Taylor & Francis
healthsciences

An Update on Management of Lung Cancer

Acta Oncologica Lecture — Västerås 21 March 2002

Heine H. Hansen

From the Department of Oncology, Copenhagen University Hospital, The Finsen Center, Copenhagen, Denmark

Correspondence to: Heine H. Hansen, Department of Oncology, Copenhagen University Hospital, The Finsen Center, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark. Tel.: +45 3545 4090. Fax: +45 3535 6906. E-mail: a.secher@rh.dk

Acta Oncologica Vol. 41, No. 6, pp. 500–506, 2002

Globally, the incidence of lung cancer continues to rise drastically in parallel with increased tobacco consumption but with wide geographic variations. Despite the enforcement of more rigid health policies in many countries, lung cancer will for many years to come be a recurrent disease which most physicians will be confronted with at regular intervals. Furthermore, variations in the management of lung cancer occur from region to region influenced by differences in traditions, knowledge, healthcare systems and available resources. In this article a brief overview is presented of the management of both non-small cell and small cell lung cancer including recent results that may have an impact on the management of this disease.

Received 14 June 2002
Accepted 22 August 2002

Globally, the incidence of lung cancer continues to rise drastically in parallel with increased tobacco consumption. The picture, however, varies from country to country. Cancer statistics from the United States confirm that the downturn in the incidence of lung cancer in men began in the late 1980s, whereas in women, the incidence has increased steadily during the past four decades. Lung cancer has thus emerged as a common disease among women, particularly younger women, in contrast to the situation only 30 years ago, when lung cancer was a disease mainly found in men. A similar pattern has been observed in other countries including the UK and countries in northwestern Europe. The picture in eastern and southern European countries is markedly different, resembling the situation in the United States of 30 years ago, with a continuing increase among men, though the incidence is also rising drastically among women as well as in populated areas. A similar situation is seen in other populated areas, such as China, Indonesia, India and Japan.

Lung cancer is largely preventable but the effort to inform the public about the hazards of tobacco smoking is still on a low flame in many countries. Fortunately, the World Health Organization (WHO) has recently strengthened its efforts against tobacco, especially in developing countries. In the next 30 years WHO estimates that tobacco will kill more people than the combined death toll from malaria, tuberculosis and maternal and childhood diseases. In addition, more rigid health policies are being enforced in many countries, although recent drawbacks have occurred in legislation in Europe and Japan. Lung cancer will therefore continue to be an important issue, which most oncologists will be confronted with at regular intervals.

Among many physicians, the management of lung cancer is often characterized by a negative therapeutic attitude and wide variations occur from region to region, and from country to country, influenced by variations in traditions, knowledge, healthcare systems and available resources. In recent years, clinical guidelines have been developed in both North America and Europe based on evidence-based medical information, which is aimed at helping the physician to improve the treatment of lung cancer patients and public awareness of its treatment (1–3).

In the past decade we have seen major changes in the treatment of lung cancer. First and foremost, there is a more optimistic therapeutic approach using a combination of the three major treatment modalities: surgery, chemotherapy and radiotherapy, applied concurrently and/or sequentially in early-stage disease.

The purpose of this review is to present a brief overview of the management of lung cancer including data on recent results, which may have an impact on the future treatment of this disease.

 ISSN 0284-186X

Table 1

Histologic types of the major lung and pleural tumours

WHO classification Histologic type	% distribution*
Squamous cell carcinoma	25–35
Small cell carcinoma	15–25
Adenocarcinoma	20–35
Large cell carcinoma	10–15
Adenosquamous carcinoma	<1
Carcinomas with sarcomatous elements	<1
Pulmonary blastoma	<1
Carcinoids	<2
Mesothelioma	<2
	<2

*Varies from country to country.

HISTOPATHOLOGY

According to the WHO classification, more than 95% of all malignant lung tumours consist of four major histologic cell types: squamous cell carcinoma, small cell carcinoma, adenocarcinoma and large cell carcinoma (Table 1) (4). During the past 10 years there has been a relative decrease in squamous cell carcinoma and small cell carcinoma and an increase in adenocarcinoma, most likely caused by changes in smoking habits, with increasing use of filter cigarettes (5).

