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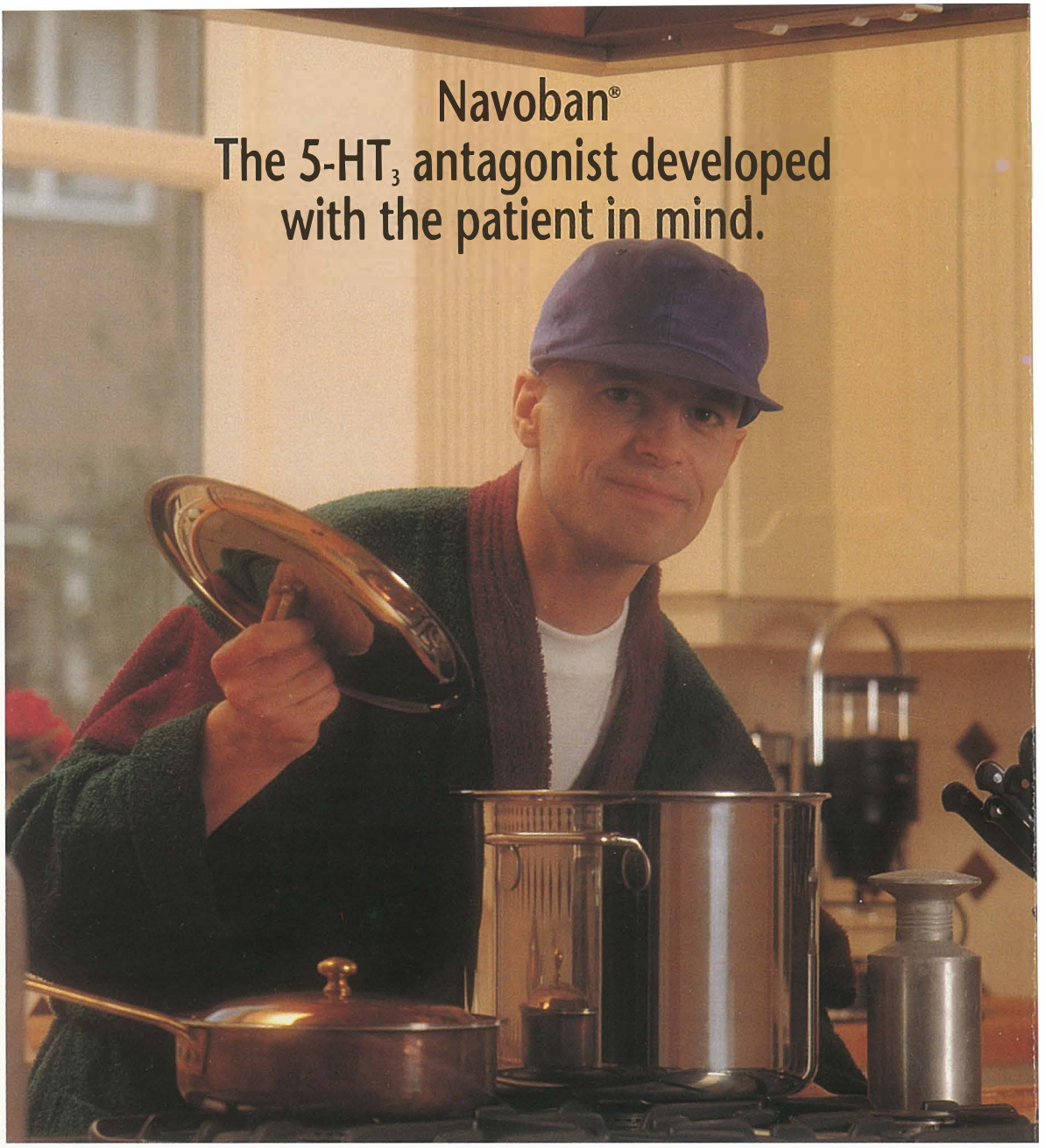

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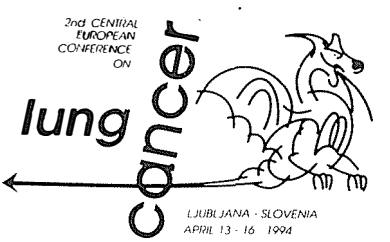
LUNG CANCER
BIOLOGY AND CLINICAL ASPECTS

13-16 April 1994

LJUBLJANA -SLOVENIA



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CONTENTS

PROGNOSTIC FACTORS, DIAGNOSTIC METHODS AND IMAGING OF LUNG CANCER

SURGICAL AND LASER TREATMENT OF LUNG CANCER

RADIATION THERAPY OF LUNG CANCER

CHEMOTHERAPY AND IMMUNOTHERAPY OF LUNG CANCER

TREATMENT OF PULMONARY AND BRAIN METASTASIS

RECOMMENDATIONS

The papers were presented at the 2nd Central European Conference on Lung Cancer; Ljubljana – Slovenia, April 13–16, 1994.

Radiol Oncol 1994; 28: 257-60.

Second Central European Conference on Lung Cancer Biology and Clinical Aspects, 13–16 April 1994 Address of the Chairman of the Organizing Committee at the Opening Ceremony

Your Excellency Mr. President of Slovenia, Mr. Minister, Mr. Mayor, Members of the Honorary Committee, Members of the International Scientific Committee, Invited Lecturers, Colleagues and Guests, Ladies and Gentlemen

More than a year and a half has passed since Professor Karl Karrer from Vienna, a long-standing, respected friend of the Department of Thoracic Surgery in Ljubljana, and coordinator of an international collaborative study on small cell lung cancer, surprised us with a letter offering our Department the organization of the 2nd European Conference on Lung Cancer. He had recommended Ljubljana as the venue for the Conference to Professor Heine H. Hansen from Copenhagen, Executive Director of the International Association for the Study of Lung Cancer. We accepted Professor Karrer's offer with pleasure, regarding it as an honour, acknowledgement of our work and a challenge to our professional and organizational skills. At the same time, we were aware of our responsibility to the national and European scientific communities as well as to Professor Hansen, who had entrusted us with this task after the very successful First Central European Conference, held in Prague in 1992.

