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Management of Small Cell Lung Cancer

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Third IASLC Workshop on Small Cell Lung Cancer
Elsinore, Denmark, 18–22 June 1989

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INTRODUCTION

The management of small cell lung cancer (SCLC) remains a great challenge and during the last two decades much effort has been exerted to increase our understanding of this biological and clinical disease entity.

The workshop on small cell lung cancer in June 1989, Elsinore, Denmark, was the third on this subject arranged by the International Association for the Study of Lung Cancer. Previous meetings were held in Ireland 1981 and in Scotland 1984 and resulted in valuable contributions to the literature.

In spite of continuous progress in the understanding of the biology of SCLC, the therapeutic achievements reached a plateau by the start of the 1980'es. Since the previous workshops some ideas have changed and new tools have been introduced, such as new imaging techniques, monoclonal antibodies and biological modifiers. New cytostatic compounds have been introduced for clinical evaluation, resulting in a number of phase II trials. In addition, mature results from several large randomized trials have been published. Data from other important studies have shed new light on local treatment modalities, such as radiotherapy and surgery in combination with chemotherapy. Critical reappraisal of the role of known treatment components along with an increased insight into the mechanisms of action and toxicities have challenged some therapeutic concepts. Progress may come solely from learning to use our tools better.

The purpose of the third SCLC workshop was to reevaluate the available data on therapy in SCLC and to develop a consensus on important clinical topics. To meet these goals 63 colleagues were invited, some senior and some younger, but all deeply involved in clinical research on SCLC. Seventeen nations from four continents were represented. Prior to the workshop 21 participants were asked to review the literature on particular topics and these reviews were distributed to all participants before the workshop. In addition all participants were invited to submit abstracts for internal use at the workshop only.

Reviews and selected abstracts were presented as the basis of discussion in 6 plenary sessions on different key topics. The discussions were continued in separate committees with the aim of reaching a written consensus. Finally, the content of the consensus reports was presented at a plenary session. The chairmen of the committees are first authors of the consensus reports, and the subsequent authorship is listed alphabetically. Hopefully, the agreed strategies will lead to further therapeutic improvements in the 1990'es.

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Heine H. Hansen
Paul E.G. Kristjansen

List of Contents

II. Chemotherapy

III. Local Treatment Modalities

IV. Central Nervous System - Therapy

V. Biological Modifiers

VI. Complications and Supportive Care

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Part I: Consensus Reports

Staging and prognostic factors in small cell lung cancer: a consensus report

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Small cell lung cancer is an aggressive and rapidly growing neoplasm which tends to be disseminated at the time of diagnosis. Most patients present with mediastinal metastasis, extrathoracic metastasis, or both. The natural history of this neoplasm and investigational techniques strongly suggest the presence of microscopic metastasis in many patients considered to have limited disease when examined by conventional staging techniques only. Systemic chemotherapy is the major effective therapeutic modality in small cell lung cancer. Additional radiation therapy may be beneficial in limited disease, and surgery may be useful in selected patients. Anatomical staging is necessary in individual patients, if it influences treatment decisions on the use of local treatment modalities, and remains necessary in clinical trials, where staging is important for the interpretation of results and allows comparisons between different trials. Since the identification of all sites of metastasis is not mandatory for patients treated with chemotherapy alone, the exact anatomical staging is of marginal importance in clinical practice outside a clinical trial setting, especially in patients presenting with distant metastases.

The simple staging system introduced by the Veterans Administration Lung Cancer Study Group (VALG) of 'limited' and 'extensive' disease is generally applied in clinical practice and has proven adequate for most clinical situations [1]. A revised TNM staging system for malignant lung tumors has been introduced in 1986 [2]. While the previously used TNM staging has

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been shown to have limited use in small cell lung cancer, the only exception being patients undergoing surgical resection [3], the revised TNM system now awaits validation in future clinical trials.

As an alternative to anatomical staging, grouping of patients according to simple laboratory parameters have been proposed [4]. Such parameters have allowed the definition of prognostic subgroups of small cell lung cancer and thus might be useful in prospective clinical trials as tools for stratification. Since treatment decisions such as the use of local modalities will remain dependent upon knowledge of the anatomical distribution of the disease, these parameters might complement but do not replace anatomical staging.

Excessive staging procedures can be a burden for the individual patient and unnecessarily increase the cost of medical care. Thus it is important to limit the number of staging procedures to the minimum necessary for responsible patient care in a given situation. The recommendations for staging differ according to the therapeutic options considered and according to whether a patient is treated outside or inside a clinical trial.

