

Cancer

What is cancer?

Cancer is a disorder in which there is unregulated multiplication of cells in the body. The resulting cell mass, called a tumour, may eventually develop its own blood system and begin to invade neighbouring organs. Some cancers, known as 'malignant', shed cells into the blood or lymph and these cells become trapped in small blood vessels in organs such as the liver, lung or brain, where they form secondary tumours called metastases. These can often be more serious than the primary tumour. In late disease, solid tumours release substances that depress appetite and cause weight loss and often lead to death from overwhelming infection, such as pneumonia.



Tumours can develop in any organ. Depending on where they arise, they pose very different medical and management problems. Some can be treated medically, but many are hard to cure except through surgical or radiological intervention. Advances in medical research have made many more tumours treatable, and today many people with cancer live longer than previously, with a better quality of life.

Who does cancer affect?

Cancer can affect any of us, and there can be few families that do not have a relative or friend who has some form of cancer. It affects one in two men and more than one in three women at some time in their lives, though some types of tumour are much less common than others.

There were over 12 million new cancer cases and 7.6 million cancer deaths (about 20,000 deaths a day) worldwide in 2007. This estimate stems from the Global Cancer Facts & Figures report of the American Cancer Society (ACS). In the EU, the commonest form in women is breast cancer, followed by colorectal (bowel), lung, ovarian and uterine cancer. In men, prostate cancer is the most common, followed by lung, colorectal and bladder cancer. The ACS report estimated that 5.4 million of those cancers and 2.9 million deaths occurred in economically developed countries, while 6.7 million cases and 4.7 million deaths occurred in economically developing countries.

Cancer affects many people in the EU. Therapeutic advances mean that people with many different types of cancer now live longer and have a better quality of life. And research continues; pharmaceutical companies are investigating new medicines and novel therapies, such as gene therapy to reduce the toll of cancer on patients and families.

In contrast to economically developed countries, the three most commonly diagnosed cancers in economically developing countries are cancers of the lung, stomach, and liver in men, and cancers of the breast, cervix uteri, and stomach in women. In developing countries, two of the three leading cancers in men (stomach and liver) and in women (cervix and stomach) are related to infection. In both economically developed and developing countries, the three most common cancer sites are also the three leading causes of cancer death.

Approximately 15 per cent of all cancers worldwide are infection-related, with the percentage of cancers related to infection about three times higher in developing than in developed countries. The burden of cancer is increasing in developing countries as deaths from infectious diseases and childhood mortality decline and more people live to older ages when cancer most frequently occurs. This cancer burden is also increasing as people in the developing countries adopt western lifestyles such as cigarette smoking, higher consumption of saturated fat and calorie-dense foods.

The International Agency for Research on Cancer (IARC) estimated that in 2002 there were approximately 24.6 million people worldwide who had been diagnosed with cancer in the past five years. Survival rates for many cancers are poorer in economically developing countries than in developed countries largely because of lack

of availability of early detection and treatment services. For example, overall five-year childhood cancer survival rates are around 75 percent in Europe and North America, compared to three-year survival rates of only 48 to 62 percent in Central American countries.

Present treatments:

It is not possible to detail here all the available treatments for cancer, many of whose side effects are well known. Radiotherapy, surgery and chemotherapy are all used for treatment, depending on the tumour type. There are several classes of chemotherapy agents and it is common for oncologists to use combinations of several, to maximise effectiveness. Some can make the recipients feel very unwell, causing nausea and loss of hair, and depress the immune system, leaving them vulnerable to infection.

Other side-effects include loss of fertility, as well as liver or cardiac damage. Medicines used for hormone-dependent tumours (e.g. breast and prostate cancer) are generally better tolerated than the older alkylating agents. In general, cancer treatment

requires a large number of medicines to destroy a tumour, e.g. cytotoxic and cytostatic compounds; to compensate for the harmful effects of chemotherapy, e.g. antiemetics, analgesics and folinates; to control cancer-related complications, e.g. factors to grow red and white blood cells; and also including artificial intravenous nutrition.

Radiotherapy may be helpful in reducing the size of a tumour before surgical removal, or to eliminate any cells remaining after surgery. Chemotherapy used for this purpose is termed 'adjuvant therapy'. The disadvantages of radiotherapy mainly arise from the unavoidable irradiation of surrounding healthy tissue or organs - the intestines, the bone marrow and kidneys are particularly sensitive. The shortcomings of chemo-

