit in progression-free and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy, in patients without disease progression after 4–6 cycles of therapy.
• Initiation of pemetrexed after 4–6 cycles of first-line platinum-doublet chemotherapy for patients with histologies other than squamous cell carcinoma (category 2B).
• Initiation of erlotinib after 4–6 cycles of first-line platinum-doublet chemotherapy (category 2B).
• Initiation of docetaxel after 4–6 cycles of first-line platinum-doublet chemotherapy in patients with squamous cell carcinoma (category 2B).
• Close surveillance of patients without therapy is a reasonable alternative to maintenance.

Principles of Third-Line Therapy[1]

• If not already given, options for patients with PS 0–2 include docetaxel, pemetrexed (nonsquamous), erlotinib, or gemcitabine (category 2B for all options).

Continuation After Disease Progression[1]

• With the exception of targeted agents (erlotinib, gefitinib, afatinib, crizotinib, ceritinib) in patients with EGFR-sensitizing mutations or ALK rearrangements who have experienced objective regressions with targeted therapy, no agent should be continued after disease progression has been documented except in selected situations. (refer to discussion section of NCCN Guidelines for Non-Small Cell Lung Cancer v.5.2015)

Systemic Treatment Options for Patients with NSCLC[1,‡]

• Cisplatin[14–21] • Carboplatin[17,18–23] • Paclitaxel[14,17,18,20–23] • Docetaxel[5,6,19,23,24] • Vinorelbine[6,20,21] • Gemcitabine[5,16,18–20,24] • Etoposide[17]	• Irinotecan[20] • Vinblastine • Mitomycin • Ifosfamide[23] • Pemetrexed[7,8] • Erlotinib[25] • Bevacizumab[26]	• Cetuximab[27] • Albumin-bound paclitaxel[28–30§] • Crizotinib[31] • Afatinib[32] • Ceritinib[33] • Ramucirumab[34] • Nivolumab[35]

First-Line Systemic Therapy for Advanced Disease[1]

Bevacizumab carboplatin + paclitaxel[26,36]	**Day 1:** Paclitaxel 200mg/m^2 IV **Day 1:** Carboplatin AUC=6 IV. Repeat every 3 weeks for 6 cycles. **Day 1:** Bevacizumab 15mg/kg IV every 3 weeks until disease progression.
Cetuximab + cisplatin + vinorelbine[27‖]	**Day 1:** Cetuximab 400mg/m^2 IV + cisplatin 80mg/m^2 IV, **plus** **Days 1 and 8:** Vinorelbine 25mg/m^2 IV, **plus** **Day 8:** Cetuximab 250mg/m^2 IV once weekly. Repeat every 3 weeks for 6 cycles.
Erlotinib[37,38¶]	**Day 1:** Erlotinib 150mg PO once daily; following 4 cycles of platinum-based chemotherapy.
Cisplatin + paclitaxel[19]	**Day 1:** Paclitaxel 135mg/m^2 IV over 24 hours **Day 2:** Cisplatin 75mg/m^2 IV. Repeat cycle every 3 weeks.
Cisplatin + gemcitabine[19]	**Day 1:** Cisplatin 100mg/m^2 IV **Days 1, 8 and 15:** Gemcitabine 1,000mg/m^2 IV. Repeat cycle every 4 weeks.
Cisplatin + docetaxel[6]	**Day 1:** Cisplatin 75mg/m^2 IV + docetaxel 75mg/m^2 IV. Repeat cycle every 3 weeks.
Cisplatin + vinorelbine[6]	**Day 1:** Cisplatin 100mg/m^2 IV **Days 1, 8, 15 and 22:** Vinorelbine 25mg/m^2 IV over 10 minutes. Repeat cycle every 4 weeks.
Carboplatin + paclitaxel[19]	**Day 1:** Carboplatin AUC=5–6 IV **Day 1:** Paclitaxel 225mg/m^2 IV over 3 hours. Repeat cycle every 3 weeks.
Pemetrexed + cisplatin[24,39]	**Day 1:** Pemetrexed 500mg/m^2 IV + cisplatin 75mg/m^2 IV. Repeat cycle every 3 weeks.
Crizotinib[40#]	Crizotinib 250mg PO twice daily.[**]
Afatinib[32¶]	Afatinib 40mg PO once daily.

