Recent Advances in the Diagnosis and Treatment of Lung Cancer

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Epidemiology

Lung cancer, the most common cancer in the world today is responsible for more cancer deaths than any other solid tumours. World-wide, it accounts for approximately 1 million deaths per year, of which about 30% occur in developing countries[1]. Lung cancer is a rapidly growing problem in many Asian countries[2]. Smoking is responsible for 78% to 87% of lung cancers[3,4]. While there is a decline in smoking rates in developed countries[5], the continuously high smoking rate in developing countries will contribute to an increase in the incidence of lung cancer. In 1980, lung cancer accounted for 10 - 15% of all cancers in men in most Asian countries[1]. The incidence of lung cancer continues to increase, especially in women. In many countries, including the United States, more women die from lung cancer than from breast cancer.

In the last two decades, there have been shifts in the distribution of histological cell types that accompanied changes in lung cancer incidence. In recent years, Kreyberg Type II lung cancers (adenocarcinoma, alveolar cell or undifferentiated carcinomas) and in particular adenocarcinoma of the lung are becoming more prevalent than Kreyberg Type I lung cancers (squamous cell, small cell or large cell carcinomas) in the West[6-10].

Similar trends showing a relative increase of adenocarcinoma compared to squamous cell carcinoma have also been noted in Asian countries[11-14]. This change in the distribution of lung cancer histological cell types may be due to the changing composition of the cigarette from high to low tar and nicotine.

The most widely accepted lung tumour classification schema is that of the World Health Organisation (WHO). The classification has been periodically updated. The most recent update was published in 1999[15] while the one prior to that was compiled in 1981[16]. In the 1999 compilation, the broadest categories are retained from the previous schema. During the past decade, a considerable body of information on immunohistochemical staining properties of lung cancer has been used to refine classical microscopic classification. While in most cases, histological features alone are sufficient to guide therapy, in a minority of cases tumours are insufficiently differentiated or biopsies too small to be classified by conventional histological methods and immunohistochemical staining may permit more accurate histological classification[17].

The great pessimism regarding the management of patients with lung cancer has stemmed from the fact that there were few good options for the early detection, prevention or treatment of lung cancer in the past. In recent years, however, there have been many advances in the early detection, staging and treatment of this disease that are bringing about a change in the nihilistic attitude of doctors towards lung cancer patients.

This article was accepted: 15 January 2001

Non-small cell lung cancer

Non-small cell lung cancer (NSCLC) accounts for 80 to 85% of all lung cancer cases. The most common cell types are adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Surgical resection is the best chance for cure in patients with localised NSCLC, i.e., clinical stage I and II disease. Unfortunately, 70% or more of all NSCLC patients present with locally advanced (stage III) or disseminated (stage IV) disease[18]. Some may have co-existing medical conditions that make them unsuitable candidates for surgery.

Revision in the International System for staging non-small cell lung cancer

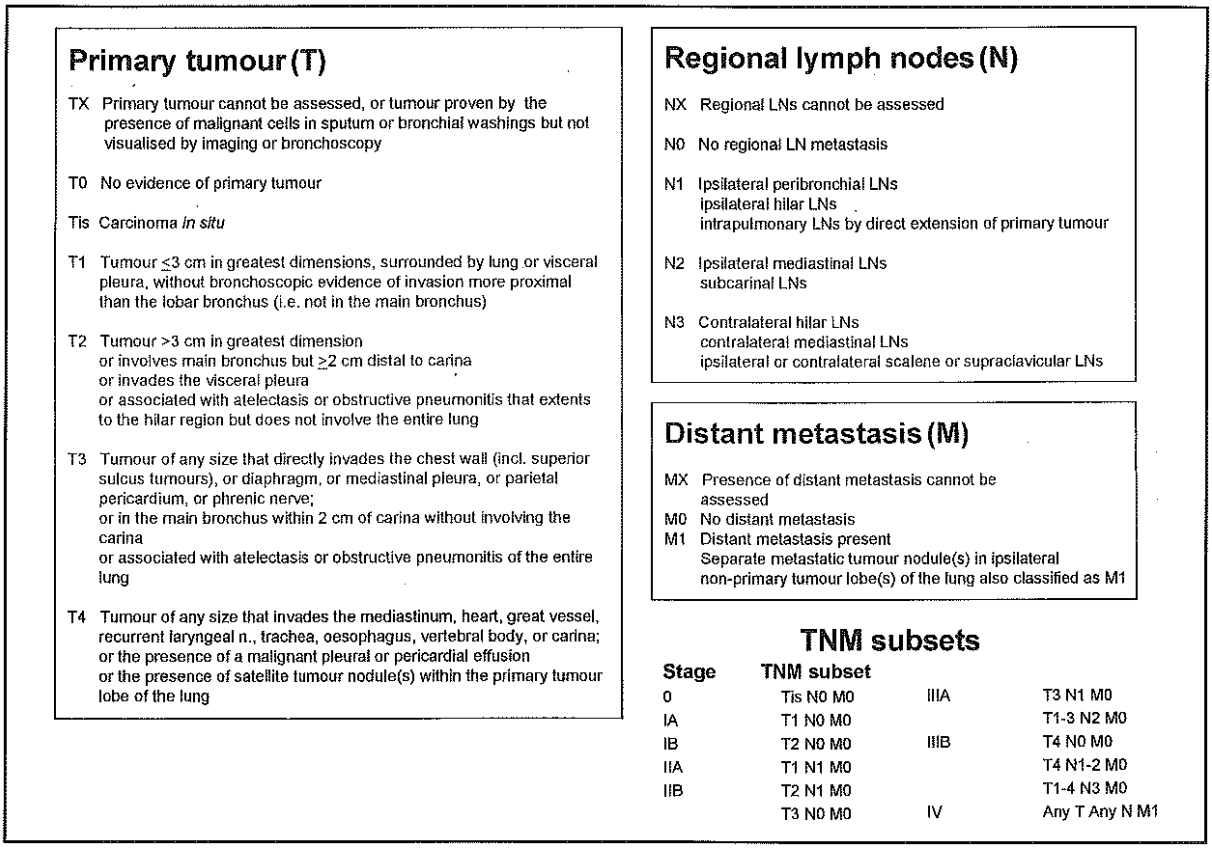
Based on the analysis of a collected database of 5,319 patients treated for primary lung cancer, the Union Internationale Contre le Cancer and American Joint Committee on Cancer have revised the TNM staging of lung cancer to more accurately reflect the appropriate treatment options and prognosis of the various subsets (Figure I and Table I)[19]. Changes from the previous system include the division of stage I into two categories (IA and IB) based on tumour size, and the division of stage II into two

