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In the United States, lung cancer is the most frequent site of cancer in men (22%) and tied for the third most common site (uterus) in women based on the 1986 estimated cancer incidence[1]. It is the most frequent cause of cancer death in men (35%) and 1986 estimates suggest it is the most frequent cause of cancer death in women (19%), slightly greater than breast cancer (18%).

Although the cause of lung cancer is almost certainly multifactorial, the most important factor is clearly tobacco use. There is a very high frequency of this malignant tumour in smokers; in addition, there appears to be a passive effect with an increased incidence in the occupants of households exposed to smokers. Asbestos and other occupational materials may also play a part in this disease.

Histological Classification

Although elaborate, pathologic classifications of lung cancer exist[2] such as that developed by the World Health Organization, a simple classification is much more practical (Table I). Squamous cell carcinoma is probably still the most common type but there is evidence that the incidence of adenocarcinoma is increasing significantly worldwide. There is no clear explanation for this observation. Small cell lung cancer has remained relatively constant at 20-25% of cases.

TABLE I – Major histologic types of lung carcinoma

CELL TYPE*	%
Small cell (oat cell)	20
Large cell (anaplastic)	15
Squamous cell (epidermoid)	40
Adenocarcinoma	25
Others (e.g., bronchoalveolar)	1-3

* 2% to 4% are mixed adenosquamous.

For therapeutic considerations, one can divide histological types into small cell and non-small cell with the subtypes of the latter being less important. This classification is very useful therapeutically and will be discussed later.

Screening

The screening of populations at high risk for lung cancer has been attempted in order to detect the disease earlier and hopefully to cure more patients. This would appear to be rational in that there is good evidence that the cure rate for earlier stages of disease is higher than for more advanced stages, particularly within surgically resectable patients. A number of large scale screening studies sponsored by the N.C.I. (U.S.) have had very long follow-up including studies from the Mayo Clinic, the Memorial Sloan-Kettering and John Hopkins University. These subjects were middle-aged smokers who had serial chest roentgenograms and examinations of sputum carried out. When the cytological findings were positive or suggestive, bronchoscopy and other investigations were carried out as indicated. The data has recently been updated[3-5]. Although a larger number of tumours were found in the screened groups compared to the non-screened groups, this has not translated into longer survival. Therefore at present, it would appear that routine screening of even high-risk subjects (smokers, asbestos and uranium workers) is not indicated.

Diagnosis

The investigation of a patient with possible lung cancer usually begins when there are symptoms or an abnormality is detected on a routine chest roentgenogram. Details of the symptomatology of this disease such as cough, hemoptysis and shortness of breath etc., are well known.

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The standard methods of investigation and staging include history, physical examination, chest roentgenography, chest tomography, cytologic examination of sputum, bronchoscopy, and in many centres mediastinoscopy. When indicated, scalene or supraclavicular node biopsies may be carried out. Metastatic lesions should be biopsied if they are easily accessible for diagnostic purposes. Pulmonary arteriography may be used before operation in some cases. More commonly, computerized chest tomography has been used.

Local staging is particularly important in non-small cell lesions which are potentially resectable and give the patient the greatest chance of long-term survival. The major controversies that exist in the staging of this disease relate to some of the new, non-invasive techniques such as gallium scanning, computerized tomography and magnetic resonance (MR) of the thorax[6-8]. Gallium scans give a significant false-negative rate[6], but when positive they appear to be specific. Therefore, a positive gallium scan may obviate the need for mediastinoscopy while a negative one certainly cannot be relied upon to evaluate the mediastinum. Computerized tomography will reveal many but not all the lesions and may show enlarged nodes in the mediastinum that may not be due to tumour. On the other hand, it may miss normal sized or small nodes that are involved by tumour[7]. In recent studies it does not appear to replace mediastinoscopy and our own experience comparing it to mediastinoscopy and magnetic resonance[9] suggests that mediastinoscopy is still probably more accurate than either of the other two staging procedures and that an MR does not appear at present to offer significant advantages over CT of the thorax. More studies with mediastinoscopy compared to other non-invasive techniques are necessary to define the place of these new techniques in the diagnosis and staging of lung cancer.