Principals of First-Line Therapy[1]

• Bevacizumab + chemotherapy or chemotherapy alone is indicated in patients with PS 0–1 with advanced or recurrent NSCLC. Bevacizumab should be given until disease progression.
• Cetuximab + vinorelbine/cisplatin is an option for patients with PS 0–1 (category 2B).
• Erlotinib is recommended as a first-line therapy in patients with sensitizing EGFR mutations and should not be given as first-line therapy to patients negative for these EGFR mutations or with unknown EGFR status.
• Afatinib is indicated for select patients with sensitizing EGFR mutations.
• Crizotinib is indicated for select patients with ALK rearrangements.
• There is superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous histology compared with cisplatin/gemcitabine.
• There is superior efficacy for cisplatin/gemcitabine in patients with squamous histology, in comparison to cisplatin/pemetrexed.
• Two drug regimens are preferred; a third cytotoxic drug increases response rate but not survival.
• Single-agent therapy or platinum-based combinations are a reasonable alternative in PS 2 patients or the elderly.
• Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, etoposide, vinblastine, vinorelbine, pemetrexed, or albumin-bound paclitaxel.
• New agent/non-platinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (e.g., gemcitabine/docetaxel, gemcitabine/vinorelbine).
• Response assessment after 1–2 cycles, then every 2–4 cycles.

Subsequent Second-Line Systemic Therapy for Advanced Disease[1]

Docetaxel[23]	**Day 1:** Docetaxel 75mg/m^2 IV. Repeat cycle every 3 weeks.
Pemetrexed[7]	**Day 1:** Pemetrexed 500mg/m^2 IV. Repeat cycle every 3 weeks.
Erlotinib[25]	Erlotinib 150mg PO once daily.
Ceritinib[33#]	Ceritinib 750mg PO once daily.
Ramucirumab + docetaxel[34]	**Day 1:** Ramucirumab 10mg/kg IV + docetaxel 75mg/m^2 IV. Repeat cycle every 3 weeks.
Afatinib[32¶]	Afatinib 40mg PO once daily.
Nivolumab[35]	Nivolumab 3mg/kg IV over 60 minutes every 2 weeks.

Principles of Subsequent Therapy[1]

• In patients who have experienced disease progression either during or after first-line therapy, single-agent docetaxel, pemetrexed, or erlotinib are established second-line agents.
• Docetaxel is superior to vinorelbine or ifosfamide.
• Pemetrexed is considered equivalent to docetaxel with less toxicity in patients with adenocarcinoma and large cell carcinoma.
• Ramucirumab + docetaxel improves survival when compared to docetaxel alone.
• Erlotinib is superior to best supportive care.
• Afatinib is indicated for select patients with sensitizing EGFR mutations.
• Ceritinib is indicated for patients with ALK rearrangements who have disease progression on or are intolerant to crizotinib.
• If not already given, options for patients with PS 0–2 include docetaxel, pemetrexed (nonsquamous), erlotinib, or gemcitabine (category 2B for all options).

Continuation After Disease Progression[1]

• With the exception of targeted agents (erlotinib, gefitinib, afatinib, crizotinib) in patients with