A review on staging of small cell lung cancer has been published recently [5] and the value of individual staging procedures is outlined elsewhere in this issue [6]. This paper outlines the consensus about staging in small cell lung cancer formed at the 3rd International Workshop on Small Cell Lung Cancer and updates the first consensus report published in 1983 [7].

1. Staging systems

Two systems are currently available for the staging of small cell lung cancer: the system proposed by the VALG and the revised TNM system [1,2]. These two systems are sufficient for the needs of the clinician and the clinical investigator and additional staging systems do not seem necessary at present.

The system of the VALG classified patients into two categories of 'limited' and 'extensive' small cell lung cancer, depending on whether all known tumors could be treated within a tolerable single radiotherapy port or not. This system is generally used in clinical practice, is sufficient for treatment decisions regarding local radiotherapy, and carries prognostic information independent of whether chemotherapy is used or not [1]. The classification of patients with contralateral mediastinal or supraclavicular lymph node metastases and of patients with ipsilateral pleural effusions has not been precisely defined and has not been uniformly handled by different investigators. For future reference the participants reached the following consensus regarding these questions (Table I). The classification of 'limited' disease small cell lung cancer should include patients with disease restricted to one hemithorax with regional lymph node metastases,

Table 1

Staging of small cell lung cancer in 'limited' and 'extensive' disease

Limited	Disease confined to one hemithorax
	– with or without ipsilateral or contralateral mediastinal or supraclavicular lymph node metastasis
	– with or without ipsilateral pleural effusions independent of cytology
Extensive	Any disease at sites beyond the definition of limited disease

Table 2

Recommendation of staging procedures in small cell lung cancer

Procedure	Clinical practice		Clinical trial
	Local treatment modality under consideration		
	No	Yes	
General procedures			
Patient history	+	+	+
Physical examination	+	+	+
Blood counts	+	+	+
Serum biochemistry	+	+	+
Cytological or histological documentation of SCLC	+	+	+
Procedures for local disease			
Chest X-ray	+	+	+
Chest CT	–	–	+[a]
Fiber bronchoscopy	–	–	+[b]
Mediastinoscopy	–	–	+[c]
Cytology of effusion	–	–	+
Cytology of supraclavicular node	–	–	+[d]
Procedures for distant disease			
Bone:			
Bone scan	–	+[e]	+
Bone X-rays	–	+[f]	+[f]
Liver and retroperitoneal organs:			
Ultrasound or abd. CT	–	+[e]	+
Fine-needle aspiration/biopsy	–	+[e]	+[d]
Bone marrow: Aspirate and biopsy	–	+[e]	+
Brain: CT	–	+[e]	+

[a] Especially for trials of limited disease.
[b] If use of bronchoscopy anticipated at restaging, surgery for limited disease is considered or diagnosis cannot be obtained otherwise.
[c] Only if needed by surgeon for preoperative work-up.
[d] If the findings are doubtful and the establishment of a positive finding affects the treatment.
[e] If one of tests is positive further evaluation can be discontinued.
[f] Only in areas of increased uptake on bone scan.

including hilar, ipsilateral and contralateral mediastinal, and ipsilateral and contralateral supraclavicular nodes, and should also include patients with ipsilateral pleural effusion independent whether the cytology is positive or negative. The inclusion of contralateral mediastinal and supraclavicular metastases and ipsilateral pleural metastases in 'limited' disease is recom-

mended because the prognosis of patients with these sites of disease is superior to the prognosis of patients with distant sites of metastases [8] and because the revised TNM system groups these sites of disease in stage IIIb, not in stage IV. The classification of extensive disease small cell lung cancer should comprise all patients with sites of disease beyond the definition of limited disease. Thus extensive disease as proposed here is equivalent to stage IV, whereas limited disease is equivalent to stage I–III of the revised TNM system.

The TNM system for malignant lung tumors has recently been revised and published [2]. Patients with ipsilateral pleural effusions are to be classified as follows: cytologically positive effusions are classified as T4 lesions, effusions that are repeatedly cytologically negative or effusions too small to be aspirated are classified as the appropriate lower T stage. It has been demonstrated that the number of sites of extrathoracic metastasis carries prognostic information in small cell lung cancer [9]. The consensus group therefore recommends that stage IV disease should be subdivided in stage IVA for patients with a single organ system involved with extrathoracic metastasis and stage IVB with more than one organ system involved with extrathoracic metastasis. It is recommended that the revised TNM system be used for future clinical trials, especially trials involving local treatment modalities, in order to validate its use prospectively.