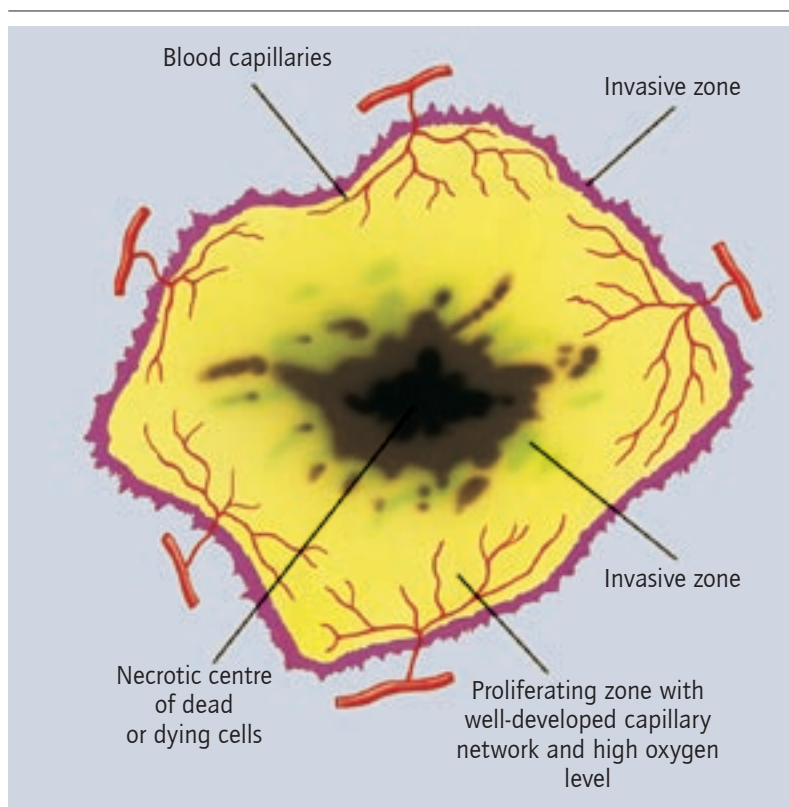


FIGURE 1: Simplified cross section of a solid tumour

therapeutics, apart from their toxicity, relate mainly to lack of efficacy. Many tumours are very responsive to chemotherapy initially, but the impact on survival still remains small in many cases and complete cures are difficult to achieve. Hence there is a big need for less toxic and more curative forms of medication for most solid tumours.

Class	Uses (non-exhaustive)
Alkylating agents	Ovarian cancer; small-cell lung cancer; brain tumours; breast cancer; testicular cancer; cervical cancer; bladder cancer; malignant glioma
Anti-metabolites	Colorectal cancer; bladder cancer; pancreatic cancer, non small-cell lung cancer; breast cancer; lung cancer; ovarian cancer; head & neck cancers
Topoisomerase inhibitors	Testicular cancer; small-cell lung cancer; colorectal cancer; ovarian cancer
Cytotoxic antibiotics	Testicular cancer; uterine cancer; rhabdomyosarcoma; breast cancer; ovarian cancer; stomach cancer; lung cancer; colorectal cancer; bladder cancer
Microtubule disruptors	Breast cancer; non small-cell lung cancer; ovarian cancer; small-cell lung cancer; head & neck cancers, leukaemias
Hormonal agents	Breast cancer; prostate cancer
Aromatase inhibitors	Breast cancer
Monoclonal antibodies	Breast cancer; colorectal cancer; head & neck cancer
Other agents, i.e. interferons	Kaposi's sarcoma; melanoma; gastro-entero-pancreatic cancers; breast cancer

Table: Examples of selected anti-cancer agents used to treat solid tumours

What's in the development pipeline?

The development of new anti-cancer medications is made especially difficult by the fact that cancerous cells differ very little from the non-cancerous cells from which they arise. Knowledge of the molecular, genetic and biological characteristics of tumour cells has improved greatly in recent decades and newer anti-cancer medicines are generally much more specific in the way they work than the older cytotoxic medicines.

Breast cancer is often treatable with surgery followed by radiotherapy or chemotherapy. For the majority whose breast tumours are dependent on steroids for growth, steroid receptor blockers can prevent recurrence and the development of metastases. For advanced breast cancer, different aromatase inhibitors are in use. Adjuvant therapy for postmenopausal women with hormone-receptor positive breast cancer should include an aromatase inhibitor, in order to lower the risk of tumour recurrence. In advanced metastatic breast cancer, microtubule disruptors may also be considered. A monoclonal antibody (mAb) has also been shown to improve survival in advanced breast cancer where the tumour is herceptin receptor (HER2) positive.

New compounds with a wide range of modes of action are in clinical development. New compounds which work in a wide range of ways are in clinical development. Three new microtubule-disrupting agents are in Phase 3 trial. They either belong to the class of taxanes or are agents of a new type that bind to microtubules in a different way.

New mAbs are also in development for treating breast cancer. One antibody binds to vascular endothelial growth factor (VEGF) and prevents it from stimulating the growth of new blood vessels into tumours. Another mAb binds to epidermal growth factor (EGF) receptors on tumour cells, inhibiting cell growth and repair, and is given together with chemotherapy.