Percutaneous fine-needle aspiration biopsy, particularly of peripheral lesions has become a common diagnostic aid[10, 11]. The aspiration biopsy will accurately differentiate between malignant and non-malignant lesions but is not always accurate for a specific histologic type, particularly when small cell carcinomas of the lung is found. In some cases, definitive staging procedures such as mediastinoscopy or open biopsy may result in the diagnosis of non-small malignant tumours which can be resected, possibly for cure. If one were to rely only on the original needle biopsy in such cases, surgery might not take place and this obviously would affect long-term survival. Very few complications are seen with this approach, but pneumothorax complicates about 10% of cases as does hemoptysis. Implantation metastases and air embolism are extremely rare. The contraindications to this procedure include unconscious or uncooperative patients, hemorrhagic diathesis, severe respiratory distress or high fever and uncontrollable cough.

Another new technique recently introduced is transbronchial needle aspiration of peritracheal lymph nodes and this has been moderately successful, at least in one series[12]. Of course, a biopsy of a more distant lesion as previously mentioned may turn out to be the method of choice. Examples include nodes in the neck, skin metastases, liver metastases and occasionally, bone lesions. If easily available, these sites should be considered for primary diagnostic procedures.

Exploratory thoracotomy is the ultimate method when other diagnostic procedures have failed. This may be associated with mortality and morbidity and should therefore be reserved for use primarily by very experienced thoracic surgeons.

Staging

Efficient and appropriate staging of the patient should take place once a tissue diagnosis of lung cancer is obtained. The purpose of staging is to aid in the selection of treatment, estimate the probability of cure and survival and facilitate proper communication to the patient and his family. Also, this information can be used to compare outcomes of different clinical series.

Anatomic Staging:

The most common, surgical staging of non-small cell lung cancer cases uses the TNM classification of either the American Joint Commission for Cancer Staging and End-Results reporting or the Union Internationale Contre le Cancer. The disease can then be divided into stage I, II or III lesions. Stage I, according to the American Joint Commission consists of $T_1 N_0$, $T_1 N_1$ and $T_2 N_0$. T_1 lesions are less than 3cm and T_2 are greater than 3cm in greatest dimension. N_1 lesions involve hilar or intralobar nodes. Stage II disease includes only $T_2 N_1$ lesions. The stage III category is more advanced than stage II and in-

cludes patients with disease confined to the chest (stage III M_0) and as well may include patients with extrathoracic metastatic disease (stage III M_1). Some of the stage III patients are surgically resectable but the majoriy may require radiotherapy and/or chemotherapy. The patients with stage I disease have approximately a 70% 5-year survival with the subset with $T_1 N_0$ doing particularly well with up to an 80% 5-year survival (Lung Cancer Study Group data). The stage II 5-year survival may be as low as 30% while patients with stage III resectable disease may have less than a 20% 5-year survival. Dr. Clifton Mountain at the M.D. Anderson Hospital in Houston, Texas recently suggested a new staging system that is a modification of that previously mentioned by the American Joint Commission but has international agreement and will probably be adopted worldwide within the next few years[13]. These changes in staging are not of a major nature but rather define special subsets of patients, but may prove to be very important. Since surgery is the most useful curative modality for the treatment of lung cancer, every effort should be made to avoid missing the opportunity of a curative resection.

In addition to the previously mentioned staging system other studies such as hematology, blood chemistry, and radionuclide scans of brain, liver or bone should be done where indicated to identify possible metastatic disease. In the case of non-small cell lung cancer this should only be done if evidence of advanced disease is present either based on physical examination, significant history or laboratory tests (ex. abnormal liver function tests). CT scans of the abdomen or brain may be indicated in patients in whom nuclear medicine scans are equivocal. An ultrasound of the liver may also be a useful procedure if it is decided it is necessary to investigate this site for possible metastases.

In patients with small cell carcinoma of the lung, it is routine worldwide to do the radionuclide scans of liver, brain (or CT scans) and bone since these may frequently be positive in contradistinction to patients with non-small cell lung cancer. CT scanning, especially of brain and possibly of the abdomen, etc. as previously mentioned, may also be appropriate. Most groups around the world suggest bone marrow aspiration and biopsy but our own data would suggest this is probably of little importance[14]. Some groups also suggest percutaneous liver biopsy, often using peritonoscopy but this is not routinely done in most centres.