Table I
Cumulative Survival of Non-small Cell Lung Cancer Patients According to Stage of Disease[19]

		Months after Treatment (Cumulative % surviving)				
Stage	**TNM subset**	**12 (%)**	**24 (%)**	**36 (%)**	**48 (%)**	**60 (%)**
Clinical stage*						
IA	T1 N0 M0	91	79	71	67	61
IB	T2 N0 M0	72	54	46	41	38
IIA	T1 N1 M0	79	49	38	34	34
IIB	T2 N1 M0	61	42	34	26	24
	T3 N0 M0	55	37	31	27	22
IIIA	T3 N1 M0	56	17	12	9	9
	T1-3 N2 M0	50	26	19	15	13
IIIB	T4 N0-2 M1	37	15	10	8	7
	T1-4 N3 M0	32	11	6	4	3
IV	Any T any N M1	20	5	2	2	1
Surgical-pathological stage**						
IA	T1 N0 M0	94	86	80	73	67
IB	T2 N0 M0	87	76	67	62	57
IIA	T1 N1 M0	89	70	64	61	55
IIB	T2 N1 M0	78	56	47	42	39
	T3 N0 M0	76	55	47	40	38
IIIA	T3 N1 M0	65	38	30	30	25
	T1-3 N2 M0	64	40	32	26	23

* *Clinical stage as determined by pre-treatment clinical and imaging evaluation (based on data of 5,230 patients)*

** *Surgical-pathological stage which depends on intra-operative assessment by the surgeon and post-operative assessment by the pathologist (based on data of 1,910 patients)*



Primary tumour (T)

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 ≤3 cm in greatest dimensions, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)

T2 Tumour >3 cm in greatest dimension
or involves main bronchus but ≥2 cm distal to carina
or invades the visceral pleura
or associated with atelectasis or obstructive pneumonitis that extents to the hilar region but does not involve the entire lung

T3 Tumour of any size that directly invades the chest wall (incl. superior sulcus tumours), or diaphragm, or mediastinal pleura, or parietal pericardium, or phrenic nerve;
or in the main bronchus within 2 cm of carina without involving the carina
or associated with atelectasis or obstructive pneumonitis of the entire lung

T4 Tumour of any size that invades the mediastinum, heart, great vessel, recurrent laryngeal n., trachea, oesophagus, vertebral body, or carina;
or the presence of a malignant pleural or pericardial effusion
or the presence of satellite tumour nodule(s) within the primary tumour lobe of the lung

Regional lymph nodes (N)

NX Regional LNs cannot be assessed

N0 No regional LN metastasis

N1 Ipsilateral peribronchial LNs
ipsilateral hilar LNs
intrapulmonary LNs by direct extension of primary tumour

N2 Ipsilateral mediastinal LNs
subcarinal LNs

N3 Contralateral hilar LNs
contralateral mediastinal LNs
ipsilateral or contralateral scalene or supraclavicular LNs

Distant metastasis (M)

MX Presence of distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis present
Separate metastatic tumour nodule(s) in ipsilateral non-primary tumour lobe(s) of the lung also classified as M1

TNM subsets

Stage	TNM subset		
0	Tis N0 M0	IIIA	T3 N1 M0
IA	T1 N0 M0		T1-3 N2 M0
IB	T2 N0 M0	IIIB	T4 N0 M0
IIA	T1 N1 M0		T4 N1-2 M0
IIB	T2 N1 M0		T1-4 N3 M0
	T3 N0 M0	IV	Any T Any N M1

Fig.1: International Staging System for Lung Cancer[19].

categories (IIA and IIB) based on tumour size and nodal status. The category T3N0 has been moved from stage IIIA to IIB. Tumours classified as T3 are neoplasms that have grown beyond the lung parenchyma to involve structures still amenable to resection, while T4 defines those tumours with extensive extrapulmonary extension, usually precluding curative or complete resection. Satellite tumour nodules in the same lobe as the primary tumour are now also classified as T4 while separate metastatic tumour nodules in the ipsilateral, non-primary tumour lobe are now classified as M1.

The importance of accurate lung cancer staging

Once lung cancer is diagnosed, accurate staging is essential for therapeutic decision making and estimation of prognosis. It is important to accurately differentiate stage I to IIIA (potentially resectable) from stage IIIB to IV (non-resectable) cancer. Following surgical resection, both local and distant relapse rates increase with increasing T and N stages and distant failure is more common than local failure. Adenocarcinomas and large cell undifferentiated carcinomas are more likely to spread distantly than squamous cell carcinomas.