EGFR-sensitizing mutations or ALK rearrangements who have experienced objective regressions with targeted therapy, no agent should be continued after disease progression has been documented except in selected situations (refer to discussion section of NCCN Guidelines for Non-Small Cell Lung Cancer v.5.2015).	
Small Cell Lung Cancer (SCLC)	
Chemotherapy as Primary or Adjuvant Therapy‡‡	
Limited Stage (maximum of 4–6 cycles)[1]	
Cisplatin + etoposide[41–43§§]	**Day 1:** Cisplatin 60mg/m^2 IV **plus** **Days 1–3:** Etoposide 120mg/m^2 IV. Repeat cycle every 3 weeks for at least 4 cycles. **OR** **Day 1:** Cisplatin 80mg/m^2 IV **plus** **Days 1–3:** Etoposide 100mg/m^2 IV. Repeat every 4 weeks for 4–6 cycles.
Carboplatin + etoposide[44]	**Day 1:** Carboplatin AUC=5–6 IV **plus** **Days 1–3:** Etoposide 100mg/m^2 IV. Repeat every 3 weeks for 4–6 cycles.
Extensive Stage (maximum of 4–6 cycles)[1]	
Cisplatin + etoposide[45–47]	**Day 1:** Cisplatin 75–80mg/m^2 IV **Days 1–3:** Etoposide 80–100mg/m^2 IV. Repeat every 3 weeks for 4–6 cycles. **OR** **Days 1–3:** Cisplatin 25mg/m^2 IV + etoposide 100mg/m^2 IV. Repeat cycle every 3 weeks for 4-6 cycles.
Cisplatin + irinotecan[41,48,49]	**Day 1:** Cisplatin 60mg/m^2 IV **Days 1, 8 and 15:** Irinotecan 60mg/m^2 IV. Repeat cycle every 4 weeks for 4 cycles. **OR** **Day 1 and 8:** Cisplatin 30mg/m^2 IV **Day 1 and 8:** Irinotecan 65mg/m^2 IV. Repeat every 3 weeks for 4–6 cycles.
Carboplatin + irinotecan[50]	**Day 1:** Carboplatin AUC=5 IV **plus** **Days 1, 8 and 15:** Irinotecan 50mg/m^2 IV. Repeat cycle every 4 weeks for 4–6 cycles.
Carboplatin + etoposide[51]	**Day 1:** Carboplatin AUC=5–6 IV. **Days 1–3:** Etoposide 100mg/m^2 IV. Repeat every 4 weeks for 4–6 cycles.
Subsequent Chemotherapy	
Relapse <2–3 months, PS 0–2[1]	
Paclitaxel[18,52]	**Day 1:** Paclitaxel 175mg/m^2 IV over 3 hours **plus** **Day 1:** Cisplatin 80mg/m^2 IV. Repeat every 3 weeks for at least 2 cycles. **OR** **Day 1:** Paclitaxel 80mg/m^2 IV over 1 hour. Repeat every week for 6 weeks, followed by a 2-week break.
Docetaxel[53]	**Day 1:** Docetaxel 100mg/m^2 IV over 1 hour. Repeat every 21 days.

Topotecan[54–57]	**Days 1–5:** Topotecan 1.5mg/m^2 IV once daily over 30 minutes. Repeat every 3 weeks. **OR** **Days 1–5:** Topotecan 2.3mg/m^2 PO once daily. Repeat every 3 weeks.
Irinotecan[58]	**Day 1:** Irinotecan 100mg/m^2 IV over 90 minutes. Repeat every week.
Temozolomide[59]	**Day 1–21:** Temozolomide 75mg/m^2 PO for a 4-week cycle.
Gemcitabine[60,61]	**Days 1, 8, and 15:** Gemcitabine 1,000mg/m^2 IV for a 4-week cycle.
Ifosfamide[62]	**Day 1:** Ifosfamide/mesna 5,000mg/m^2 IV. Repeat every 3 weeks.
Relapse > 2–3 months up to 6 months[1]	
Topotecan (Category 1) [54–57]	**Days 1–5:** Topotecan 1.5mg/m^2 IV once daily over 30 minutes. Repeat every 3 weeks. **OR** **Days 1–5:** Topotecan 2.3mg/m^2 PO once daily. Repeat every 3 weeks.
Paclitaxel[18,52]	**Day 1:** Paclitaxel 175mg/m^2 IV over 3 hours **plus** **Day 1:** Cisplatin 80mg/m^2. Repeat every 3 weeks for at least ^{2} cycles. **OR** **Day 1:** Paclitaxel 80mg/m^2 IV over 1 hour. Repeat every week for 6 weeks, followed by a 2-week break.
Docetaxel[53]	**Day 1:** Docetaxel 100 mg/m^2 IV over 1 hour. Repeat every 21 days.
Irinotecan[58]	**Day 1:** Irinotecan 100mg/m^2 IV over 90 minutes. Repeat every week.
Gemcitabine[60,61]	**Days 1, 8, and 15:** Gemcitabine 1,000mg/m^2 IV for a 4-week cycle.
Vinorelbine[63,64]	**Day 1:** Vinorelbine 25–30mg/m^2 IV. Repeat every week
Etoposide (PO)[65,66]	**Day 1–21:** Etoposide 50mg/m^2 PO.
Temozolomide[59]	**Day 1–21:** Temozolomide 75mg/m^2 PO for a 4-week cycle.
Cyclophosphamide + doxorubicin + vincristine (CAV)[54]	**Day 1:** Cyclophosphamide 1,000 mg/m^2 IV **plus** **Day 1:** Doxorubicin 45mg/m^2 IV **plus** **Day 1:** Vincristine 2mg IV. Repeat every 21 days.
Relapse> 6 months[1]	
• Original regimen[67,68‖‖]	

˙ For adenocarcinoma, large cell carcinoma, and NSCLC NOS without specific histologic subtype.