I would like to express our gratitude to Professor Hansen, who thanks to his understanding of the situation in this part of Europe, managed to persuade the IASLC Board of Directors to award the organization of the Second Conference to Ljubljana. Considering the completely altered geopolitical circumstances in this area, the general unfamiliarity of a large part of Europe and the greater part of the world with the conditions in Slovenia, which had only recently acquired its independence, and in view of the tragic war raging in close proximity, this must have been a difficult or even hazardous decision.

After the final selection of Ljubljana as the venue, the Slovenian Surgical Association, the Slovenian Respiratory Society and the Slovenian Cancerologic Association, all members of the Slovenian Medical Society, joined forces, knowledge and experience in preparations for our present meeting. We hope that this building, named after Slovenian greatest writer Ivan Cankar, will provide the necessary technical back-up and a pleasant setting for both the scientific and social parts of our program, and we apologize in advance for any inconveniences. Please bear in mind that each member of the Organizing Committee has treated many patients in his professional career, but has rarely participated in the organization of such an important gathering. We all undertook this task as amateurs, with a lot of enthusiasm but little experience.

The organizers were aware that the professional impact and scientific value of meetings like ours is determined largely by the standard of the invited lectures. Therefore, invitations were sent out to a suitable number of renowned

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European experts in different medical specialties, involved in the study, detection and treatment of lung cancer, most of whom kindly agreed to participate.

Our program thus features 29 invited lectures, to be presented by 23 speakers from 11 European countries, which should outline the state of the art in the field and present the speakers' rich experience and latest scientific achievements.

In addition, the program includes 61 free papers and 22 posters prepared by 265 authors from 23 countries, even from distant Japan. They are meant to provide the authors with an opportunity to present the methods and results of clinical work and research being carried out by their institutions and teams. In the program these contributions have been grouped as logically as possible according to topics and professional fields.

In preparing this Conference the Organizing Committe was guided by several aims. The main aim of the Conference is to provide a comprehensive survey of the scientific and clinical work being done in Europe in connection with lung cancer. We tried to achieve this by including in the announcements a fairly large selection of tentative topics. Since most of them attracted considerable interest, the number of topics to be discussed exceeds the number of Conference sessions, and so most sessions will be devoted to more than one topic. We hope that this will add variety to the program, rather than make it confusing.

It is the organizers' wish that the time allocated for each session would not be spent only listening to the presentations or reading silently the posters, but also in animated discussion and confrontation of views. Let us show that European medical scentists are a group of open-minded individuals, capable of critical thinking and ready to accept contrary opinions.

We also hope to give the participants opportunity to become familiar with the Slovenian medicine, its efforts and victories in the battle with lung cancer. The Slovenian medical profession has always tried to keep abreast of the progressive trends in Europe. The results of our work will be presented for your ciritical evaluation. We believe that only international comparison can reveal the true value of professional work.

Aside from the professional goals, it is our sincere wish to show the participants and guests our country and its capital Ljubljana. Many of you have crossed for the first time the borders of this land, which after centuries of unfulfilled dreams, finally rejoices in its recently acquired independence. The independent Slovenia is making every effort to join the current European trends of integration, not only in the spheres of politics and economy but – what is mainly the desire of us, professionals – also in the spheres of science and education. Probably, many of you looked for this country on the map of present-day Europe and found a small dot indicating Ljubljana. Our aim was achieved in part already by the fact that you located us on your map and decided to come. We want you to feel comfortable in our city, to enjoy its attractions and assign it in your mind a proper place in Europe. We also hope that you can spare the time to visit our countryside. We will be happy to show you around and help you in every possible way.

The ultimate goal of our efforts is, however, to enable the participants to get to know each other better, to exchange views, identify common problems, wishes and aims, to make new friends and draw up many plans for future international professional and scientific collaboration. Our social program should be of help in this respect.

Members of the Organizing Committee fully realize that good will and effort alone cannot guarantee success. The goals set can be reached only with your help and cooperation. The Conference Secretariat and staff of this Center will be continuously at your disposal to help you with any problem you may have during your stay.

This Conference would not have been possible without the organizational support, material help and useful advice contributed by a number of institutions, companies and individuals.

On behalf of the Organizing Committee, I

extend our respect and gratitude to Mr. Milan Kučan, President of the Republic of Slovenia, who granted us the honour of assuming the high patronage over this Conference, thereby acknowledging the national and international significance of our meeting and underlining its institutional validity.

Among our official sponsors, Dr. Rado Bohinc, Minister of Science and Technology, and Dr. Božidar Voljč, Minister of Health, deserve out thanks for serving on the Honorary Committee and sponsoring the Conference.

Our thanks are also due to Mr. Jože Strgar, Mayor of Ljubljana, who has shown a very friendly disposition towards the Conference and is hosting a reception for the participants at our historic Town Hall. Valuable technical support and material assistance was received from Professor Primož Rode, General Director of the University Medical Center Ljubljana, who thereby confirmed the traditional willingness of our university hospital to participate in prestigious medical events.

We are further indebted to Professor A. Dolenc, President of the Slovenian Medical Society, Professor Mitja Bartenjev, Dean of the Faculty of Medicine in Ljubljana, Dr. Matjaž Zwitter, Director of the Institute of Oncology in Ljubljana, and to numerous other unnamed individuals for valuable advice and other forms of support.

As I mentioned initially, this Conference would not have been possible without the patronage and financial support of IASLC. Therefore let me express again our most sincere thanks to Professor Heine Hansen, Executive Director, who unfortunately cannot be with us today because of other obligations.

In dispatching the announcements and materials we were assisted by collaborating societies: the Croatian Pneumologic Society, the Austrian Cancer Society, the Austrian Society of Hematology and Oncology, the ICS-Lung Cancer Study Group and the EORTC Lung Cancer Cooperative Group.

The greatest part of the funds were contributed by our general sponsor, the Krka Pharmaceutical Company, Novo Mesto, Slovenia, for which I extend our sincerest gratitude to the General Director, Mr. Miloš Kovačič, and his co-workers.

I also wish to thank all our other sponsors for their generous support to the scientific and social parts of our Conference. Their names are listed in the Program, indicating the events that each helped to finance.

Physicians and surgeons are generally realistic, skeptical and pragmatic professionals. This is why we feel an irresistible need for the beautiful, irrational and agreeable – for art. Therefore a special effort was made to weave into our program some music, which should enliven our sessions and provide a pleasant ending to the Conference days. I wish to thank all singers and musicians, participating in the musical program and Mr. Janez Pirnat for the artistic prints dedicated to active participants.