The accurate evaluation of nodal status requires invasive staging with mediastinoscopy or a variant of this procedure. The disappointing false-positive and false-negative rates associated with computed tomography (CT); about 50% and 20%, respectively[20] have resulted in the search for a more accurate non-invasive procedure. Nodal staging studies using positron emission tomographic (PET) scanning with 2-fluoro-2-deoxy-D-glucose (FDG) have shown correct diagnosis and staging in 94% and 96% of cases, respectively, compared to 61% and 79% of cases evaluated by CT. A negative mediastinum on PET FDG scan reduces the need for mediastinoscopy[21-23]. However, PET scanning facility is not widely available.

After stage, the next important prognostic features are performance status, weight loss, and gender (female patients fare better than male), in that order[24]. Age does not appear to be a major independent risk factor.

The role of chemotherapy in the treatment of non-small cell lung cancer

The general pessimism regarding lung cancer chemotherapy and prognosis is probably related to results of studies in the early 1980s that alkylating agents in lung cancer chemotherapy actually reduced survival[25,26]. However, clinical trials investigating the treatment of non-small cell lung cancer (NSCLC) have shown significant improvement in survival with the use of new chemotherapeutic agents and multi-modality treatment[26]. A survey of British physicians identified that physician beliefs did not resonate with current medical knowledge and portrayed a negative impression of NSCLC prognosis[27]. A nihilistic attitude toward the prognosis of patients with NSCLC may result in both the underuse of potentially beneficial therapies and delay in the widespread adoption of newer therapies. A 1998 article appealed to the medical community to change its nihilistic attitude toward the prognosis of patients with NSCLC in light of the findings of new chemotherapeutic studies[26].

The role of chemotherapy in the management of NSCLC is well-established[18,28]. A meta-analysis revealed that cisplatin-based chemotherapy provided a modest survival benefit in virtually all stages of NSCLC, including stage IV disease[28]. Compared to the best supportive care alone, cisplatin-containing chemotherapeutic regimens extend the median survival time by 2 to 4 months and increase the 1-year survival rate by 10 to 15%. With modern chemotherapy, median survival averages 9 to 10 months in advanced NSCLC[29], a figure comparable to that achieved with treatment of extensive-stage small-cell lung cancer, a malignancy which is viewed as chemotherapy-sensitive. Despite widespread perceptions to the contrary, combination chemotherapy improves the quality of life in patients with NSCLC. Even when there is no overt tumour regression, tumour-related symptoms such as cough, dyspnoea, chest pain and haemoptysis frequently improve following combination chemotherapy[29]. In stage IV NSCLC, chemotherapy prolongs survival and provides relief of symptoms in a significant percentage of patients[30]. The American Society of Clinical Oncology recommends chemotherapy for NSCLC patients with stage III and IV disease who have good performance status[18].

Patients with poorer performance status have higher risk of developing life-threatening toxicity with chemotherapy. Survival is also directly correlated with performance status. While patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 survive an average of approximately 9 month following cisplatin-based chemotherapy; those with an ECOG performance status of 1 have a median survival of about 6 months; and those with a performance status of 2 have a much shorter median survival averaging about 3 months[31]. In view of these data, chemotherapy in advanced stage NSCLC, should be reserved for patients with good performance status and rarely for patients with performance status 3 or 4[29,32]. The optimal number of chemotherapy courses is controversial but extrapolating from small cell lung cancer, it seems

reasonable to discontinue chemotherapy after four to eight cycles of treatment unless there is evidence of continued tumour shrinkage and the patient is tolerating chemotherapy without major adverse effects[18,29]. The American Society of Clinical Oncology guidelines state that platinum-based chemotherapy prolongs survival in patients with good performance status and should be started early while the patient still has a good performance status and the duration of chemotherapy should not exceed eight treatment cycles[18].

Compared to thoracic radiotherapy alone the addition of chemotherapy to thoracic radiation sequentially or concurrently in unresectable stage III NSCLC clearly improves the long-term survival rate, especially in patients with good performance status and less than 5% weight loss[33,34]. Recent studies indicate that chemotherapy followed by thoracic radiotherapy improves 5-year survival by three to fourfold. The American Society of Clinical Oncology guidelines also recommends combined chemotherapy plus thoracic radiotherapy in patients with unresectable stage IIIA/IIIB NSCLC rather than thoracic radiotherapy alone[18]. Increased local tumour control by radiotherapy combined with decreased distant metastasis by systemic chemotherapy is the paradigm. The effectiveness of cytotoxic chemotherapy and radiation therapy is inversely related to tumour burden; for any given level of treatment intensity, small amounts of tumour are more likely to be eradicated than larger ones.