The remaining malignant lung tumours (less than 5%) include mesothelioma, carcinoids and mucoepidermoid carcinomas.

MANAGEMENT

Before a treatment plan can be discussed with the patient, careful clinical evaluation is necessary together with a proper histopathological diagnosis. For both biological and therapeutic reasons, the major types of lung cancer are subdivided into non-small cell carcinoma (NSCLC), consisting of squamous cell-, adeno- and large cell carcinoma, and small cell carcinoma (SCLC) (4).

Procedures commonly used for staging are presented in Table 2. The international staging system for lung cancer using TNM (tumour/node/metastases) grouping is presented in Table 3 (6). The main reason for proper staging of NSCLC is accurately to differentiate between stages I—IIIA, which are potentially resectable, and stages IIIB–IV. For SCLC the distinction between locoregional disease and extensive disease is mandatory in order to identify patients who will benefit from locoregional chest irradiation. Among the most recently developed procedures, results with FDG-PET imaging have proved this procedure beneficial in diagnosing intrathoracic disease, including local region lymph nodes, in non-small cell carcinoma (7), whereas the data for small cell carcinoma are in short supply. Furthermore, other procedures such as immunohistochemical evaluation of bone marrow using monoclonal antibodies have been evaluated in both small cell and non-small cell lung cancer, but it is too early to recommend these as routine procedures.

Table 2

Procedures for diagnosis and staging

Clinical examination
Haematologic and biochemical variables
Imaging evaluation
Chest x-ray
CT of the chest and abdomen
Ultrasound of abdomen
MRI of chest
FDG-PET imaging*
CT/MRI of the central nervous system**
Bone scan**
Invasive procedures
Bronchoscopy
Transbroncheal mediastinal biopsy
Mediastinoscopy
Thoracocentesis/thoracoscopy
Bone marrow examination***

*Increasingly used in diagnosing intrathoracic disease.
**If clinical symptoms.
***In small cell carcinoma.

The correlation between stage and survival for SCLC and NSCLC is shown in Figs. 1 and 2, respectively. For non-small cell lung cancer the data are based on records of 3043 lung cancer patients at the National Cancer Institute in Tokyo, Japan (8), while the figures for SCLC are from the Finsen Center in Copenhagen, Denmark (9).

NON-SMALL CELL LUNG CANCER

Stages I and II NSCLC

The standard therapy for stages I and II continues to be complete surgical resection whenever possible. This should include a lobectomy plus sampling of all mediastinal nodal stations or complete dissection (10). The results from a recent Chinese randomized trial suggest that complete dissection of the mediastinal lymph node has a positive impact on survival (11). Segmentectomy and wedge resections are reserved for patients with restricted pulmonary function, making lobectomy impossible. Curatively intended radiotherapy (60 Gy) is used for medically

Table 3

TNM-stage grouping for lung cancer

Stage		
I	A	T1 N0 M0
	B	T2 N0 M0
II	A	T1 N1 M0
	B	T2 N1 M0, T3 N2 M0
III	A	T3 N1 M0
	B	(Any T) N3 M0, T4 (Any N) M0
IV		(Any T) (Any N) M1