Our Conference would run like a poorly oiled machine without the professional assistance of the technical and secretarial staff of this Center. Let me thank these competent, agreeable people, who are here to protect us from many undue excitement and sleepless nights.

Last but not least, I owe my thanks to my co-workers, members of the Organizing Committee, who in addition to their professional duties, found the time to help with the organization of this Conference. Can you imagine the constant ringing of our telephones, buzzing of the fax machine, mail coming in daily, the countless people to be seen and meetings held. For more than a year, without material reward, all members of the Organizing Committee sacrificed their mental and physical energy with a single aim, that the Conference would justify the trust placed in them. I would like to express my sincere personal gratitude for their dedication.

Let me conclude with a few thoughts that are uppermost in my mind on this solemn occassion. Lung cancer is a devastating disease that is still on the rise. Few patients can be saved, in most we are forced to admit our limited abilities and content ourselves with a partial or temporary success. Yet, the growing knowledge

and understanding of this disease promises a better future to our patients. Lost battles do not mean a lost war. Generally, people at last manage to overcome any difficulty by augmenting the knowledge of natural processes and living in harmony rather than in conflict with nature. An individual means little in this battle, but all of us together make a powerful army marching towards a common goal, which can be achieved only through mutual understanding and scientific communication. The Tower of Babel could not be erected because God confused the builders' tongues. However, we have learned to understand each other's language and to appreciate the importance of communication. There never really were any personal or ideological obstacles to our mutual understanding. The barriers that used to exist were imposed by others. They could be overcome only through intellectual contacts and through the written word, which was subject to strict control. Now that the walls and barbed wire fences are no longer there, we can look into each other's eyes, shake hands and meet anywhere in Europe, from the Atlantic Ocean to the Ural Mountains, from the North Sea to the Mediterranean.

Therefore I bid a cheerful welcome to all of you, regardless of your origins. We are all passengers on the same boat, bound by faith in the same truth, the valute of honest work and commitment to the love of humanity. There is light on the horizon, we are right on course, welcome aboard, and thank you for coming.

Janez J. Orel, Chairman

Radiol Oncol 1994; 28: 261-5.

Histogenesis of carcinoma of the lung

Bryan Corrin

Brompton Hospital, London, United Kingdom

A hyperplasia – dysplasia – neoplasia sequence is well documented in the lungs. The premalignant changes are widespread and there is a high incidence of double or second lung cancers: 4% synchronous and 6% metachronous. The patients most at risk of developing lung cancer are those who have had one in the past. These patients might therefore be worth following up particularly frequently.

Lung cancer fulfils many of the criteria necessary for a successful screening programme. Unfortunately the premalignant changes cannot be easily eradicated: there is no bronchopulmonary equivalent of a uterine cone biopsy and screening for early invasive growths has not been shown to reduce mortality.

The hyperplasia – dysplasia – neoplasia sequence is again encountered in the periphery of the lung, particularly when there is diffuse pulmonary fibrosis. In this condition there is often hyperplasia of type II cells, sometimes accompanied by extension of bronchiolar epithelium into adjacent alveoli, squamous metaplasia and dysplasia. The tumours that develop in pulmonary fibrosis may be of any type but adenocarcinoma is particularly well represented.

Premalignant changes leading to the development of small cell carcinoma are not well recognised. Hyperplasia of bronchopulmonary neuroendocrine cells is described, sometimes in association with neuroendocrine neoplasms, which on occasion may be multifocal, but the neoplasms concerned are carcinoid tumours rather than small cell carcinomas.

Key words: lung neoplasma; precancerous conditions; hyperplasia

Introduction

The common histological types of lung carcinoma arise from the epithelial cells lining the bronchi, bronchioli and alveoli. A small minority closely resemble various types of salivary gland tumour and are thought to arise from the submucosal bronchial glands.

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Bronchoalveolar epithelial cells

Apart from the rare brush cells, bronchial surface epithelium consists of four cell types: basal, neuroendocrine, ciliated and mucous cells. Only ciliated cells appear to be terminally defferentiated; the other three cell types are capable of division and thus have malignant potential. Bronchiolar Clara cells and alveolar type II cells also have stem cell properties and are found in some adenocarcinomas of the lung.

Histogenesis of central lung tumours

Proliferation and metaplasia

Proliferation of bronchial epithelial cells has been extensively studied in various experimental models, including mechanical damage, chemical damage and vitamin A deficiency. Proliferation of both basal and mucous cells has been reported as the first response to mechanical or chemical damage.[1-4] Early in the healing process there is hyperplasia of small basally located cells reminiscent of basal cell hyperplasia of the endocervix. This may be followed by loss of the overlying ciliated epithelium and flattening of the new surface layer of cells. Small mucin droplets can be demonstrated in many of the metaplastic cells, and it is suggested that these "small mucous granule cells" are important in the histogenesis of many lung cancers.[4] Frank squamous metaplasia is often seen in the repair process. Squamous metaplasia of bronchial neuroendocrine cells has also been elicited experimentally.[5] It is clear that basal, mucous, neuroendocrine and metaplastic squamous cells within the bronchial epithelium are closely related, and that transformation of one to another is common. Because of the marked metaplastic potential of epithelial cells of the lower respiratory tract, it would not be correct to assume that similarities in phenotype between a particular type of lung carcinoma and one of the normal bronchial epithelial cells prove that the tumour has arisen from that particular cell type.[4]

Atypia and dysplasia

A hyperplasia – dysplasia – carcinoma in situ – invasive carcinoma sequence is well documented in the airways.[6,7] Uranium miners in the USA provided Saccomanno and his colleagues with the opportunity of studying the gradual evolution of bronchial carcinoma. By periodic cytological examination of sputum, they were able to detect squamous metaplasia and gradually increasing cellular atypia in those miners who later developed invasive carcinoma of either squamous or small cell type. Atypical cells could be identified in the sputum for four to five years prior to the development of invasive tumours.[6] Similar evidence derived from a large autopsy study in which the whole bronchial tree was examined in a series of patients dying of lung cancer.[8] This showed widespread premalignant changes involving mucosa that appeared normal macroscopically, including foci of carcinoma-in-situ and occasional microinvasive cancers distant from the main tumour. Focal hyperplasia, metaplasia and dysplasia are frequently seen adjacent to invasive tumours[9] and occasionally full thickness dysplasia and frank carcinoma in situ are observed. Similar changes have also been described in experimental dogs exposed to cigarette smoke.[10, 11] Full thickness squamous metaplasia is not necessary before atypical features are seen in the proliferating basal cells and dysplasia may be present beneath an intact surface layer of columnar cells.[8] The transition from normal bronchial epithelim to squamous epithelium is usually abrupt. Atypical epithelium may extend deeply into bronchial glands replacing duct and acinar lining cells. That squamous metaplasia is truly premalignant is supported by the demonstration of genetic abnormalities similar to those found in adjacent invasive cancer.[12]