Treatment of Non-small Cell Lung Cancer:

Surgery:

For patients with non-small cell tumours that are potentially resectable, operation is still the best approach to maximize the possibility of long-term survival. There have been no recent major technical advances in pulmonary surgery other than the use of the stapler. As previously mentioned, survival is related to TNM staging. The Lung Cancer Study Group in North America is doing a study comparing segmental resection versus lobectomy[15] in an attempt to spare lung tissue in patients with small tumours. The early results of this study are optimistic, that is, there appears to be no detriment to doing lesser surgery but the final results will not be available for a number of years. Prior to major surgery it is essential that patients' physiologic and clinical performance status is evaluated so that one can be certain that the patient will be able to tolerate a thoracotomy and possible pulmonary resection. In Canada it is often suggested that most patients with N_2 disease proven by mediastinoscopy are ineligible for surgery but there are differences of opinion with Martini and his colleagues in New York being particularly enthusiastic about at least exploratory surgery in such cases[16]. The final answer is not yet available. The modern 30 day postoperative mortality rate is approximately 9% based on a review of Lung Cancer Study Group data[17]. More than 80% of patients recover after an uneventful postoperative course however, significant morbidity can occur and therefore both morbidity and mortality must be considered when a decision for surgery is made. Approximately 45% of all lung cancer patients will undergo thoracotomy and a third will have a definitive resection. The end results of the individual surgeon will be determined mainly by the preoperative assessment of physiologic operability and the proportion of patients falling into each histologic type and anatomic stage. The individual expected overall results by stage were previously described. It should be noted that in patients with resectable tumours, epidermoid carcinomas do somewhat better than adeno or large cell carcinomas, even in stage I[18].

Radiotherapy as Primary Treatment

Radiotherapy can be used when there are serious contraindications to thoracotomy or the patient refuses to undergo operation. There may

be up to a 20% 5-year survival after radical radiotherapy for otherwise operable lung cancer patients but this will vary. This has not been reported in all series. A 5-6% 5-year survival has been found in most patients treated with inoperable or unresectable lung cancer[19]. Increasing doses of radiation have been used by a number of groups in the U.S. Groups such as the Radiotherapy Oncology Group (RTOG) suggest that continuous radiation in excess of 6,000 cGy may be the most appropriate treatment when radiation is used as the primary form of aggressive therapy[20, 21]. Treatment planning must be improved with the use of CT scanning. Radiation doses to the spinal cord should be kept below 4,000 cGy to prevent serious complications. Despite these precautions long-term complications including radiation fibrosis, radiation induced cardiac disease, esophagitis and spinal cord injuries are still noted in most series. To date, there has been little evidence for the use of preoperative radiation therapy, except perhaps in patients who have Pancoast tumours where this procedure followed by surgery may be useful[22].

Postoperative irradiation has been looked at quite carefully by the Lung Cancer Study Group in squamous cell carcinoma of the lung. Patients with stage II and III squamous cell carcinoma of the lung were randomized to receive no additional treatment or 5,000 cGy in five weeks postopeatively. The only benefit to date has been a small improvement in recurrence rates in the thorax, but overall relapse rates are approximately the same and there is no apparent effect on survival[23]. Therefore this cannot be recommended routinely at present. A group from the Memorial Hospital in New York advocate the use of interstitial irradiation applied at thoracotomy using I—127 seeds or I—R—192 implanted directly into the surgical bed[24, 25]. This data needs confirmation from other centres. Radiotherapy is of course useful for palliation in all types of lung cancer. It is often used for cerebral metastases, bony metastases, spinal cord compression, etc. and often relieves much of the discomfort of these often very ill patients.

Laser Treatment for Lung Cancer

A hematoporphyrin derivative which is specifically concentrated by cancer cells is administered through a bronchoscope and after irradiation with light of appropriate wave length it produces a characteristic fluorescence that can allow the surgeon or chest physician to accurately localize the tumour. This can allow for very small tumours to be detected before they become bronchoscopically visible. Cortese, from the Mayo Clinic, has recently reviewed the use of phototherapy (lasers) for both diagnosis and treatment[26]. This is usually reserved for cancers that are within the reach of the flexible fiberoptic bronchoscope, are < 2-3cm in diameter and give no evidence of eroding through the bronchotracheal wall.