The role of neoadjuvant and adjuvant chemotherapy in non-small cell lung cancer

The 5-year survival rate in stage IIIA-N2 disease is approximately 5% - 10% for patients treated with surgery plus radiotherapy. Induction or neoadjuvant therapy can be defined as cytoreductive therapy administered before definitive locoregional therapy. Cytoreductive therapy consists of either chemotherapy or radiotherapy or combined chemoradiotherapy. The aim of cytoreductive therapy is to downstage primary tumours and hence, increase the resectability rate. Neoadjuvant (pre-operative) chemotherapy may eradicate micrometastases, rendering subsequent surgical resection possible and improve long-term survival. Although the role of neoadjuvant or induction chemotherapy needs to be better defined by large studies, three randomised control studies with a maximum of 30 NSCLC patients per treatment arm have demonstrated improved survival following neoadjuvant chemotherapy[35-37]. Rosselli *et al*[35,38] in a study involving 60 patients with stage IIIA showed that preresectional chemotherapy with 3 courses of cisplatin, ifosfamide and mitomycin offers a significant long-term survival benefit compared to surgery without prior induction chemotherapy. Patients treated with neoadjuvant chemotherapy plus surgery had a median overall survival time of 26 months and a 3-year survival rate of 25% in comparison to 8 months and 3%, respectively, for patients treated with surgery alone ($p < 0.001$ for median survival time)[35,38]. Roth *et al*[36] compared surgery alone with peri-operative chemotherapy consisting of three preoperative courses of cisplatin and etoposide, followed by surgery, and then an additional three courses of chemotherapy. The 3-year survival rate was 56% for patients treated with peri-operative chemotherapy and 15% for patients treated with surgery alone. For induction therapy, the current reference standard is platinum-based chemotherapy and thoracic radiotherapy[39].

The role of adjuvant (post-operative) chemotherapy following resection of NSCLC remains controversial and is not routinely recommended in patients with completely resected stage I and II NSCLC[40] because no survival benefit is observed following postoperative adjuvant radiotherapy, chemotherapy or chemoradiation in a recent review of adjuvant and neoadjuvant trials by Einhorn[41]. As the new chemotherapy drugs such as paclitaxel, docetaxel, vinorelbine and gemcitabine improve survival in advanced NSCLC[26], compared to older agents, results of adjuvant and neoadjuvant trials with chemotherapeutic regimens using these newer agents may be better and are eagerly awaited.

Ongoing studies are evaluating the optimal type and timing of chemotherapy and the role of radiation therapy both before and after surgical resection of stage IIIA N2 disease.

The role of radiation therapy in non-small cell lung cancer

Radiotherapy is effective for the control of local disease and is valuable for palliation of symptoms such as haemoptysis, cough, shortness of breath and pain. There is a linear correlation between radiotherapy dose and local control of NSCLC[42]. Based on studies conducted more than 20 years ago, radiotherapy alone affords intrathoracic control in up to 50% of NSCLC patients with locally advanced disease, provided a total dose of at least 60 Gy is employed[43]. Several phase III trials and a meta-analysis demonstrated the superiority of combined modality treatment with chemotherapy and radiotherapy of locally advanced, unresectable stage III NSCLC over radiotherapy alone[44-46]. In the meta-analysis which included data from 2,589 patients with locally advanced, unresectable NSCLC, the addition of chemotherapy to radiotherapy sequentially or concurrently especially in patients with good performance status extended median survival from 10.3 to 12.0 months and a fourfold increase in 2-year survival rates[34,42,46]. This is because many patients with locally advanced (stage III) NSCLC develop recurrent disease outside the chest when they are treated with thoracic radiotherapy alone. However, combined modality treatment with chemotherapy and radiotherapy is accompanied by increased host toxicity such as oesophagitis and pulmonary toxicity, and the optimal method and sequence of radiotherapy administration with other treatment modalities have not been determined. In a study which compared sequential with concomitant chemoradiotherapy, Takada *et al* showed superior results with the concomitant regimen over the sequential regimen in terms of response (84% versus 66%), median survival (16.5 months versus 13.3 months) and three-year survival rate (27% versus 12.5%)[47]. Similarly, the Radiation Therapy Oncology Group in a three arm 600 patient trial comparing induction chemotherapy with cisplatin/vinblastine followed by standard radiation therapy (60 Gy at 2.0 Gy per fraction) with two concurrent regimens, one based on the same chemotherapy and another using cisplatin/oral etoposide with hyperfractionated irradiation using 1.2 Gy twice daily to a total dose of 69.6 Gy in 6 weeks, showed a statistically significant improvement in survival with concurrent chemotherapy compared to sequential chemotherapy and irradiation[48].

Preoperative radiotherapy with doses more than 45 Gy increases the operative morbidity and mortality and should not be used alone or with chemotherapy[49]. However, preoperative radiotherapy may be beneficial to patients with Pancoast tumour.

Although postoperative adjuvant thoracic radiation therapy after complete resection does not confer survival benefit, it reduces local-regional recurrences[50]. Therefore, it may be advisable to irradiate these patients post-operatively in order to maintain their quality of life for the longest possible time. However, some may prefer careful observation and periodic chest radiographs, with radiotherapy reserved for patients with regional failure because a recent meta-analysis of nine randomised controlled studies including 2,128 patients showed a worse survival in patients with stage I and II completely resected NSCLC receiving postoperative radiotherapy[51].

New radiotherapy strategies

New strategies designed to enhance local tumour control including the use of radiation-sensitising drugs (such as cisplatin, paclitaxel, gemcitabine and topoisomerase-inhibiting agents), three-dimensional radiotherapy planning techniques, or altered radiation fractionation schedules may further improve survival outcome. With three-

dimensional treatment planning, total radiation doses can be escalated to as high as 85 to 90 Gy without causing major damage to normal tissues[52,53]. Another method of increasing radiotherapy dose while minimising normal tissue toxicity is the use of multiple daily fractions[54]. The British CHART (continuous hyperfractionated accelerated radiotherapy) trial showed that hyperfractionated radiation therapy yields better results than conventional radiation therapy in patients with unresectable NSCLC in terms of improved local tumour control, reduced distant metastasis and better median and long-term survival[55]. In that study, CHART which consisted of thrice daily 1.5 Gy fractions of irradiation given for 12 consecutive days (36 fractions) to a total dose of 54 Gy was compared with standard daily radiotherapy (total dose, 60 Gy in 30 fractions). Combining chemotherapy with newer techniques of thoracic radiotherapy may provide additional survival benefit[56].