Development of neuroendocrine neoplasms

Apart from Saccomono's studies described above, premalignant changes leading to the development of small cell carcinoma are not well recognised. Hyperplasia of bronchopulmonary neuroendocrine cells is described, sometimes in association with neuroendocrine neoplasms, which on occasion may be multifocal, but the neoplasms concerned are carcinoid tumours rather than small cell carcinomas.[13–15] Carcinoid tumours do not progress to small cell carcinoma.

Double primary cancers

In view of the extent of these premalignant changes, it is not surprising that there is a high

incidence of double or second lung cancers. Using standard criteria of a double primary growth – involvement of different lobes, or different histological types, or a time interval over three years – it has been shown that 4% of lung cancer patients have more than one lung tumour at presentation and that a further 6% develop a second primary lung growth later.[16] The patients most at risk of developing lung cancer are therefore those who have had one in the past. These patients might therefore be worth following up particularly frequently.

Histogenesis of peripheral lung tumours

The hyperplasia – dysplasia – neoplasia sequence is again encountered in the periphery of the lung, particularly when there is diffuse pulmonary fibrosis.[17–20] In this condition there is often hyperplasia of type II alveolar epithelial cells, sometimes accompanied by extension of bronchiolar epithelium into adjacent alveoli and occasionally by squamous metaplasia and dysplasia. The tumours that develop in pulmonary fibrosis may be of any histological type but there is a disproportionately large number of adenocarcinomas, especially bronchiolo-alveolar carcinomas.[21–22] Atypical alveolar cell hyperplasia is also reported as a focal premalignant change accompanying carcinoma in lungs which are not affected by fibrosis.[23–25] Sometimes multiple foci of alveolar cell proliferation are evident naked eye; these have been described as bronchioloalveolar cell adenomas and an analogy drawn with the development of colonic adenocarcinoma from multiple adenomas.[26–27] The micronodular hyperplasia of type II pneumocytes reported in tuberous sclerosis[28–29] is not recognised as having any premalignant potential. Congenital lung cysts have a low but appreciable malignant potential.[30]

Some adenocarcinomas show pronounced pleural puckering and central scarring and it is often assumed that such tumours represent scar cancers, with the implication that the scar preceded and predisposed to the cancer. However, the amount of stroma formed within an adenocarcinoma may be considerable and it is often impossible to tell whether a tumour has developed in a pre-existing scar, and can therefore be designated a true scar cancer, or whether the central scar is secondary to the tumour.[22] Only in the rare cases in which there is clinical or histological proof of a pre-existing lesion which has induced pulmonary scarring, can the tumour be designated a scar cancer with confidence. In many cases, elastin stains show that the central scar is formed on an area of collapse consequent upon airway or arterial obstruction by the tumour.[31–32] Other reasons for believing that central scars are usually a product of the tumour rather than the reverse include: (1) the scar is not usually evident in previous radiographs, (2) the size of the scar generally matches that of the tumour, (3) similar scars develop in extrapulmonary metastases, (4) similar scars are found in the pulmonary metastases of other adenocarcinomas, (5) psammoma bodies derived form the carcinoma may be found deep within the central scar, and (6) the scars often show a predominance of myofibroblasts and type III collagen.[33–35]

Lung cancer fulfils many of the criteria necessary for a successful screening programme: the condition is common, the population at risk is well known and premalignant changes can be detected cheaply (by sputum cytology). Unfortunately the premalignant changes cannot be easily eradicated, or indeed localised: there is no bronchopulmonary equivalent of a uterine cone biopsy. Nor does screening for early invasive growths by a combination of sputum cytology and radiography appear to reduce mortality.[36–38]

Conclusions

Changes preceding the emergence of squamous cell carcinoma are frequently observed in the lung.

Metaplasia accompanying widespread pulmonary fibrosis has malignant potential but scar cancer is generally over-diagnosed.

Few changes are recognised to precede small cell carcinoma.

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Possibilities and limitations of cytology in the diagnosis of lung tumors

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The possibilities and limitations of pulmonary cytology are presented. In a two-year period, 744 primary lung carcinomas were diagnosed. In 96.5 % of patients any kind of material was cytologically examined. The sensitivity of cytology was 92.0 % and the predictive value of positive cytologic finding was 99.7 %. The most frequently bronchoscopically obtained material (BOM), which gives the highest rate of positivity was examined. In 56.4 % of patients lung cancer was microscopically verified only by cytology. In 65.7 % of histologically and cytologically diagnosed lung cancers cytologically determined type agreed with the histological typing. The main advantages of pulmonary cytology could be expressed as follows: the method is minimally invasive, inexpensive, rapid, safe and reliable. Yet, in some cases the nature of the material prevents additional stainings or immunocytochemistry and therefore in nonepithelial and poorly differentiated tumors the results are less satisfactory.

Key words: lung neoplasms; cytodiagnosis

Introduction

Over the last decades the use of cytology in the diagnosis of lung cancer has gained in its frequency and importance.[1] In its development, pulmonary cytology is going hand in hand with technical advances, such as fiberoptic bronchoscopy and transthoracic needle aspiration biopsy (TNAB) performed under X-ray or computed tomography guidance. At the same time pulmonary cytology has also been following modern trends in material processing. Standard cytologic staining methods such as May-Grünwald-Giemsa and Papanicolaou have been accomplished by immunocytochemistry, electron microscopy, flow cytometry and image analysis.

With the improvement of diagnostic and therapeutic regimens for the treatment of lung cancer, precise diagnoses have become very important. In the evaluation of cytology two important questions arise. First, to what extent is the method capable of detecting the presence of malignant cells, and second, to what extent it can determine the histologic type of cancer[2], or at least to what extent small-cell carcinomas could be cytologically distinguished from non-small-cell lung cancers.