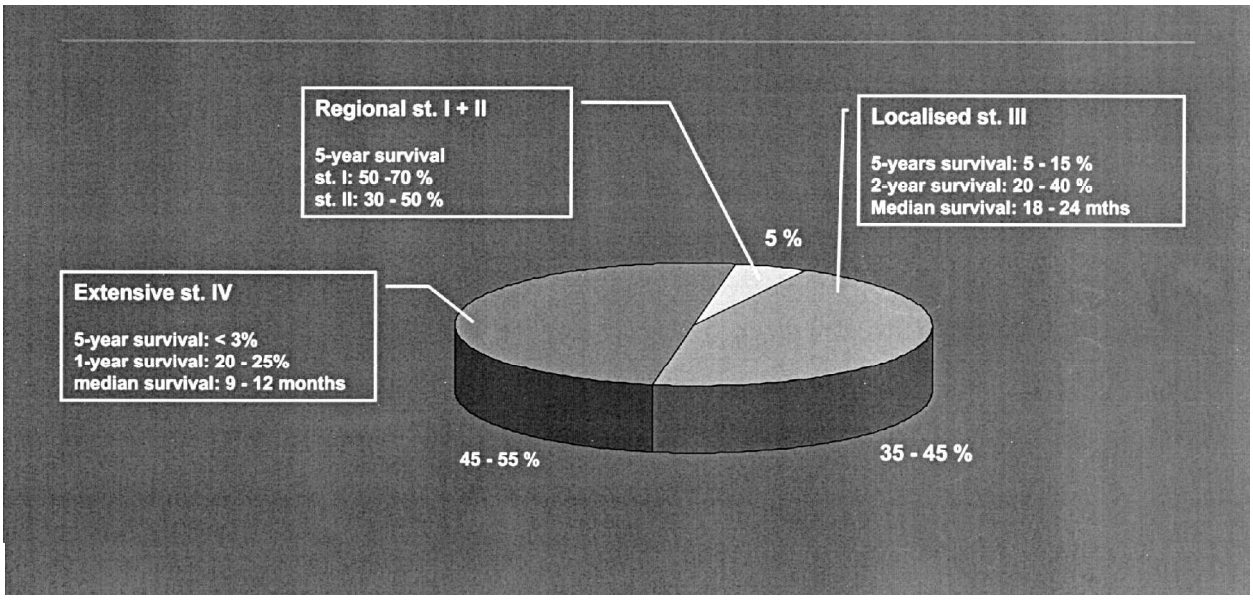

Fig. 1. Stage and survival in small cell lung cancer.

inoperable patients. There is no proven role for preoperative or postoperative radiotherapy after complete surgical resection (12). With recent technical advances, such as the application of 3-dimensional conformal treatment planning, it is conceivable that this situation may change. Postoperative chemotherapy is a controversial treatment. Meta-analyses have not yet proved any survival advantage, and treatment should not be considered as a standard therapy outside clinical trials (Table 4) (3). With respect to postoperative chemotherapy with platinum-based regimens, a meta-analysis of all randomized trials showed a 13% reduction in the hazard rate of death, which led to a 5% improvement in the 5-year survival rate (Table 4). Still, the differences were not statistically significant ($p = 0.08$), perhaps owing to the small number of patients (13). Fortunately, a large number of trials evaluating postoperative and cisplatin-based regimens are nearing completion in Europe and North America, and these should provide a final answer. However, the initial results from the ALPI study including