2. Staging procedures

Staging procedures in small cell lung cancer allow one to identify sites of tumor involvement for the monitoring of the therapeutic effect and the selection of individual patients considered for local treatment modalities. Results of staging procedures and the incorporation of these results in staging systems supply prognostic information and allow for uniform groups of patients to be entered into clinical studies.

The extent of clinical staging necessary depends upon the clinical situation of individual patients, whether a local modality is considered as part of the treatment, and whether such treatment is given outside or inside a clinical trial. The recommended staging procedures are summarized in Table 2.

In *clinical practice* outside a trial setting patient history, physical examination, histological or cytological confirmation of small cell lung cancer, chest X-ray, hematology with complete blood count, biochemistry including electrolytes, liver function tests, alkaline phosphatase and creatinine are often sufficient for staging work-up. Additional examinations need only to be done when indicated by the presenting symptoms (e.g. neurologic symptoms, hepatomegaly, or thrombocytopenie) or findings or if the diagnosis of limited disease affects the selection of treatment. In the latter case, extensive disease should be excluded by bone scan, ultrasound or CT scan of the abdomen, examination of bone marrow and/or CT scan of the brain. If one of these tests is positive further evaluation can be discontinued.

For *clinical trials* a continuation of the anatomical staging with examination of the major extrathoracic systems is recommended, in particular for trials of previously untreated patients (Table 2). For patients with refractory or relapsed small cell lung cancer treated in phase II studies requirements may differ and less stringent staging procedures might be sufficient. It is recommended that the staging procedures required be included in the trial reports.

To evaluate the thoracic spread of tumor, a CT scan of the chest is recommended and should be a part of all trials focusing on limited disease. CT scans will provide information about parenchymal, mediastinal and pleural extension of disease. Fiber bronchoscopic evaluation is necessary, if the use of bronchoscopy is anticipated at restaging. Otherwise it could be reserved

for patients in whom the diagnosis cannot be obtained by other means and for patients with limited disease considered for surgical intervention. Mediastinoscopy is only necessary if needed by the surgeon for preoperative work-up or if needed to establish the diagnosis. In patients with pleural effusions attempts should be made to obtain cytology. Cytological or histological confirmation of supraclavicular lymph node metastasis should be obtained if the result of clinical examination is doubtful and if the establishment of positive findings might change the clinical approach.

Extrathoracic spread of small cell lung carcinoma most often involves bone, liver, retroperitoneum, bone marrow, and central nervous system [9]. The evaluation of extrathoracic spread of tumor should therefore include a bone scan which is more sensitive than skeletal X-rays to evaluate bone metastases and often is positive in the absence of symptoms or an elevation of the alkaline phosphatase [10]. Areas of increased uptake on scan should be evaluated with skeletal X-rays to exclude benign bone or joint disease and to identify the infrequent asymptomatic metastases in weight bearing bone with cortical erosion which might require irradiation. An abdominal ultrasound or CT scan should be used to evaluate the possibility of liver, adrenal or retroperitoneal metastasis. Cytological confirmation might be necessary if the findings are doubtful and if the establishment of a positive finding might affect the treatment. Recent reports suggest that ultrasonic guided fine needle aspiration or biopsy of suspected liver lesions can be as sensitive as peritoneoscopy with multiple liver biopsies [11]. Other staging procedures should include bone marrow aspiration and biopsy for the detection of bone marrow metastasis and a brain CT for detection of brain metastasis. Although fewer than 5% of patients will present with bone marrow involvement as the only site of extrathoracic disease, this procedure is recommended, since it complements evaluation of bone metastasis by bone scan and when positive is unequivocal and does not need further pathologic confirmation [12]. Patients with CNS metastasis as the only site of metastatic disease have a median survival similar to those with disease limited to the chest, but long-term survivors are virtually non-existent [13]. For clinical trials brain CT scans to be performed as part of the staging evaluation of asymptomatic patients are thus recommended.