To establish the real possibilities and limitations of pulmonary cytology, the diagnostic

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sensitivity and tumor typing accuracy were analysed in all patients with primary lung cancer diagnosed in two-year period.

Material and methods

In patients with primary lung cancer diagnosed during the years 1990 and 1992, the data on cytologically examined patients, materials, efficiency of examinations of different materials, sensitivity of cytology and predictive value of positive cytologic findings have been retrospectively analysed. Also the data on the efficiency, expedience and cost-effectiveness of the examination of different materials have been evaluated. The agreement between cytological and histological typing of lung cancer has been assessed as well.

Cytologically, several materials were examined: sputum, bronchoscopically obtained material (BOM), TNAB, pleural effusions and aspiration biopsies of metastatic lesions. In BOM the imprints of bronchial and transbronchial forceps biopsy specimens, brushings, perbronchial aspiration biopsies and bronchoalveolar lavage were included. Material obtained by TNAB may originate from the lungs or mediastinal lesions.

In BOM the cytological examination is performed first. If cytology of imprints is positive and the type of carcinoma is clearly determined, the histology of forceps biopsy specimens is usually not performed. The exceptions are small cell lung cancers which are in most cases histologically verified as well.

Most of the cytological smears are stained by the May-Grünwald-Giemsa method. If the material is appropriate, some smears are stained according to Papanicolaou. If cancer cannot be typed on the basis of cell morphology, the smears stained by Papanicolaou are used for appropriate immunocytochemical staining.

The results of cytology were recorded as positive, suspicious or negative. The type of primary lung cancer was in most cases determined on the basis of the morphology of malignant cells. In patients with both cytologically and histologically verified lung cancer, the accuracy of cytologic typing was compared with histologically established diagnosis. The results of cytological typing were classified into three groups: 1) both typings were in agreement, 2) typings were only partly in agreement, 3) typings were not in agreement. In the first group those cases were included in which the type was cytologically clearly defined and was in agreement with histologically determined type.

The second group comprised the cases in which the type had not been definitively cytologically determined. For example, we noted that the cells probably belonged either to squamous cell carcinoma, small-cell or adenocarcinoma. In this group also those cases were included which had been cytologically classified as large-cell carcinoma, while histologically they were classified as squamous cell carcinoma or adenocarcinoma.

In the third group there were the cases in which the type was cytologically definitively determined however, later histology proved the diagnosis to be incorrect.

Results

In the years 1990 and 1992, 744 primary pulmonary carcinomas were diagnosed at our Institute. Any type of material was cytologically examined in 96.5% of patients. Cytological findings were positive in 661 patients (Table 1). In two patients cytological findings were false positive. From these data it was concluded that the sensitivity of cytological examination was 92.0% and the predictive value of positive cytologic finding was 99.7%.

Table 1. Cytology in patients with lung cancer: examinations and results.

Patients	N
Without cytology	26
Cytologically examined	718
– positive	661
– suspicious	18
– negative	39
All patients	744

BOM was examined in most patients with lung cancer. The examination of this material yielded the highest rate of positivity (86.6%) (Figure 1). TNAB was examined in 9.3% of

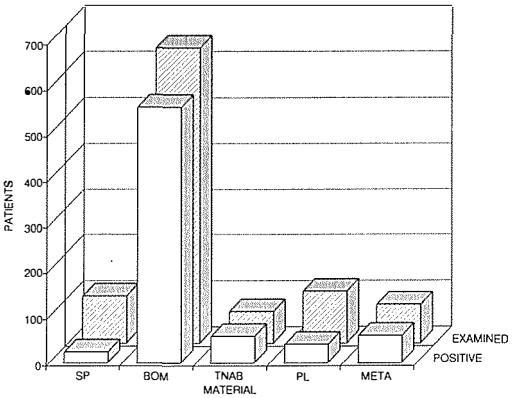

Figure 1. Frequency and efficiency of cytology of several materials. SP = sputum; BOM = bronchoscopically obtained material; TNAB = transthoracic needle aspiration biopsy; PL = pleural effusion; META = metastatic lesions.

patients, its sensitivity being 82.6%. Rather poor positive results were obtained by the examination of sputum (22.5%) and pleural effusions (34.8%).

In most patients malignant cells were found only in one type of material. For example, in both BOM and sputum malignant cells were found in six patients only while in BOM and TNAB they were found in seven patients only.

In more than half of the patients the cancer was microscopically verified by cytology only (Figure 2). In nearly one third of cases cancer was verified both histologically and cytologically, while in 2.4% it was confirmed only histologically. In 9.7% of the patients cancer was not microscopically verified. Also, in most of the surgically treated patients, lung cancer was preoperatively microscopically verified only by cytology (Table 2).

Table 2. Microscopic verification of lung cancer before surgery.

Verification	N
Cytology only	93
Cytology and histology	17
Histology only	3
Unverified	2
All patients	115

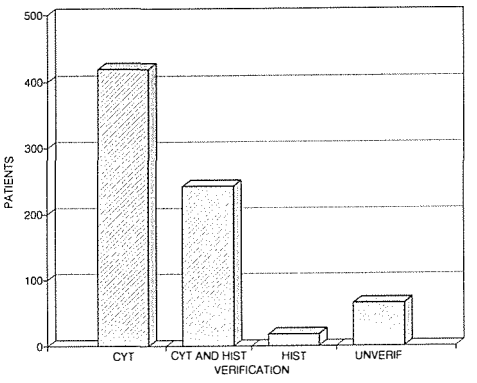

Figure 2. Microscopic verification of lung cancer. N = 774. CYT = only cytologically verified; CYT and HIST = cytologically and histologically verified; HIST – only histologically verified; UNVERIF = without microscopic verification.

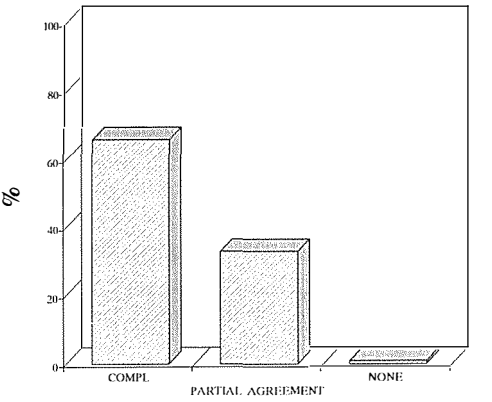

Figure 3. Agreement of cytological and histological typing. N = 242. COMPL = both typings are in full agreement; PARTLY = both typings are in partial agreement; NONE = histological and cytological typings are in disagreement.