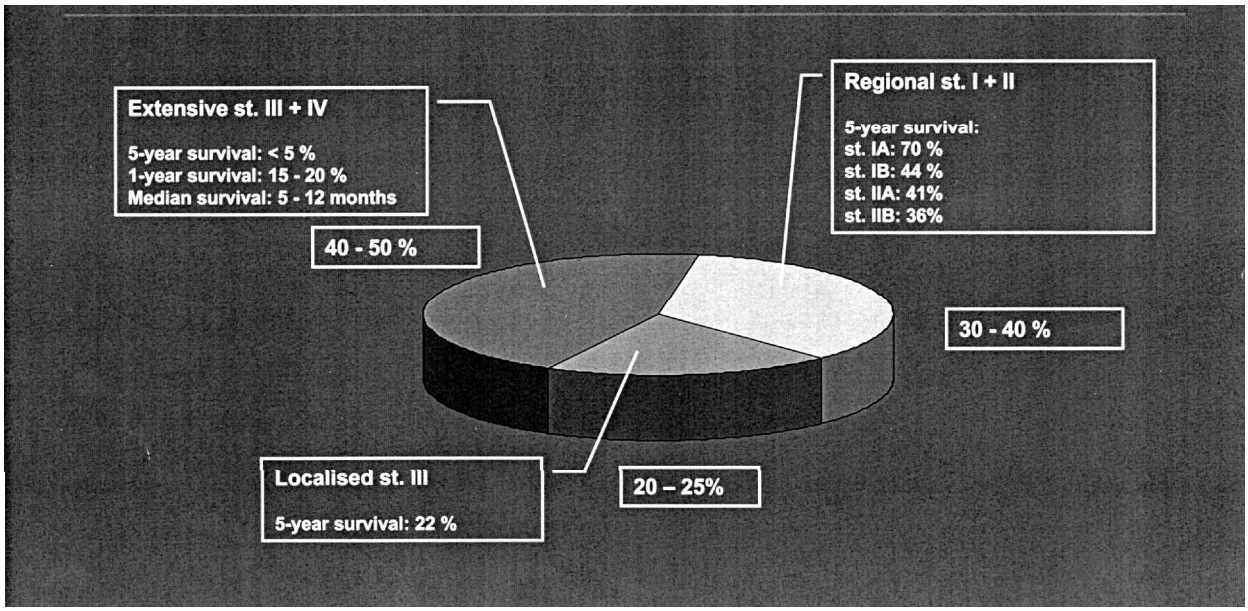

Fig. 2. Stage and survival in non-small cell carcinoma.

1209 patients are not encouraging. The combination chemotherapy applied in this trial consisted of cisplatin, mitomycin and vindesine (14).

Stage IIIA

This is a heterogeneous stage and there are marked differences in outcome depending on T-stage and the number and size of the mediastinal nodes. This heterogeneity makes it difficult to draw firm conclusions (15).

Surgery

The results of surgery alone for patients with multiple sites of mediastinal node involvement or for those with bulky mediastinal nodes are poor (5-year survival rate $< 10\%$) (8). Many consider these patients to be inoperable. The post-surgical results for patients with less extensive mediastinal node involvement are slightly better, but are still dismal (5-year rate 10–25%). Accordingly, there has been an increased tendency to use combined-modality therapy because of the poor results with surgery alone.

Preoperative chemotherapy

Long-term follow-up results of the three randomized trials comparing surgery alone with preoperative cisplatin-based chemotherapy plus surgery were published recently and confirm the survival advantage from non-randomized trials associated with the use of preoperative chemotherapy reported earlier. In the largest trial by Depierre et al., which includes 355 patients, the median survival time was 36 months for surgery and chemotherapy vs. 26 months for surgery alone in a mixed group of patients with stage I, II and III disease ($p = 0.15$) while the 3-year survival rate was 51.6% and 41.2%, respectively (16). Although impressive differences in 3-year survival were observed, they were not statistically significant, except in stage I and II disease.

Preoperative chemo/radiotherapy

Many phase II studies have demonstrated the feasibility of this approach, but results from large randomized trials examining the triple-modality approach have not been produced yet (15). Considerable toxicity has been observed in some studies, especially with certain drugs with high pulmonary toxicity (mitomycin C) or with high doses of radiotherapy. The long-term results of a multicentre study confirmed high 5-year survival rates ($> 20\%$), especially in certain patient subsets (15). As already mentioned, no randomized trials have been undertaken to examine triple-modality approaches, but there is an ongoing intergroup study in the US comparing chemotherapy (Etoposide, cisplatin) plus radiotherapy (60 Gy) alone with chemotherapy (Etoposide, cisplatin) plus radiotherapy (45 GY) followed by surgery. For radiotherapy, a total dosage of 55–65 Gy is usually applied. In a British study it was found that continuous, hyper-fractionated, accelerated radiotherapy (CHART) consisting of 36 fractions of 1.5 Gy 3 times per day to a total of 54 Gy in 12 consecutive days was superior to conventional radiotherapy with 30 fractions of 2 Gy to a total dosage of 60 Gy in 6 weeks (17).