There are three main types of medical laser systems for direct ablation of tissue. These include: the Carbon Dioxide Laser which delivers radiation in the far infrared region with a wave length of 10,600nm., the Argon Laser which delivers blue-green light with a wave length of 514nm., and the Neodymium-YAG Laser which delivers radiation in the near infrared with a wave length of 1,064nm. Carbon Dioxide Lasers, because of the use of long wave length radiation, cannot be conducted by a quartz monofilament and therefore is limited to rigid endoscopic systems. The Argon laser can be conducted by a flexible quartz monofilament and therefore can be used with a fibre bronchoscope. Poor tissue penetration limits its value. The YAG laser can be conducted by a quartz monofilament and is therefore also useful with a flexible fibre bronchoscope. It can penetrate somewhat further. The laser can be used to open obstructed airways by producing thermal necrosis of tissue, which allows debulking of the tumour while photocoagulation helps control some of the superficial bleeding during treatment. The major complications include: hemorrhage from tumour necrosis or perforation of a large blood vessel. Cortese recommends that laser therapy be used in airway obstruction that has been unresponsive to other reasonable therapy and when the lesion is protruding into the bronchial wall without obvious extension beyonde the cartilage[26]. The bronchoscopist should be able to see the bronchial lumen and there should be functioning lung tissue beyond the obstruction. We must await further data on the value of this new modality of therapy.

Chemotherapy

There is little evidence that chemotherapy is of benefit in the treatment of non-small cell lung cancer, although 25 to 40% of patients responde to current chemotherapy combinations[27]. The most frequent combinations used at present include those containing cisplatin (etoposide plus cisplatin, cyclophosphamide,

Adriamycin (doxorubicin) plus cisplatin (CAP) and vindesine plus cisplatin) and the MACC regimen (methotrexate, Adriamycin, CCNU and cyclophosphamide). One randomized trial by Cormier et al suggests that this leads to improved survival compared to placebo. Woods et al in an Australian study show no significant benefit in their early results[28]. The National Cancer Institute of Canada has recently completed a trial comparing vindesine plus cisplatinum to cyclophosphamide, Adriamycin plus cisplatin versus best supportive care in unresectable patients. The results of this study will soon be available and should better define the place of such treatment.

Because of the response rates noted in advanced disease, combination chemotherapy has also been used in the adjuvant setting. In one study carried out by the Lung Cancer Study Group in patients with stage II and III adenocarcinoma of the lung, fully resected patients were randomized to either receive CAP or to receive intrapleural BCG plus levamisole. The chemotherapy arm proved to be superior[23]. A second trial in patients with incomplete resection (all non-small cell histologies) were randomized to receive postoperative radiation or postoperative radiation plus CAP. The latter has proved to be significantly better with an improvement in survival of approximately six months over the radiation arm[23]. It is not clear whether the additional six months of life is warranted in view of the fact that most of this time was associated with the chemotherapy and its potential significant detrimental effects on "quality of life". Further confirmation of this data is necessary before it becomes standard treatment.

In the last few years a new approach to the use of chemotherapy has evolved. A number of groups including the Lung Cancer Study Group have used various regimens to attempt to convert unresectable, localized, non-small cell lung tumours to a resectable state with the combination of chemotherapy and radiation. This has met with limited success but fortunately, most of the regimens with or without radiotherapy do not increase the surgical resection rate significantly and the complications at surgery may be quite serious. This warrants further exploration perhaps with new drugs resulting in more active combinations making this approach more successful in future years.

Radiotherapy + Chemotherapy

As previously mentioned, radiotherapy + chemotherapy may be useful to attempt to make unresectable tumours resectable. In addition the combination has been used in patients with localized unresectable disease in an attempt to attain long-term survival without surgery. Eagan et al, at the Mayo Clinic, suggests a combination of radiotherapy and chemotherapy with cisplatincontaining regimens may be better that their previous historical data using radiotherapy alone[29]. As previously mentioned CAP + radiotherapy appeared to be superior to radiotherapy in the randomized trial carried out by the lung cancer study group in patients with attempted complete resections[23]. All this data suggests that combined modality therapy may be better than either modality used alone but further studies are needed to confirm this conclusion.

Treatment of Small Cell Carcinoma of the Lung

This disease has historically been divided into limited (confined to the hemithorax and ipsilateral supraclavicular nodes) and extensive disease (beyond the definition of limited disease). Untreated patients in studies done in the late 60s had a median survival of approximately 6 weeks for patients with extensive disease and up to 12 weeks in patients with limited disease[30, 31]. The results of present day studies should take this into account.