The efficiency of cytological typing was assessed in 242 patients (Figure 3) in whom cancer was verified both cytologically and histologically. In 65.7% of cases the cytologic and histologic typings were in full agreement, in 33.1% of cases the typings were only in partial agreement, while in 1.2% of patients the cytological typing of carcinoma was incorrect.

Table 3. Agreement of cytological typing with histology in different types of lung cancer.

Type	Number of patients	Correctly typed	
		N	%
Squamous	52	37	71.2
Small cell anaplastic	91	70	76.9
Adenocarcinoma	51	24	47.1
Large cell	32	19	59.4
All patients	226	150	66.4

Cytological typing was most successful in small-cell lung cancer where cytologically determined type was in agreement with histologically determined type in 76.9% of cases, and in squamous cell carcinoma where the typings were in agreement in 71.2% of cases. Less successful was cytological typing in adenocarcinoma and large cell carcinoma where the typings were in agreement only in 47.1% and 59.4% of cases, respectively (Table 3).

Discussion

Among the methods available for the diagnostics of lung cancer, cytology plays a very important role. Different materials for cytological examinations are available. However, each type of material has some advantages as well as drawbacks. For example, the examinations of sputum yield the diagnostic sensitivity of 85% or more when three or more sufficient samples are examined.[3] However, the examinations of sputum are rather time-consuming; besides, positive sputum cytology does not provide information on the extent and localisation of tumor. Therefore, in the past years sputum is examined only in patients in whom for various reasons a more aggressive method of sample taking is not indicated.

Recently, examinations of BOM have been performed in most patients suspected of having lung cancer. Since the sensitivity of BOM cytology is high, most lung cancers are proven by this examination. By bronchoscopy, different kinds of material for cytology may be obtained. The diagnostic sensitivity of different types of BOM was not analysed in our material. Better results are usually obtained by the examination of imprints than by brushings. The results of imprint cytology are also better than those of histological examination of forceps biopsy specimens.[4] The sensitivity of BOM cytology is higher in central than in periphery tumors.[5]

TNAB is generally indicated for the diagnosis of nodules, masses or infiltrates that are not accessible by a bronchoscope. It provides a quick and accurate diagnosis. If performed in an early phase of diagnostic workup, it can save many other laboratory tests and examinations.[6] It is also a reliable method for reducing the need for diagnostic thoracotomy.[7] At our Institute it is performed in 9.3% of patients with lung cancer. The diagnostic sensitivity of these examinations is usually high.[8] In most cases the examinations are more efficient in pulmonary than in mediastinal lesions.[9] In the mediastinum tumors of nonepithelial origin are rather frequent and their identification requires additional immunochemical stainings.

Malignant pleural effusion is a sign of inoperability of lung cancer. So the cytology of pleural effusion is important not only for the diagnosis but also for the staging of disease. However, the cytology of pleural effusion is complicated since in many cases, even in patients with lung cancer, the effusion is not due to a direct pleural involvement[10] but may also be caused by a lymphatic or venous obstruction, endobronchial obstruction with atelectasis, postobstructive pneumonitis and severe hypoproteinemia.[11] In cases where the pleura is not involved, malignant cells will not be found in the effusion. Even if there are few malignant cells in the effusion or effusion is very hemorrhagic, malignant cells may not be present in the examined sample. Therefore it is difficult to establish the real diagnostic sensitivity of cytology of pleural effusion. Direct involvement of the pleura might be established only on autopsy, thoracotomy or thoracoscopy, but these are performed in a rather small number of patients with pleural effusion.

However, in cytological examinations it is not enough to find malignant cells only. The type of primary lung cancer should also be determined or at least small-cell carcinomas

should be differentiated from non-small-cell carcinomas. Undoubtedly, the histological typing is more reliable than the cytological one. Yet, many a sample from the lung is suitable for cytologic examination only. In routine, cytological examinations are quick and inexpensive. Therefore, at our Institute in more than half of the patients with lung cancer the preoperative microscopic diagnosis and typing of tumor are based on cytological finding only (Figure 2).

The reliability of cytological typing may be improved if immunochemistry is applied in addition to standard stainings. Yet, some cytological samples do not contain enough material or it is of poor quality for additional stainings. Therefore, cytologic diagnostics and typing are based mostly on the examination of routinely stained smears. Yet, in 65.7% of cases with cytologically and histologically verified lung cancer, the cytological typing was in full agreement with the histological type. Cytological typing was most efficient in small-cell and squamous-cell lung cancer. In prospective studies including a small number of patients, the results of cytological typing may be better[12, 13] than those indicated in our review.

Yet, it should be considered that our criteria were very strict. Those cases in whom the type had not been cytologically clearly defined were included into a separate group. It is known that cytological typing is less reliable in poorly differentiated non-small-cell lung cancers which are mostly typed as large-cell carcinomas or adenocarcinomas. It is also evident that cytologically, non-small-cell lung cancers are hardly ever falsely typed as small-cell cancers or vice versa.

According to our data it can be concluded that the basic advantages of pulmonary cytology are as follows: sample taking is relatively well tolerated by patients, the method is quick and cost effective, the yield of diagnostic sensitivity can reach up to 90% or even more, the rate of false positive results is under 1% and the accuracy of tumor typing exceeds 60%.

As to the disadvantages of pulmonary cytology, it should be mentioned that for good diagnostic results several materials should be examined. If the material was sputum, examinations should be repeated. The nature of the material often renders additional stainings impossible therefore particularly in nonepithelial and poorly differentiated tumors the results are not as good as it might be desired.