New cytotoxic agents for non-small cell lung cancer

Newer cisplatin-based regimens containing the two taxanes paclitaxel and docetaxel; vinorelbine, a semisynthetic vinca alkaloid mitotic spindle inhibitor; the nucleoside analogue anti-metabolite gemcitabine or the camptothecin derivative topoisomerase-1-inhibitors topotecan and irinotecan (Table II) are more effective and less toxic than older cisplatin-based combination regimens with etoposide or vindesine and have been shown to yield responses in 40 to 50% of patients[26] and improved survival[57-59]. None of the new cisplatin-based two-drug combinations (doublets) is clearly superior, with respect to efficacy or toxicity, over the other. The Southwest Oncology Group and the ECOG are conducting a direct comparison of five of the new combinations to determine the most effective and least toxic combination[32]. Meanwhile, the preliminary results of a study employing a triplet regimen containing cisplatin, gemcitabine and vinorelbine (PGV) have shown it to be superior to the doublet regimen containing cisplatin and vinorelbine (PV) in terms of a significant improvement in survival; median survival time was increased by more than 3 months with the triplet regimen[60]. The response rate to the PGV regimen was 57%. The median survival time for patients treated with PGV was 51 weeks compared to 35 weeks for patients receiving PV and the 1-year probability of survival was 45% and 34%, respectively; while haematological and non-haematological toxicities were not worse with the triplet regimen[60].

Although carboplatin, a less toxic analogue of cisplatin, has never been compared head-to-head with cisplatin, one can appropriately substitute cisplatin with carboplatin (with dosing according to renal function)[61] in the treatment of NSCLC patients[29]. Randomised controlled trials involving patients with metastatic NSCLC showed carboplatin given in combination with other active drugs yielded equivalent or superior survival rates compared with an identical regimen containing cisplatin[62,63]. In circumstances such as renal dysfunction, pre-existing neuropathy or pre-exicting heart disease which make it impossible to administer cisplatin because of its requirement for intravenous hydration, carboplatin is an alternative to cisplatin.

As regards non-platinum-based doublet regimens using the new agents, the combination of vinorelbine and gemcitabine has been the most extensively studied in Phase III trials. Response rates have ranged from 22% to 72% in patients with stage IIIB and IV NSCLC. The median survival has ranged from 8 to 12 months and the regimen was well tolerated by the patients[64,65]. For patients with poor performance status and especially for elderly patients, these new cytotoxic agents with high single agent activity (Table II) and favourable toxicity may offer attractive chemotherapeutic options for palliation in advanced NSCLC, both in combination and as single agent therapy. Despite the largely undefined role of second-line chemotherapy for good performance status patient who relapse after initial treatment with a platinum-based regimen, several trials have shown some of these

Table II
Phase II Trial with New Cytotoxic Agents for NSCLC[26]

Drug	No. of Patients	Response Rate (%)	Median Survival (week)	1-year Survival (%)
Paclitaxel (Taxol®)		26		
Docetaxel (Taxotere®)		26		
Vinorelbine	621	20	33	24
Vinorelbine/cisplatin	328	41	38	35 - 40
Gemcitabine	572	21	41	39
Gemcitabine/cisplatin	245	47	57	61
Topotecan		13		
Irinotecan	138	27	35	Not reported
Irinotecan/cisplatin	185	44	34	Not reported

new drugs such as docetaxel and gemcitabine also have considerable activity when used for second-line therapy[66].

Small cell lung cancer

Small cell lung cancer (SCLC) is rapidly fatal if left untreated, with most patients surviving less than 6 months. SCLC differs from other types of lung cancers in its biological characteristic of a more aggressive clinical behaviour and a rapid tumour doubling time. Tumour doubling times as low as 23 days have been reported for SCLC[67,68]. In contrast, tumour doubling times of 88 days for squamous cell carcinoma and 161 days for adenocarcinoma have been reported[67-69]. Unlike NSCLC, SCLC is usually disseminated at the time of diagnosis and is therefore not amenable to cure with surgery or thoracic radiotherapy alone. The vast majority of patients have stage IIIA, IIIB or IV disease at diagnosis. In rare circumstances, surgical resection may play a potentially curative role in the occasional patient who presents with a solitary pulmonary nodule[70-72]. As such patients still have a chance of developing systemic disease after surgical resection, it is currently recommended that they receive chemotherapy[72]. In a Canadian study, the 5-year survival after surgical resection was 51% for patients with stage I disease, 28% for those with stage II, and 19% for patients with stage III disease[73].

As proposed by the Veteran's Administration Lung Cancer Study Group, a two-stage classification is used to stage patients as either having limited or extensive disease[74]. Limited-stage disease is confined to one hemithorax with or without ipsilateral supraclavicular lymph node metastases and encompassed in one radiation port, while extensive-stage disease comprises lesions at sites beyond the definition of limited disease. Sixty to 80% of patients with SCLC have extensive disease at presentation. The Mayo Clinic and North Central Cancer Treatment Group database, which includes 1,617 patients in clinical trials, documented a median survival of 15.1 months for limited disease and 9.3 months for extensive disease with treatment[75]. The overall survival for limited disease and extensive disease is 29% and 8% at 2 years, 12% and 2% at 5 years, and 4% and 1% at 10 years, respectively[75].