Other clinical research projects with monoclonal antibodies include (i): a product in Phase 2 which binds to a tumour cell surface protein known as epithelial cell adhesion molecule (Ep-CAM) enabling antibodies and the complement system in blood to kill the tumour cells selectively; (ii): a compound in Phase 2 which binds to the MUC-1 cell membrane protein of tumours of epithelial cell origin, helping the body's immune system to destroy them; (iii): a molecule in Phase 3 which binds to a key protein (RANK ligand) of bone cells and has been shown to suppress the bone turnover (leading to pain and fractures) associated with metastases in women with advanced breast cancer.

Tyrosine kinase inhibitors make up another class of new medicines for treating breast cancer. One compound inhibits the tyrosine kinase associated with cell proliferation, tissue invasion and metastasis. It is being studied further for its potential in treating metastases that have spread to the brain.

Other late stage projects involve new oral therapies or development of agents already authorised for use in other cancers. In Phase 3 trial are an aromatase inhibitor for prevention rather than treatment, an agent that inhibits cell growth and a compound that blocks the growth of a new blood supply into tumours.

Colorectal cancer (CRC) is a type of cancer in which chemotherapy has had only moderate success, partly because the disease is often not detected until an advanced stage. Surgery is still the primary therapy and makes up the treatment of about 50 per cent of patients. A first-line therapy with medicines tends to be a combination of a fluoropyrimidine, a folate and a platinum compound.

The combination of 5-FU, folinic acid and oxaliplatin is often known as the FOLFOX regimen. Meanwhile, there are products available that are broken down to 5-FU at the tumour site and are taken orally, whereas 5-FU is given by injection. More recently, two mAbs have been made available for use in metastatic CRC.

New monoclonal antibodies are among the agents being developed as new therapies for CRC. One is directed against EGF receptor and is in clinical phase 2. Another mAb acts by making tumour cells self-destruct through a natural process known as programmed cell death (apoptosis). The compound is also being studied to see whether, in combination with the FOLFOX regimen, it can reduce the risk of a relapse in people with no evidence of disease after curative surgery for CRC.

Major progress has been achieved in understanding the role of the adenomatous polyposis coli (APC) gene, which is considered to play a major role in the "adenoma-carcinoma sequence"; when benign adenomas in the bowel turn into malignant carcinomas. In about 85 per cent of CRC, the APC gene is defective.

Immunological approaches are also being tried. Trials have been started with a therapeutic vaccine, using a poxvirus vector to introduce a gene into tumour cells to stimulate an immune response. Survival results were sufficiently encouraging for this vaccine to be taken into Phase 3 study in early stage CRC.

Lung cancer is the leading cause of cancer deaths worldwide - each year more than one million people die of the disease. It is a form of cancer which can be very difficult to treat, particularly 'small cell' lung cancer, in which average survival from diagnosis is approximately one year. Platinum compounds, anti-metabolites and microtubule

disruptors and topoisomerase inhibitors are often used for chemotherapy, usually in combination, and side-effects can limit therapy.

One promising class of new medicines that may help to extend survival are the kinase inhibitors. These inhibit enzymes involved in key cell functions and their effects vary according to which enzymes they inhibit. Many, but not all, of them are given orally. One compound has already shown a survival benefit in non-small lung cell cancer (NSCLC) and is indicated for use in advanced disease where chemotherapy has failed. Another multi-kinase inhibitor targets an even wider range of enzymes.

Several mAbs are being investigated in NSCLC, partly in clinical Phase 2 and 3 trials. Also in Phase 2 are a variety of cell cycle-disrupting agents. Vaccine approaches are also being tried. One preparation stimulates an immune response against the epithelial cell adhesion molecule (Ep-CAM) on some tumour cells and is in Phase 2/3.

With such a large array of new initiatives under development, it must be hoped that survival rates in NSCLC, which have hardly risen over the last 20 years, can be substantially improved.

Ovarian cancer is less common than lung cancer, but it is still a significant cause of death. If platinum-based therapy is unsuccessful, there is only a limited choice of second-line medicines and new therapies are therefore being sought. Five-year survival rates are still below 30 per cent.

A topoisomerase inhibitor is being studied in Phase 3 trial for first-line use, as is a mAb and a microtubule stabiliser. A completely new agent also at Phase 3 is a molecule originally discovered in a marine organism that inhibits cell division and DNA repair. Several topoisomerase blocking agents and mAbs are in Phase 2 trials. Therapeutic gene therapy is also under trial in ovarian cancer, but studies are still at an early stage.

Pancreatic cancer is another condition which is difficult to treat. Most tumours are carcinomas that originate in the exocrine duct cells or digestive enzyme-producing cells. The survival rate for all stages of pancreatic tumours is poor, with most studies showing a five-year survival rate of less than five per cent. About 220,000 people worldwide are diagnosed each year with pancreatic cancer, with 60,000 new cases in Europe and 30,000 in the US.