ADVANCED NON-SMALL CELL LUNG CANCER (STAGES IIIB + IV)

Stage IIIB NSCLC

A meta-analysis from 1995 has shown that combined-modality therapy with (cisplatin-based) chemotherapy and radiotherapy provides a superior survival rate compared with that from radiotherapy alone (13), and other studies performed since then have also shown improved quality of life with the combined-modality approach. The only randomized trial to evaluate the treatment schedule showed the superiority of concurrent chemo/radiotherapy compared with sequential therapy (15).

Stage IV (and IIIB with pleural effusion) NSCLC

Around 50% of all NSCLC patients present at the time of diagnosis with advanced disease stage (IIIB or, usually, stage IV). The group is very heterogeneous and includes subgroups with a dismal prognosis of a few weeks to months, including patients with metastasis to the liver,

Table 4

Non-small cell carcinoma meta-analysis. Results with cisplatin-based chemotherapy

Treatments	HR (95% CI)	p-value	Reduction risk of death	% Abs 2-year	Benefit 5-year
Surg. vs. Surg. + CT	0.87 (0.74–1.02)	0.08	13%	3	5
Surg. + RT vs. Surg. + RT + CT	0.94 (0.74–1.02)	0.46	6%	2	2
RT vs. RT + CT	0.87 (0.79–0.96)	<0.01	13%	4	2
SC vs. SC + CT	0.73 (0.63–0.96)	<0.001	27%	10% (1-year)	MST* <1.5 months

CI = confidence intervals.
Meta-analysis, Br Med J, Oct 1995 (Ref. 12)
*MST = Median survival time.

CNS, or bone marrow. Many of the patients have a poor performance status and are afflicted with tobacco-related co-morbid disorders, such as chronic obstructive lung disease, arteriosclerotic heart disease, previous vascular attacks, etc. Symptomatic treatment with palliative radiotherapy of 10 Gy as a single dose or two 8.5 Gy fractions one week apart to the primary tumours is indicated if obstruction or haemoptysis occurs, or if there are bone or CNS metastases (18, 19). Frequent use of analgesics, including morphine, is commonly indicated, while systemic treatment with chemotherapy should be used with caution in patients with advanced disease and performance status III and IV (19).

In contrast, evidence has accumulated since the introduction of platinum-based regimens in the 1980s showing that chemotherapy improves both survival and quality of life (13, 19–21) in patients with advanced disease and good performance status. Prior to 1999, standard chemotherapy for patients with unresectable disease and good performance status consisted primarily of cisplatin (or carboplatin) combined with, for example, etoposide, vindesine, vinblastine, ifosfamide, or mitomycin C. A review of the literature shows that no single combination of these agents appears to have superior efficacy. Since then, several drugs with substantial activity as first-line single agents have been introduced: vinorelbine, the taxanes (paclitaxel and docetaxel), gemcitabine, topotecan, irinotecan and tirapazamine (Table 5) (19). These drugs have toxicity profiles that compare favourably with that of cisplatin, but whether these drugs have superior efficacy will have to await confirmation from the results of large, ongoing trials, while two-drug combinations clearly are superior to one-drug treatments. There is still no evidence to confirm that any three- or four-drug regimen provides superior results to those of two-drug regimens. Toxicity is almost always increased with three- and four-drug combinations. With several two-drug combinations, one-year survival rates are in the range 35–40% and two-year survival rates are 15–20% in cooperative group randomized studies (19).

Prior to 1999 there was no evidence that second-line chemotherapy could improve survival rates compared with best supportive care. Two recent randomized trials have indicated that docetaxel offers a modest survival prolongation compared with best supportive care or with single-agent ifosfamide or vinorelbine in patients who progress after platinum-based therapy (22, 23). The clinical relevance of these observations is now being debated in many countries. Several very recent phase II trials also indicate symptom improvement with oral receptor tyrosine-kinare inhibitors, e.g. Iressa (ZD-1839) or Isis 3521 (an antisense inhibitor of Prokinase C) in patients not responding or relapsing after second-line treatment (24). Elderly patients with NSCLC have less tolerance to intensive chemo- and or radiotherapy than younger patients, and individualized treatment is indicated (25).