As previously mentioned, small cell carcinoma of the lung accounts for approximately 20 to 25% of all lung cancer. In the late 1960s the Medical Research Council in the United Kingdom showed that radiotherapy was preferrable to surgery and thus it became the standard form of therapy for this disease[32]. A number of studies showed the benefit of single agent chemotherapy, particularly cyclophosphamide in addition to radiotherapy[33, 34]. It thus gained a place in the treatment of this obviously systemic tumour. Following this, a number of active agents were combined to form combination chemotherapy some of which have given even better results than with single drugs[35]. The most frequently used agents included cyclophosphamide, Adriamycin (doxorubicin), vincristine, etoposide (VP-16), cisplatin, procarbazine, lomustine (CCNU) and methotrexate. This has resulted in improved results over single drug therapy. Frequently used combinations include cyclophosphamide, Adriamycin and vincristine (CAV), cyclophosphamide, CCNU and methotrexate (CCM), CAV with VP-16 (ECHO), as well as VP-16 and cisplatin, to name but a few. Many of these have been combined with irradiation

to the chest in limited disease patients, and in some cases with prophylactic cranial irradiation.

Although it is very clear at present that combination chemotherapy appears to be the mainstay of treatment in this disease, there also appears now to be a place for thoracic irradiation, at least in limited disease. A number of controlled trials suggest a benefit in survival[36], while one in extensive disease shows no benefit[37]. Prophylactic cranial irradiation has reduced relapses in the central nervous system in a number of controlled trials but to date has not affected survival. Most frequently today it is recommended only for patients in complete remission.

Present day approaches result in approximately an 80 to 85% response rate in patients with limited disease (40 to 60% achieve complete responses) and approximately 70% in patients with extensive disease (10 to 35% of patients achieve a complete response). The median survival of patients with limited disease is approximately one year, while that of patients with extensive disease is approximately 9 moths[38]. The 2-year disease-free survival rate is approximately 20% for patients with limited disease and 4 to 5% for those with extensive disease. Unfortunately, the 5 year survival rates have not been quite so encouraging with limited disease patients falling down to the 7 to 10% range and extensive disease being well under 5%.

A number of significant questions are still unanswered including the intensity of chemotherapy, the use of alternating non-cross resistant chemotherapy combinations and the value of maintenance chemotherapy. These are discussed in more detail in recent reviews[38-41].

Although Cohen and his group have shown in a randomized trial that more intensive therapy is superior to standard therapy[42] a large number of trials using very aggressive approaches have failed to improve the overall survival in this group of patients[40]. Studies including single dose therapy with high dose cyclophosphamide, VP-16 or other aggressive approaches along with autologous bone marrow transplants have achieved similar outcomes to that observed with less intensive, that is moderate dose chemotherapy. Of course the toxicity of the more aggressive therapy was significant and often required patients to stay in hospital a large proportion of their relatively short survival. Additional active agents used in very high doses might help to settle this specific question. One of the major problems when bone marrow transplantation is used is that the patient may have tumour cells reinfused from his stored marrow. Newer methods of separation using monoclonal antibodies directed at small cells may obviate this problem in the future[43].

There has been a great interest in recent years in the use of alternating non-cross resistant chemotherapy combinations based on the Goldie-Coldman hypothesis[44]. This has apparently been successful in Hodgkin's disease using alternating combinations consisting of MOPP (nitrogen mustard, vincristine, procarbazine and prednisone) and ABVD (Adriamycin, bleomycin, vinblastine and DTIC) by Bonadonna's group from Milan[45]. A large number of studies have been carried out by groups around the world and there are studies with both positive and negative results. Much of this data has recently been reviewed by Elliott et al from the Finsen Institute in Copenhagen[46]. He points out that there are many problems in design. In addition, many of these studies have not used two combinations that are both truly active as induction therapy and that are both non-cross resistant in the clinical setting. Recently, a number of trials have shown that etoposide and cisplatin is an active combination in patients who have failed treatment with cyclophosphamide, Adriamycin and vincristine. This combination as well as CAV are also both useful as induction therapy[40]. These therefore may meet the requirements to truly test the Goldie-Coldman hypothesis. A recent trial carried out by the National Cancer Institute of Canada in patients with extensive disease compares six courses of CAV versus three each of CAV and VP-16 plus cisplatinum given as alternating regimens. Patients who failed CAV or relapsed on CAV could be given sequential VP-16 and cisplatin. The results of this study to date suggest a survival advantage to the alternating regimen of approximately two months[47]. Whether this is due to VP-16 and cisplatin in fact being more active then the CAV regimen or whether the method of administration of the drugs is the more important factor is yet to be determined. However, this study leads to some optimism that small improvements may have been observed using this approach.