An anti-metabolite and a microtubule inhibitor have been the main chemotherapy agents used, often together with radiotherapy, but response rates are not encouraging. Meanwhile, small molecule EGF-receptor-tyrosine kinase inhibitors have been authorized as they were shown to significantly prolong survival in advanced pancreatic cancer. A high-affinity anti-CEA antibody has been awarded orphan drug designation by the European and US Medicines Agencies which is also being tested in imaging metastatic colorectal cancer.

In the search for new and more effective medicines, there is an oral farnesyl-transferase inhibitor in Phase 3 trial. Farnesylation markedly increases the stimulation of cell growth and so the hope is that this compound will reduce the rate of tumour growth and spread. Another target is an enzyme frequently found in pancreatic cancer cells through the use of a pro-drug that is only activated once it has penetrated the malignant cell.



A gene therapy approach is at the Phase 2 stage. Direct injection of this material into the tumour, followed by chemotherapy, causes the generation of an anti-cancer substance called tumour necrosis factor alpha (TNF α) in the tumour itself. Researchers are also investigating an agent which delivers a gene into the tumour where it stimulates local production of a cytotoxic substance.

Prostate cancer has a much better prognosis than pancreatic cancer. While a tumour confined within the prostate itself is usually treated by surgery (radical prostatectomy) or radiation therapy, about half of all cases have already metastasised by the time they are discovered and require additional treatment.

This usually involves therapy with hormonal agents such as gonadotrophin releasing hormone (GnRH) agonists or anti-androgens. Typically, these are indicated for advanced disease. However, recently, approval has been given for the use of once-daily oral anti-androgen in early stage disease. A microtubule disruptor compound is also available for metastatic disease that has not responded to hormonal treatment.

Medicines development has tended to concentrate on agents for treating late stage disease. A number of new small molecule agents are in Phase 2 development. These include a laminin receptor binding peptide, an endothelin-A receptor antagonist, an agent that targets the growth of the tumour's blood vessels, a multi-targeted

kinase inhibitor, a tubulin-disrupting molecule, a surviving expression inhibitor and a marine-derived cyclic peptide. These compounds are generally at too early a stage of development for their efficacy to be judged.

Some encouraging data on efficacy are available for a number of anti-tumour vaccines that have progressed further in development. One product contains two genetically modified cancer cell lines and is in clinical Phase 3. Another preparation is being studied in patients with hormone-resistant metastatic cancer. Monoclonal antibodies are also being explored in prostate cancer, especially for their effects on bone metastases.

While some prostate tumours progress only slowly, others are much more invasive. Unfortunately, tests are not yet available to determine the risk of progression. The commonly-measured prostate specific antigen (PSA) has been found to be an unreliable marker of progression of malignancy. Several genes, including the E2F3 gene, have been suggested to be better markers.

Other tumour types are less common. However, the need to improve chemotherapy is just as acute and pharmaceutical companies have not excluded them from their development programmes. For example, alkylating agent implants for malignant glioma have increased the therapeutic options available for tumours of the brain, and tyrosine kinase inhibitors are being studied in glioblastoma. Recent positive developments in kidney cancer include the introduction of a blocker of angiogenesis (blood vessel growth) and a tyrosine kinase inhibitor, while several other compounds are all in Phase 3. Furthermore, a tyrosine kinase inhibitor has been authorised for use in gastrointestinal stromal tumours.



Other approaches include small molecules that activate a key tumour suppression pathway and could eventually provide a new anticancer therapy. The compounds act as MDM2 antagonists. MDM2 is a protein that is over-expressed in some tumours and down-regulates transcription and activity of the tumour suppressing protein, p53. Such compounds are likely to be most effective against tumours with abnormally high levels of MDM2, although other patients may also benefit from p53-activating therapy.

Supportive treatment is also needed to ensure that chemotherapy works most productively. Erythropoietic growth factor has been registered for its ability to counteract the anaemia that may develop with some existing chemotherapy agents. There is also a recombinant human keratinocyte growth factor under investigation as a treatment for mucositis of the mouth and throat that is often seen with radiotherapy. Vomiting is also a problem with many chemotherapy regimens, and new anti-emetics have been authorized recently. Studies are going on with new analgesic compounds to relieve cancer patients from pain.

The longer-term future:

A great deal of effort is being put into researching anti-cancer medicines and there has been encouraging progress over the past decade. Nevertheless, achieving long-term disease-free survival in many solid tumours remains an ambitious goal rather than an accomplished fact.

Over time, however, as increasingly selective agents are developed, backed up by growing insight into the biology of cancer, disease management is being improved and patients' quality of life and life expectancy are continually being improved.

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