Table 5

Frequently used drugs in lung cancer

Drug	Non-small cell lung cancer	Small cell lung cancer
Carboplatin	+	+
Cisplatin	+	+
Docetaxel	+	
Doxorubicin	+	+
Etoposide		+
Gemcitabine	+	
Ifosfamide	+	+
Irinotecan		+
Mitomycin-C	+	
Paclitaxel	+	
Topotecan		+
Vincristine		+
Vindesine	+	
Vinorelbine	+	

SMALL CELL LUNG CANCER

A short summary of the management of SCLC is now presented based on the evidence from randomized trials, but it should be realized that patients included in clinical trials are not representative of the patient population as a whole.

Limited disease

Combined-modality therapy using combination chemotherapy and irradiation is the standard treatment (26). In the rare case of a patient presenting with stage I disease, surgical treatment followed by postoperative chemotherapy yields results for SCLC that are equivalent to those for treatment of NSCLC.

For chemotherapy, etoposide combined with cisplatin (or carboplatin) is the primary regimen of choice because of the less toxic effects and slightly superior activity compared with doxorubicin- or cyclophosphamide-containing regimens. Duration of chemotherapy in responding patients is usually 6 cycles. The impact of dose intensification is uncertain, even though some investigations show superior median survival when intensification of the dosages is applied (26).

Based on meta-analyses, patients receiving chest irradiation have a 5% improvement in 3-year survival when a combination of chemotherapy and radiotherapy is applied, compared with those receiving chemotherapy alone (27).

The optimal timing and dosing of chest irradiation is uncertain, but there is a tendency to initiate radiotherapy early during the first two courses at total doses of at

least 50 Gy. Similarly to NSCLC, hyper-fractionated irradiation is beginning to be adopted. Results from two randomized trials (27, 28) have been published—one of these including 147 patients who showed statistically significant superiority of 10 twice-daily irradiation sessions compared with daily irradiation, with 5-year survival rates of 26% and 16%, respectively. A similar effect was not observed in the other study, possibly because radiotherapy was started after 3 cycles of chemotherapy and given as a split-course rather than continuously starting on day 1 with cycle 1 (28).

Furthermore, in several meta-analyses, prophylactic cranial irradiation (PCI) has been demonstrated to have a statistically significant impact on survival in patients with limited disease who achieve a complete remission. Three-year survival with PCI was 20.7% versus 15.3% without PCI (29). The optimal dose and timing of radiotherapy are again uncertain; usually the total dose does not exceed 30 Gy, given in fractions of 2.5 Gy daily (23). In patients with limited disease and complete remission, an ongoing European study compares a standard dose (25 Gy in 10 days) with a higher dose of 36 Gy (18 fractions in 24 days) and accelerated dose (36 Gy in 24 fractions in 16 days); 700 patients are expected to be enrolled in this study, in which the main endpoint is quality of life, but late sequelae and survival will also be evaluated.

Extensive disease

Again, a combination of etoposide and cisplatin (or carboplatin) is the preferred standard treatment. Carboplatin can be substituted for cisplatin because of a similar activity and fewer mucosal side effects, even though myelosupression is higher. In a newly published Japanese study, survival rates with a combination of irinotecan + cisplatin were superior to those with etoposide and cisplatin (one-year survival 56% vs. 34%) (30). More intensive treatment, e.g. with four drugs instead of two drugs, has also resulted in improved 1-year survival (40% vs. 29%), but with more severe haematologic toxicity (31). In patients presenting with poor prognostic factors, such as WHO performance status 3–4, involvement of the liver and bone marrow, severe concomitant co-morbid diseases, etc., the initial dose of chemotherapy should be reduced, and careful monitoring is recommended over the first few weeks.

Recurrent disease

The treatment options depend on the anatomic site of relapse, symptomatology and previous treatment. Local relapse in patients without prior chest irradiation is best treated with palliative radiotherapy. Late relapse in patients initially responding to a platinum-containing regimen should be treated with the same regimen again. Otherwise either combination chemotherapy with, for example, cyclophosphamide, doxorubicin, vincristine, or single-agent chemotherapy with topotecan is the treatment of choice (32).