In the recent past it was commonly suggested that 12 to 24 months of maintenance combination chemotherapy was necessary for patients with small cell lung cancer. In recent years, there has been a slow but definite move to shorter treatments of 4 to 6 months. The Toronto Group has published a study involving 360 pa-

tients treated with six courses of CAV, thoracic and prophylactic cranial irradiation with no maintenance therapy[48]. We found the response and survival data to be virtually identical to those seen in a previous study in our group involving 161 patients who were treated with induction therapy with the same regimen and oral maintenance therapy with CCNU, procarbazine and methotrexate for one year. Our survival data are also similar to those of other studies in the literature using various approaches. Moreover, other studies using short-term therapy have reported equally good results. Woods et al from Australia have compared maintenance therapy versus no maintenance therapy and have not found any benefit in survival using a randomized clinical trial design[49]

Although surgery was thought not to be of value based on the MRC trial in the 1960s as previously mentioned, in recent years there has been a renewed interest in this approach. In fact, our group and others have suggested that small peripheral nodules (< 3cm in diameter without hilar mediastinal node involvement) probably do best with surgery[50]. Additional radiotherapy and chemotherapy may also be indicated. Because of apparent early data suggesting improved results with surgery in somewhat more advanced patients, it has become more fashionable to induce a significant remission with chemotherapy and follow this with surgery. As a result of this a large-scale study involving the Lung Cancer Study Group, the Eastern Cooperative Oncology Group and the EORTC is ongoing. This involves giving patients with disease confined to the hemithorax who are medically fit for resection 5 courses of CAV. If they then have sufficient response to make them surgically resectable they are eligible to be randomized after appropriate informed consent to receive surgery or not with both groups receving additional thoracic and prophylactic cranial irradiation. This international study will hopefully put this question to rest.

Of paramount importance is the discovery of new active drugs that may improve the results of treatment in both small cell and non-small cell lung cancer. Since small cell lung cancer is responsive to a large number of agents, all potentially active agents should be tested in phase II studies in previously treated patients. There may be some evidence that using untreated patients with extensive disease, since they are unlikely to be cured, may give a better indication of activity. Recent trials have shown significant activity with carboplatin, epirubicin and VM-26. Further confirmation of this activity is necessary to find out if this adds to already available therapy.

Althought one randomized trial has shown that the immunological stimulant thymosin may have some value in patients with small cell lung cancer[51], this has not been confirmed[40]. The use of BCG and methanal extractable residue of BCG, or Corynebacterium parvum have not resulted in improved results in this disease and are not recommended at present.

A major new area of interest in the near future will be further information on the biology of all forms of lung cancer, particularly small cell lung cancer. The leader in this field is Dr. John Minna at the Bethesda Naval Hospital in the U.S. Some recent publications from this group have suggested that with the growth of small cell carcinoma and non-small cell carcinomas of the lung, that these can be distinguished by some of their markers and growth factors[52]. In addition, it would appear that a "variant" form of small cell carcinoma of the lung has been found by this group which has specific in vitro characteristics which can be identified and correlates well with the very poor prognosis group of patients with this disease seen by all investigators in this field. An important growth factor for small cell lung cancer is the peptide hormone bombesin (or the mamalean equivalent of gastrin-releasing peptide). This has lead to the concept of trying to interrupt this growth factor using a monoclonal antibody directed against bombesin in a study to be carried out by Dr. Minna's group in Bethesda in patients with small cell lung cancer in complete remission. Only time will tell whether this and other important discoveries from basic biological data will prove to be important in the treatment of all types of lung cancer.

Although at present only about 10% of all patients with lung cancer will survive five years, with improvements in our understanding of this disease for example by the study of biology and the availability of new active drugs and perhaps other new therapies hopefully, better results will be seen.

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