Chemotherapy in small cell lung cancer

Combination chemotherapy is the mainstay of SCLC management. Although multiple regimens such as cyclophosphamide/doxorubicin/vincristine (CAV), cisplatin/etoposide (PE) and CAV alternating with PE yield approximately equivalent survival results, PE appears to have the best therapeutic index with fewer episodes of life-threatening toxicities[25,70,76]. PE, therefore

has become the standard treatment for SCLC patients, regardless of the stage at presentation[70]. Also, PE is more easily administered with concurrent radiotherapy than other combinations. In situations where pre-existing renal dysfunction or neuropathy exists or aggressive hydration is a problem, carboplatin may be substituted for cisplatin without apparent loss of therapeutic efficacy[77,78]. The combination of carboplatin and etoposide is now often employed to treat SCLC patients[79].

Despite high initial response rates of 65 to 95% depending on the stage of disease, relapse and progression occur in the majority of SCLC patients. Patients with extensive disease respond to combination cytotoxic chemotherapy less well than those with limited disease[25]. Patients with limited-stage disease receiving chemotherapy sometimes are cured, but in the majority of patients the median survival is limited to 15 to 20 months and the two year survival rate is 40%[79]. The probability of long-term (read as 5-year) survival usually does not exceed 5% in the overall SCLC population. The optimal duration of chemotherapy in SCLC remains controversial but the available data indicate that four to six cycles of chemotherapy is sufficient to achieve optimal outcome, regardless of response category or initial stage[25,70]. Although some reports indicate an improvement in disease-free survival with maintenance chemotherapy[80], overall survival is not improved with treatment beyond four to six courses of chemotherapy. Furthermore, quality of life is diminished with continued treatment[81]. Recently, ECOG investigators reported excellent 5-year survival results in limited stage SCLC using just four cycles of PE[82]. Ten to 30% of patients with progressive disease may respond to salvage chemotherapy regimens but the remissions are usually short-lived. A favourable response to salvage chemotherapy is most likely in patients experiencing at least a 3-month interval after cessation of induction chemotherapy and development of recurrent disease[83]. In CAV failures, PE generally effects response rates between 40 to 50%. Conversely, CAV generally is ineffective in PE failures, inducing remissions in less than 15% of patients[83].

In chemotherapy naïve SCLC patients with poor performance status, single-agent etoposide given either as a protracted low dose or 5-day oral or intravenous regimen has been found to be equally effective as multi-agent intravenous chemotherapy for the palliation of symptoms but inferior to the latter in terms of survival[84,85].

Preliminary studies on the use of high-dose chemotherapy and peripheral stem cell support in SCLC show that this relatively new approach produces better results in terms of response and survival when compared to conventional chemotherapy[86]. In this treatment method, one to three cycles of high-dose induction chemotherapy is followed by granulocyte-colony stimulating factor given at a dose of 300 µg per day for 5 to 6 days to mobilise peripheral blood stem cells.

Radiotherapy in small cell lung cancer

A meta-analysis has shown that thoracic radiotherapy is of benefit in patients with limited disease SCLC[87]. Therefore, thoracic radiotherapy is an essential component of optimal management in limited-stage disease SCLC[70]. With the addition of chest radiotherapy to combination chemotherapy, the survival of patients with limited-stage disease is further prolonged to 12 to 20 months[79]. Radiotherapy when administered concurrently with PE may provide a survival advantage but not when administered concurrently with cyclophosphamide-based chemotherapy[70]. Takada *et al*[88] reported an impressive survival advantage for concomitant radiotherapy compared with radiotherapy delivered sequentially following completion of the same combination chemotherapy with cisplatin and etoposide.

In a meta-analysis based on data on 987 patients with SCLC from seven trials comparing prophylactic cranial irradiation (PCI) in doses ranging from 24 - 40 Gy given in 8 - 20 fractions with no PCI in patients in complete remission after induction chemotherapy, PCI resulted in a modest but significant 5.4% increase in the overall survival rate at 3 years (15.3% in the control group vs. 20.7% in the treatment group)[89]. PCI also significantly increased the rate of disease-free survival and decreased the cumulative incidence of brain metastases by about 50%[89]. Larger doses of radiation was found to have led to greater decreases in the risk of brain metastases, while the effect on survival did not differ significantly according to the different radiation doses. On the basis of these data, it is now reasonable to include PCI as part of the standard treatment of patients with limited disease SCLC who are in complete remission after chemotherapy. However, there is little evidence that it provides any benefit in patients with limited disease who fail to respond completely to systemic chemotherapy[90].

Screening and early detection of lung cancer

There is no question that the earlier lung cancer is diagnosed and treated, the better are the patient's chances of survival (Table I)[19,91,92]. There is sufficient evidence of a prolonged pre-clinical phase in lung cancer. Clones of endobronchial cell populations accumulate genetic mutations leading to a progressively more malignant and ultimately invasive malignant state. With our current diagnostic technology, by the time lung cancer reaches a point at which it is clinically detectable, the disease is already in the late stages of its natural course and is only a couple of doublings away from reaching a lethal tumour burden. At the time of diagnosis, lung cancer tumour burden typically exceeds 10^9 cells (a 1-cm^3 volume) (Figure II)[93]. An important goal for lung cancer management, therefore, is to improve our diagnostic techniques to identify the pre-metastatic phases of lung cancer when the disease can be more successfully treated. Despite its intuitive appeal, screening for lung cancer has not been demonstrated to decrease overall mortality from the disease. A successful lung cancer screening strategy needs to detect the disease in a preclinical stage when it is amenable to curative treatment, in contrast to its poor overall responsiveness to treatment after it becomes clinically detectable (Table I). The best evidence for the success of a screening strategy is a reduction in mortality.