Future aspects

As expressed in an editorial by Carney & Hansen (33):

> Lung cancer is the most preventable of all common cancers. The elimination of cigarette smoking remains the best hope for reducing mortality from this disease. For former smokers and those who continue to smoke, new techniques for the early detection of the disease, when it is most curable, and methods for preventing lung cancer are promising developments. Knowledge of the molecular events during the early stages of lung cancer, such as alteration of the expression of the fragile histidine triad (FHIT) gene and the presence in sputum of cells with genetic abnormalities, offers possibilities for early diagnosis. The use of chemopreventive agents such as orally administered vitamins has been of limited value, but the development of an aerosolised route of delivery for these agents, which would allow uniform delivery of the agent to the entire pulmonary epithelium, may enhance our ability to control or even reverse early changes associated with lung cancer. Such developments could benefit patients at risk for lung cancer.

With respect to the future treatment of lung cancer, Bunn has reviewed this topic extensively (24) summarizing that

> … with modern molecular tools it has become possible to understand specific genetic and biologic properties of individual lung cancers that might better predict therapy than standard histology. Specific growth factor signal abnormalities are the target of many new therapies. These therapies are likely to be most effective in cancer with these specific changes irrespective of their histology. Many tumour-specific antigens are also expressed independently of histology and vaccine therapies will be directed by antigene expression, not histology. Finally, recent studies have identified a number of tumour-specific angiogenic and invasion proteins. These specific proteins will undoubtedly serve as therapeutic targets in future trials for lung cancers of all histologic types.

It is to be hoped that these advances from the laboratory bench to the clinic will change the overall therapeutic picture for the management of lung cancer patients, which certainly is needed. Unfortunately, efforts in tobacco control are gaining momentum only slowly worldwide.

REFERENCES

1. Ihde DC, Bunn PA, Hansen HH. Clinical practice guidelines for the treatment of unresectable non-small cell lung cancer: how useful are they? Fall Educational Book 1997; ASCO 8th Annual Fall Education Conference: 39–56.