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p53 and lung cancer – more frequent p53 overexpression in patients with multiple primary tumours

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The tumor suppressor function of the gene p53 is abolished with its mutations, connected also with lifetime cigarette consumption, leading to growth promoting function of p53, and cancerogenesis in various organs. Seventeen resected primary lung cancers and 14 bronchial/transbronchial biopsy specimens were formalin-fixed and paraffin embedded. Fourteen specimens were from patients with multiple primary tumours. Sections were incubated with mouse anti-p53 antibodies, bound antibodies visualized by incubation with biotinilated rabbit anti-mouse immunoglobulins, followed by streptavidin-alkaline phosphatase. Using X-phosphate and nitro-blue tetrazolium, positive staining is observed as a dark bluish precipitate. Overexpression of p53 was found in 45.2% of all cases, 50% in 14 specimens of patients with multiple, and in 7 of 17 (41.2%) specimens of patients with solitary tumours. Ten of 16 (62.5%) specimens with epidermoid carcinoma showed positive reaction, 2/6 adenocarcinomas, 1/2 small cell, 1/5 large cell, and none 0/2 adenosquamous carcinomas. Bioptic specimens yielded better results than resected specimens. This difference could be attributed to inappropriate fixation. Positive reaction for p53 is more prominent in the basal layers of squamous metaplastic and dysplastic epithelium, disappearing towards better differentiated areas. It can be intense in poorly differentiated parts of invasive carcinomas. Normal respiratory epithelium did not yield positive reaction. p53 is related to the degree of tumor differentiation. We have still to elucidate the relationship between smoking and p53 expression, and controversial opinions about its influence on the survival of the patients. The detection of p53 in routine bronchial/transbronchial biopsis could reveal the patients, especially smokers at higher risk for development of solitary or multiple primary malignancies.

Key words: lung neoplasms; genes, p53; multiple lung neoplasms

Introduction

Tumors arise and progress through a series of genetic changes in cancer-associated genes known as proto-oncogenes or tumor-supressor genes. Proto-oncogenes are normal cellular genes that, when inappropriately *activated* as oncogenes, cause dysregulation of growth and differentiation pathways, and enhance the probability of neoplastic transformation. In contrast, tumour-suppressor genes are normal cellular genes, which when *inactivated* lead to a

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disturbance of cell proliferation and the development of neoplasias.[1]

So far, the best known tumor-suppressor gene is the p53 gene, localized on the chromosome 17. This gene is thought to play an important role in the regulation of cell proliferation, and it has been suggested that the loss of normal p53 function is associated with cell immortalisation or transformation in vitro, and development of neoplasms in vivo in various organs (lung, breast, ovary, colon, thyroid gland, oral cavity, head and neck, some soft tissue tumours, etc). The alterations within the coding sequences of the p53 gene are among the most frequent genetic changes detected in human cancers. The p53 gene or gene product is a common cellular target in human carcinogenesis provoked by physical factors, chemical carcinogens or tumour viruses.[2]

In cells, wild-type p53 protein has a short half-life (5–20 min) and, thus, does not accumulate to detectable levels under normal conditions. Mutations in the p53 gene often result in the production of a protein with altered composition and a prolonged half-life. As a result, mutant p53 accumulates in tumour cells and can be detected immunohistochemically. Therefore, a visualisation of this protein usually means mutation, and detection of p53 overexpression by immunohistochemical techniques is currently widely used as an indirect indicator of p53 mutations.[3]

The aim of the study was to evaluate the appearance of the suppressor gene product p53 in hyperplastic, dysplastic lesions of the lung, and in various histologic types of lung cancer. This is an interim report of our experiences in looking for p53 overexpression in patients with lung cancer. Taking into consideration that p53 gene mutations may be a pathway through which environmental carcinogens (also associated with smoking) trigger lung cancer, we expect more frequent p53 overexpression in patients with multiple primary malignancies and a history of smoking.

Material and methods

Seventeen resected primary lung cancers and 14 bronchial/transbronchial biopsy specimens, 14 of these from patients with metachronous or synchronous multiple primary tumours of the lung or other sites, were formalin-fixed and paraffin embedded.

Dewaxed sections were rehydrated and treated with 0.05 % saponin in distilled water for 30 min at room temperature. Subsequently, the sections were incubated with mouse monoclonal anti-p53 antibodies (Ab-2, clone PAb 1801, Oncogene Science, Uniondale, NY, USA, in working dilution 1 : 2000) overnight at 4°C[9]). Bound antibodies were visualized by incubation with biotinilated rabbit anti-mouse immunoglobulins for 30 min at room temperature (dilution 1 : 200, Dako E 354, Dakopatts, Glostrup, Denmark), followed by streptavidin-alkaline phosphatase for another 30 min at room temperature (dilution 1 : 100, Dako D 396, Dakopatts, Glostrup, Denmark). Alkaline phosphatase activity was developed with the McGadey reagent (4-Nitro blue tetrazolium chloride and 5-Bromo-4-chloro-3-indolyl phosphate) containing 1mM levamisole for 30 min in the dark at room temperature. Positive staining was observed as a dark bluish precipitate. Section were counterstained with Mayer's hematoxylin and mounted in glyceryl gelatine.

The sections of laryngeal squamous carcinoma, which had been previously found to overexpress the p53 protein and which reacted with this antibody, were used as a positive control. Sequential sections of patient tissues incubated in buffer without the primary antibody served as negative controls.

Results

Overexpression of p53 was found in 45.2 % of all cases, 50 % in 14 specimens from the patients with multiple malignancies, and in 7 of 17 (41.2 %) specimens from the patients with solitary malignancies.

Ten of 16 (62.5 %) specimens with epidermoid carcinoma showed positive reaction of various intensity, however in only 2 of 6 adenocarcinomas (33.3 %), 1 of 2 small cell carcinomas, in only 1 of 5 (20 %) large cell carcinomas,

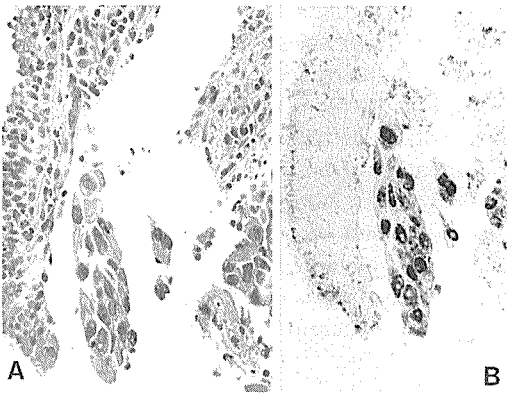

Figure 1. Bronchial biopsy. p53 overexpression in adenocarcinoma in the respiratory epithelium. A. hematoxylin-cosin staining. B. immunohistochemical demonstration of p53.