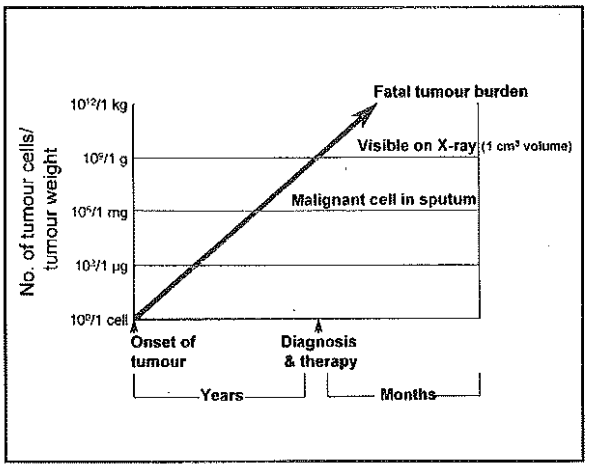


Fig.2: Progression of lung cancer[93].

It is well known that the following factors connote a higher risk for the development of lung cancer: smoking, chronic obstructive pulmonary disease, exposure to occupational carcinogens such as asbestos, previous tobacco-related cancer, family history and female gender[94,95]. One may argue that recommending lung cancer screening would undermine the impact of smoking cessation efforts. However, lung cancers occur also in individuals who have quitted smoking. In fact, the risk of lung cancer remains elevated two-fold 15 years after smoking cessation[96]. Even if all cigarette smokers were to quit smoking today, it would take 20 years before the resulting decrease in mortality from lung cancer become fully evident[25].

Screening with chest radiograph and sputum cytology

The role of screening with plain chest radiographs (CXR) remains controversial. In a review by Strauss *et al*[97], the four trials (three National Cancer Institute [NCI] trials[98] and one from Czechoslovakia[99]) published to date examined the addition of sputum cytology testing to CXR or less versus more frequent screening with sputum cytology testing and a CXR. All four studies included men older than 40 years and all reported no benefit in survival. Although screening with CXRs did detect more stage I lung cancers, the overall lung cancer mortality rate was not changed. In the NCI trials in the 1970s and 1980s[98], approximately 30,000 subjects (men who were heavy cigarette smokers and 45 years of age or older) were enrolled at the Memorial Sloan-Kettering Cancer Center, Mayo Clinic and Johns Hopkins Oncology Center. Although dual screening with annual CXRs and annual sputum cytology examinations was able to detect early stage carcinoma particularly squamous cell carcinoma[98], it was not associated with improved overall survival compared with CXR alone[100]. One reason for this inability to improve survival is likely related to the poor sensitivity of the sputum morphological studies that were available at that time. Of early lung cancer detected in the NCI trial, less than 10% were detectable only by routine sputum cytology. The negative findings of the NCI trial resulted in a loss of enthusiasm for lung cancer early detection. However, the annual sputum specimens obtained from individuals screened at Johns Hopkins were archived and the patients were monitored for 8 years[100]. Tockman *et al*[101] compared the sputum from patients who went on to develop cancer with the sputum from patients who remained cancer free. Two monoclonal antibodies were applied to the archived sputum specimens and positive staining predicted the subsequent development of lung cancer approximately 2 years before clinical recognition of the disease, with a sensitivity of 91% and a specificity of 88%[101].

In the Mayo Lung Cancer Project, subjects randomised to undergo screening CXRs and sputum cytology every 4 months for 6 years had higher number of cancers detected as stage I and stage II, and higher 5-year survival rates[102]. However, this did not translate into an improvement in mortality from lung cancer. The shift in stage distribution and 5-year survival is believed to reflect lead-time bias, length-biased sampling and/or overdiagnosis. The probable role of overdiagnosis, i.e., detection of clinically insignificant tumours, and lead-time bias was supported by the release of data which described outcomes after a mean of 20 years of follow-up: patients with lung cancer manifested a significantly longer length of survival in the screened group, but no significant differences in lung cancer mortality were observed between screened and unscreened subject populations[103].

The role of low-dose spiral computed tomography of the chest in lung cancer screening

While the ultimate role of low-radiation-dose spiral CT (low-dose CT) of the chest in screening for lung cancer remains to be determined by randomised trials with mortality endpoints which may take a decade or more to complete, several reports have documented that this imaging technique is more effective than chest radiography in detecting lung cancer at an early and potentially curable stage[104,105] Spiral CT imaging takes 15 to 30 seconds, allowing complete chest imaging in one breath-hold. The radiation dose associated with low-dose spiral CT scan is equivalent to or less than that associated with a mammogram and lesions as small as 2 to 3 mm in size can be detected. In a study by Kaneko *et al*[104] in which 1,369 individuals with at least 20 pack-year smoking histories underwent a low-dose CT scan examination, a CXR and a sputum cytology examination, primary lung cancer was detected on low-dose CT scans in 15 individuals (14 were stage I) while only 4 of these lesions

were detected on plain CXRs. The Early Lung Cancer Action Project (ELCAP)[106] screened 1,000 asymptomatic smokers with a 10 pack-year or more smoking history with CXR and low-dose CT scanning. Lung malignancy was detected in 27 individuals by low-dose CT scan and in 7 of these individuals by CXR. Of the 27 malignant tumours detected by low-dose CT scan, 23 (85%) were stage I tumours. Only 4 of the stage I tumours were detected on CXR, thus, stage I tumours were detected 6 times more frequently on low-dose CT scans than on CXRs. However, spiral CT also detected more nodules which eventually proved benign (20.6% versus 6.1%). While the ELCAP data are encouraging, it is premature to recommend low-dose spiral CT scanning as a lung cancer screening strategy until randomised trials confirm it has a positive impact on lung cancer mortality.