2. Minimum Clinical Recommendations. Ann Oncol 2002.
3. National Comprehensive Network. Small cell lung cancer. Cancer Control 2001; 8 (Suppl 2): 32–43.
4. Travis WD, Colby TV, Corrin B, et al. eds. Histological typing of lung and pleural tumours. WHO International Histological Classification of Tumours. 3rd ed. Berlin: Springer, 1999.
5. Janssen-Heijnen MLG, Coebergh J-WW. Trends in incidence and prognosis of their histological subtypes of lung cancer in North America, Australia, New Zealand and Europe. Lung Cancer 2001; 31: 123–7.
6. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997; 111: 1710–7.
7. Fischer BMB, Mortensen J, Højgaard L. Positron emission tomography in the diagnosis and staging of lung cancer: a systematic, quantitative review. Lancet Oncol 2001; 2: 659–66.
8. Naruke T, Tschiya R, Kondo H, Asamura H. Prognosis and survival after resection for bronchogenic carcinoma based on the 1997 TNM-staging classification: the Japanese experience. Ann Thorac Surg 2001; 71: 1759–64.
9. Lassen U, Østerlind K, Hansen M, et al. Long term survival in small cell lung cancer: post treatment characteristics in patients surviving 5 to 18 years. An analysis of 1714 consecutive patients. J Clin Oncol 1995; 13: 1215–20.
10. Pearson FG. Non-small cell lung cancer. Role of surgery for stages I–III. Chest 1999; 116: 500s–3s.
11. Wu Y, Huang Z, Wang S, Yang X, Ou W. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. Lung Cancer 2002; 36: 1–6.
12. PORT Meta-analysis Trialists' Group. Postoperative radiotherapy in non-small cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomized controlled trials. Lancet 1998; 352: 257–63.
13. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Br Med J 1995; 311: 899–909.
14. Tonato M. Final report of the Adjuvant Lung Project Italy (ALPI): an Italian/EORTC-LCG randomised trial of adjuvant chemotherapy in completely resected non-small cell lung cancer (NSCLC). Proc ASCO. Lung Cancer 2002; 21: 290a.
15. Bass P. Inductive and adjuvant treatment strategies for localized non small cell lung cancer in operable and inoperable patients. Curr Opin Oncol 2002; 14: 180–4.
16. Depierre A, Milleron B, Chevret S, et al. French phase III trial of preoperative chemotherapy (PCT) in resectable stage I (except T1N0), II, IIIa non-small cell lung cancer (NSCLC). Lung Cancer 2000; 29 ((Suppl 1)): 296Abstract.
17. Saunders M, Dische S, Barrett A, et al. Continuous, hyper fractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomized multicentre trial. Radiother Oncol 1999; 52: 137–48.
18. Medical Research Council Lung Cancer Working Party. Immediate versus delayed palliative thoracic radiotherapy in patients with unresectable locally advanced non-small cell lung cancer and minimal thoracic symptoms: results of a randomised trial. Br Med J 2002; 325: 465–8.
19. Hansen HH. Treatment of advanced non-small cell lung cancer—how and when? Br Med J 2002; 325: 452–3.
20. Sörenson S, Glimelius B, Nygren P. A systematic overview of chemotherapy effects in non-small cell lung cancer. Acta Oncol 2001; 40: 327–39.
21. Booton R, Thatcher N. Chemotherapy in advanced non small cell lung cancer: indication, intensity, and duration. Curr Opin Oncol 2002; 14: 191–8.
22. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000; 18: 2095–103.
23. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18: 2354–62.
24. Bunn, PA Jr. Novel targeted agents for the treatment of lung cancer: Am Soc Clin Oncol, Ed Book 2002: 683–92.
25. Gridelli C, Maione P, Barletta E. Individualized chemotherapy for elderly patients with non small cell lung cancer. Curr Opin Oncol 2002; 14: 199–203.
26. Østerlind K. Chemotherapy in small cell lung cancer. Eur Respir J 2001; 18: 1026–43.
27. Turrisi AT. Optimal use of radiotherapy in limited small-cell lung cancer: ASCO Ed Book 2000: 678–81.
28. Bunner JA, Sloan JA, Shanahan TG, et al. Phase III trial comparison of twice-daily split-course irradiation versus once daily irradiation for patients with limited small cell lung cancer. J Clin Oncol 1999; 17: 2681–91.
29. Gregor A. Small-cell lung cancer: advances in the management of limited disease—prophylactic cranial irradiation. ASCO Ed Book 2000: 672–7.
30. Noda K, Nistriwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small cell lung cancer. N Engl J Med 2002; 346: 85–91.
31. Pujol JL, Daurès JP, Rivière A, et al. Etoposide plus cisplatin with or without the combination of 4′-epidoxorubicin plus cyclophosphamide in treatment of extensive small-cell lung cancer: a French Federation of Cancer Institutes Multicenter Phase III randomized study. J Natl Cancer Inst 2001; 93: 300–8.
32. Schiller JH, Adak S, Cella D, DeVoreIII RF, Johnson DH. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593-a phase III trial of the Eastern Cooperative Oncology Group, J Clin Oncol 2001; 19: 2114–2.
33. Carney DN, Hansen HH. Non-small cell lung cancer—stalemate or progress. N Engl J Med 2000; 343: 1260–2.

Additional literature: recent textbooks

1. Hansen HH. ed. Textbook of lung cancer. London: Martin Dunitz, 2000
2. Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG. eds. Diagnosis and treatment of lung cancer. an evidence-based guide for the practicing clinician. New York: WB Saunders Company, 2001
3. Hansen HH, Bunn PA Jr. Lung cancer therapy annual. II. London: Martin Dunitz, 2002

Journals

'Lung Cancer' published monthly by the International Association for the Study of Lung Cancer