† This regimen can be used as neoadjuvant chemoradiotherapy. Cisplatin and etoposide is the preferred regimen. If weekly carboplatin and paclitaxel is used because the patient is not able to tolerate concurrent full-dose cisplatin and radiotherapy, the treating physician should consider 2 cycles of full-dose platinum therapy after local treatment is completed

‡ Most are used in combination, while others are used as monotherapy (e.g., maintenance or second-line therapy).

§ Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (dexamethasone, H2 blockers, H1 blockers) are contraindicated.

‖ Indicated in advanced NSCLC.

¶ Indicated for EGFR mutation–positive patients and may be considered as an option for patients who test positive for an EGFR mutation.

Indicated for ALK-positive patients.

** May reduce to 200mg twice daily not tolerated or toxicity occurs. If further reduction is needed, reduce to 250mg once daily.

†† The regimens included are representative of the more commonly used regimens for small cell lung cancer. Other regimens may be acceptable.

‡‡ The use of rnyeloid growth factors is not recommended during concurrent chemotherapy plus radiotherapy.

§§ During chemotherapy + radiotherapy, cisplatin/etoposide is recommended (Category 1).

‖‖ Consider dose reductions versus growth factors in the poor performance status patient.

(Cancer Therapy Advisor).

Lowering the Risk for Lung Cancer

Lung cancer prevention is a critical topic, since lung cancer is the leading cause of cancer deaths in men and women worldwide. It is estimated that the risk for lung cancer can be lowered in 90% of cases through action and awareness. Smoking accounts for the majority of preventable lung cancers, but non-smokers can take action to lower their risk as well. Those who have already been diagnosed with lung cancer should not despair. Some of these measures have been shown to improve survival after lung cancer is already present.

Smoking cessation - smoking is responsible for the majority of lung cancers. Quitting all forms of smoking at any time can lower the risk of developing lung cancer, and appears to be beneficial after a diagnosis of lung cancer as well.

Radon exposure - exposure to radon in the home is the second leading cause of lung cancer overall, and the number one cause in non-smokers. Radon is an invisible radioactive gas that results from the normal decay of radium in the soil.

Secondhand smoke - exposure to second hand smoke increases the risk of lung cancer in non-smokers two to three fold.

Asbestos - workplace exposure to asbestos increases the risk of lung cancer, and combined with smoking the risk is exponential. Employers should have safety recommendations for those exposed.

Chemical and occupational exposures - several chemicals used in industry and around homes may increase the risk of lung cancer. Labels on home products such as wood stripper, and Material Safety Data Sheets provided by employers, provide information on safe exposure and proper masks to use to limit exposure.

Diet and exercise - a healthy diet and moderate physical activity both play a role in lowering the risk for lung cancer.
(About.Com Lung Cancer).

Complications of Lung Cancer
Lung cancer can cause complications, such as:

Shortness of breath - people with lung cancer can experience shortness of breath if cancer grows to block the major airways. Lung cancer can also cause fluid to accumulate around the lungs, making it harder for the affected lung to expand fully when you inhale.

Coughing up blood - lung cancer can cause bleeding in the airway, which can cause you to cough up blood (haemoptysis). Sometimes bleeding can become severe. Treatments are available to control bleeding.

Pain - advanced lung cancer that spreads to the lining of a lung or to another area of the body, such as a bone, can cause pain. Tell your doctor if you experience pain. Pain may initially be mild and intermittent, but can become constant. Medications, radiation therapy and other treatments may help make you more comfortable.

Fluid in the chest (pleural effusion) - lung cancer can cause fluid to accumulate in the space that surrounds the affected lung in the chest cavity (pleural space). Pleural effusion can result from cancer spreading outside the lungs or in reaction to lung cancer inside the lungs. Fluid accumulating in the chest can cause shortness of breath. Treatments are available to drain the fluid from your chest and reduce the risk that pleural effusion will occur again.

Cancer that spreads to other parts of the body (metastasis) - lung cancer often spreads to other parts of the body - most commonly the brain, bones, liver and adrenal glands. Cancer that spreads can cause pain, nausea, headaches, or other signs and symptoms depending on what organ is affected. In some cases, treatments are available for isolated metastasis, but in most cases, the goal of treatment for metastasis is only to relieve signs and symptoms.

Death - survival rates for people diagnosed with lung cancer are very low. In most cases, the disease is fatal. People diagnosed at the earliest stages have the greatest chances for a cure.
(Mayo Clinic; WebMD).

About Clinical Trials
Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials
Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer.

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.
Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body

(pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.

- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

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