Other new diagnostic technologies

Lam *et al*[107] introduced autofluorescent bronchoscopy that is capable without the use of protoporphyrins of detecting endobronchial lesions of moderate dysplasia and carcinoma-in-situ that may not be visible with standard white light bronchoscopy.

PET using FDG is accurate in differentiating benign pulmonary nodules from malignant lesions as small as 1 cm with a sensitivity of 83 to 100% and a specificity of 80 to 100%[108-110]. Although false positive studies of increased FDG activity in benign lesions such as abscesses, tuberculosis and aspergillomas have been reported, when no significant FDG activity is observed, the lesions are invariably benign. Hypermetabolic lesions are considered malignant until proven otherwise.

Three-dimensional virtual bronchoscopy is a rapidly developing form of virtual reality imaging based on actual patient data acquired during spiral CT examination of the chest[111]. It allows non-invasive visualisation of the bronchial tree by generating simulated endoluminal images. Among the many possible applications of virtual bronchoscopy is the measurement of the cross-sectional area and length of stenosis which may be difficult to estimate during bronchoscopy. Such quantitative information can be useful in planning endobronchial stent placement, laser photocoagulation, cryotherapy and brachytherapy procedures. Secondary areas of obstruction distal to the primary lesion can be seen at virtual bronchoscopy even if the more proximal lesion cannot be crossed by the bronchoscope. It also allows the relationships of the airway to extrabronchial anatomy to be appreciated.

The role of early detection techniques in lung cancer patients who have undergone surgical resection

Recurrences after an apparently complete resection may be locoregional, distant or both, and will develop over the next five years in approximately 20 to 30% of patients with stage I disease, in 50% of those with stage II, and in 70 to 80% of those with stage III disease[112]. The vast majority of recurrences are in distant sites. The recurrence rate decreases with time after resection, whereas the rate of new primary lung cancer increases with time and can be as high as 1 to 2% per year. Even those patients with the most favourable NSCLC, i.e., those with resected T1N0M0 lesions, are at high risk for developing second primary lung cancers, on the order of 2 to 3% per year for at least 10 years after initial resection[113]. Therefore, early detection techniques and continued patient surveillance are important in this group of patients. The histological type of the tumour is a determinant of time to recurrence and survival in patients with resected stage I lung cancer[114,115]. Cancer recurrences are more frequent and recurrence rates are higher in patients with non-squamous lung carcinoma[116].

A retrospective evaluation of 130 patients who underwent a complete resection of NSCLC and who were placed into a routine follow-up or symptom-driven follow-up showed no

significant difference in disease-free interval until the first detection of recurrence[117]. However, the costs associated with the two groups were significantly different. The authors of that paper concluded that routine imaging follow-up is of questionable benefit.

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MCQs on Recent Advances in Lung Cancer Diagnosis and Treatment

1. The following statements on lung cancer are true
   a. Cigarette smoking increases the risk of lung cancer in smokers by 13-fold and in passive smokers by 1.5-fold
   b. Mutations in the p53 gene have been implicated in the carcinogenesis of lung cancer
   c. Surgical resection is the treatment of choice for advanced stage non-small cell lung cancer
   d. Radiotherapy with conventional fractionation is given at doses of 1.8-2.0 Gy per day at 24-hourly intervals, 5 times a week
   e. The injury caused by radiotherapy to normal tissue cannot be reduced by 3-dimensional conformational radiotherapy

2. In non-small cell lung cancer
   a. Adenocarcinoma is more common in non-smokers than in smokers
   b. Compared with best supportive care, combination chemotherapy containing cisplatin improves the median survival for patients with advanced non-small cell lung cancer
   c. Radiotherapy alone results in improvement in survival in metastatic disease
   d. Chemotherapy does not palliate symptoms in advanced disease
   e. Neoadjuvant chemotherapy can be used to down-stage Stage IIIA disease to allow complete surgical resection

3. In small cell lung cancer
   a. The presence of metastases in the ipsilateral mediastinal lymph nodes is considered an extensive-stage disease
   b. Survival is not dependent on the stage of disease at the time of diagnosis
   c. Treatment with chemotherapy is generally not curative
   d. The overall response to chemotherapy is in the range of 80% to 90%
   e. The optimal duration of treatment with chemotherapy is eight courses

4. In the treatment of small cell lung cancer
   a. Cytotoxic chemotherapy prolongs survival even in extensive disease
   b. Response to single agent chemotherapy is superior to combination chemotherapy
   c. Single agent chemotherapy with etoposide has no role in patients of advanced age or those with poor performance status
   d. The development of recurrent disease less than 3 months after cessation of induction chemotherapy portends a poor response to salvage chemotherapy
   e. The addition of radiotherapy to the primary tumour site in patients who respond to chemotherapy does not confer any survival advantage

5. The following statements on screening and early detection of lung cancer are true
   a. The earlier lung cancer is diagnosed, the better are the patient's chances of survival after treatment
   b. By the time lung cancer is visible on chest X-ray, the disease is already in the late stages of its natural course
   c. It has been shown that lung cancer is detected at an earlier stage by screening with chest radiograph
   d. Screening with chest X-ray decreases the overall lung cancer mortality rate
   e. Compared to chest X-ray, low radiation-dose screening spiral CT has been shown to be more effective in detecting lung cancer at an early stage