3. Restaging

Restaging is essential for the evaluation of the effect of therapy, independent of whether a patient is treated on a clinical trial or not. Restaging is of particular importance, when treatment decisions, for example the use of prophylactic cranial irradiation, are based on the results of restaging procedures. Restaging should include history and physical examination, chest X-ray, hematology and biochemistry. Additional procedures should be done to re-check all findings that were abnormal at the start of therapy. Rebronchoscopy should be done in patients with limited disease considered for surgery and in patients in complete remission who had a positive bronchoscopy at the start of therapy.

It is recognized that histologic verification of positive CT scan findings at the time of restaging would be useful. Such data could be obtained from studies of surgery after chemotherapy in limited disease patients.

4. Histopathological classification of small cell lung cancer

In the last revision of the WHO classification of malignant lung tumors small cell lung

cancer was subdivided into 3 subtypes, including oat-cell or lymphocyte-like type, intermediate type, and combined oat-cell type (combined with squamous cell carcinoma or adenocarcinoma) [14]. However, data of clinical trials and laboratory studies since have lead to the following new classification proposed by the International Association for the Study of Lung Cancer [15]: (1) *small cell carcinoma* for small cell carcinoma with no non-small cell carcinoma elements; (2) *small cell/large cell carcinoma* for small cell carcinoma with a subpopulation of cells resembling large cell carcinoma; and (3) *combined small cell carcinoma* for small cell carcinoma with elements of squamous cell carcinoma or adenocarcinoma. While some retrospective studies have demonstrated prognostic differences of these subgroups [16–18], the value of the proposed classification still awaits examination in prospective trials.

Some authors have identified a tumor type which is both clinically and histologically distinct from carcinoid tumor and small cell carcinoma. This has been variously named 'well-differentiated neuroendocrine carcinoma' [19], 'atypical carcinoid' [20], or 'Kulchitzky type carcinoma' [21]. Studies are underway to determine whether there are differences in survival between patients with atypical carcinoid and small cell carcinoma, as suggested by some studies where patients who were long-term survivors of small cell lung cancer had well differentiated neuroendocrine carcinoma [22,23].

5. Investigational staging procedures

A number of procedures have been and are being examined in the disease evaluation of small cell lung cancer. The use of nuclear magnetic resonance in conventional staging and the use of PET scan for the detection of brain metastasis are under investigation. Small cell lung cancer cells produce several biomarkers, including hormones such as ACTH, calcitonin, ADH, gastrin-releasing peptide and neurophysins, enzymes such as creatine kinase (BB isoenzyme) and neuron-specific enolase, or tumor antigens such as carcinoembryonic antigens [7,24]. Up to now, determination of these serum markers remains an investigational procedure. Several techniques have been shown to detect definite or probable bone marrow metastasis in patients with no evidence of marrow involvement by conventional aspirate and biopsies. These include culture techniques [25], discontinuous gradient sedimentation [26], monoclonal antibody staining [27], and most recently nuclear magnetic resonance of bone marrow [28]. While these findings might have implications for investigations using autologous bone marrow support, their impact on the prognosis of small cell lung cancer remains to be determined.

7. Prognostic factors

Anatomical extent of disease (T and N status in surgical series, limited versus extensive disease, number of anatomic sites involved), performance status, weight loss, and sex have been shown to influence prognosis [1,3,7,9,29–33]. More recently multivariate analysis on large prospective sets of data have disclosed that determination of simple biochemical pretreatment values as albumin, LDH or alkaline phosphatase allow to identify prognostic subgroups of patients [4,34–37]. The prognostic influence of the biochemical variables needs further confirmation, but it is already clear that some of these variables will be useful for stratification of patients in phase III studies or for the selection of patients in phase II studies.

8. Areas of future investigation

The revised TNM staging system should be used prospectively to examine its utility in small cell lung cancer, especially in studies on patients with limited disease who are evaluated by chest CT scans. Findings on chest CT scans in patients undergoing surgery after chemotherapy should be correlated with histological data in order to learn more about sensitivity and specificity of chest CT at restaging. Further information about changes in morphology and biological characteristics under treatment could also be obtained in this way. CT scans of the abdomen should be examined for the location of metastasis to determine whether a CT of the whole abdomen is required for work-up or whether a CT of the 'upper abdomen' which includes the liver and adrenals is sufficient. The impact and importance of conventional staging techniques on patient care outside and within a clinical trial setting should be continuously examined. Prospective investigations are needed to learn how best to include biochemical factors into the current practice of the clinical work up. Investigational staging techniques resulting in the detection of metastases not seen by conventional techniques need to be examined for their impact on clinical management and prognosis.

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