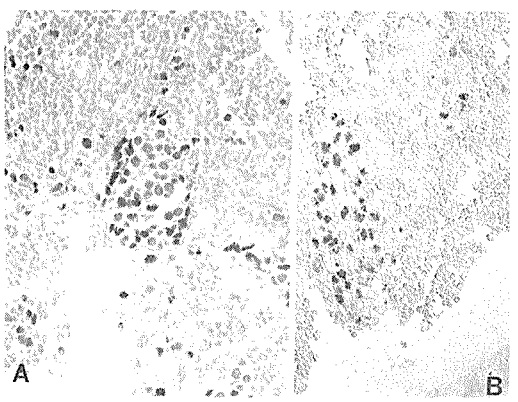

Figure 2. Bronchial biopsy. p53 overexpression in a cell group of small-cell carcinoma. A. hematoxylin-cosin staining. B. immunohistochemical demonstration of p53.

and in none of two adenosquamous carcinomas (Figures 1, 2). Bioptic specimens yielded better results (8/14, 57%) than resected specimens (6/17, 35.3%).

Positive reaction to p53 is more prominent in the basal layers of squamous metaplastic and dysplastic epithelium, dissapearing towards better differentiated areas (Figure 3). The expression of p53 was irregular in scattered or more numerous cells in the squamous epithelium: if present, there were only few p53 positive cells in squamous metaplastic respiratory epithelium,

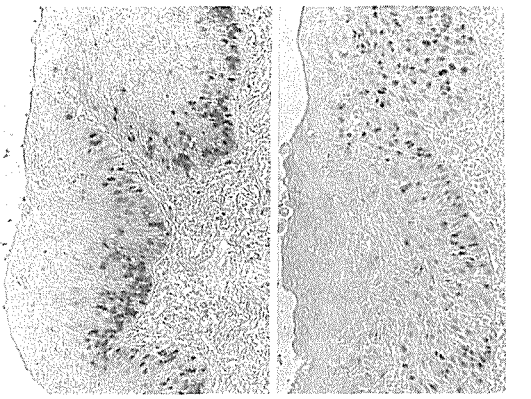

Figure 3. Lung lobe resection. More prominent p53 overexpression in the basal layers of squamous metaplastic and dysplastic epithelium, dissappearing in better differentiated areas.

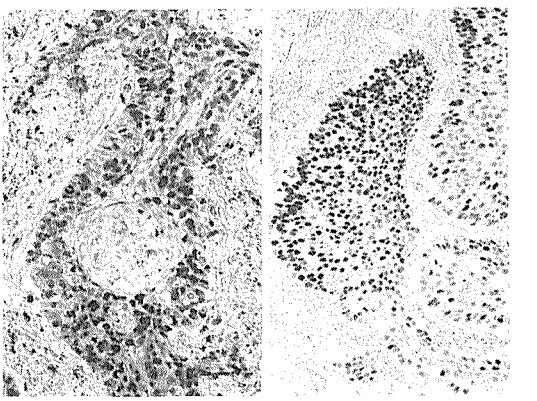

Figure 4. Intense p53 overexpression in the areas of invasive lung cancer.

some more in dysplastic epithelium and numerous in invasive carcinoma, especially in less differentiated areas (Figure 4). Normal respiratory epithelium did not yield positive reaction.

Discussion

It is now known that cancer is caused by a series of genetic changes, each potentially leading to a clonal outgrowth of cells through a selective growth advantage. The determination of the nature and timing of these changes is critical to both clinical and biological understanding of the disease.[1]

The frequency of p53 expression in our preliminary limited study is in accordance with the data from other reports (it is detected in 43–79.5 % of squamous carcinomas, in 33–52 % of adenocarcinomas, and in 20 % of small-cell carcinomas.[4-7] p53 is very probably related to the degree of tumor differentiation and grade[5], and p53 overexpression is high in cells predeterminated to differentiate and decreases upon differentiation.[8] It is present in premalignant lesions such as metaplastic and dysplastic bronchial epithelium, but not in normal respiratory epithelium.[7] There is a difference in p53 positivity in various histologic types, with best results in epidermoid carcinoma. The source of the material (biopsy, resection) is probably irrelevant for successful presentation of p53. The difference in our results could be attributed to unappropriate fixation.

Mouse anti-p53 monoclonal antibodies PAb 1801 have been reported to recognise an epitope detectable both in frozen and in formalin-fixed paraffin-embedded tissue sections.[9,10] This epitope, mapped near the amino terminus of the p53 protein between residues 32 and 79, is shared by the wild-type p53 and by almost all mutant forms so far described.[11] There have been, however, some pitfalls in the interpretation of the results of p53 immunohistochemistry described.[12,13] Negative immunostaining in the presence of a mutation might be the result of gross deletions or null-mutations abolishing all p53 production. Additional mechanisms, such as reduced half-life of p53 protein, mediated by a mutant endogenous protein, or a viral proteins such as human papilloma virus 16 or 18 E6, might contribute to the population of cells in which p53 is not detectable by this method. Positive p53 immunohistochemistry without a mutation present may be due to the interruption of the normal degradative pathway of p53. Despite possible discrepancies between the findings at the DNA level and at the protein level, we believe that p53 immunohistochemistry has value for monitoring the functional status of the p53 protein per se.

The tumor suppressor function of the gene p53, abolished with its mutations, is also associated with lifetime cigarette consumption.[14] It leads to growth promoting function of p53, as well as to carcinogenesis in various organs (lung, breast, colon, thyroid gland, oral cavity, some soft tissues etc). Thus it is important for the initiation of malignancies.

As expected, more frequent p53 presentation was also found in tumor specimens from patients with solitary or multiple tumours. But the number of cases is still to small for definite conclusions. Therefore, further study is under way.

The association of tobacco smoking with p53 expression suggests that the p53 gene is a target for specific mutagens in tobacco smoke.[5] Therefore, we still have to elucidate the relationship between smoking and p53 expression, and also explain the controversial opinions as to whether immunohistologic expression of p53, in any group of patients with lung tumors has really no influence on the patients' survival as believed by some authors,[4,6] or p53 mutations and accumulation in primary human lung cancers have a statistically significant negative prognostic value, as reported by the others.[15,16]

Conclusion

Taking into consideration the gradual increase in the p53 overexpression in metaplastic, dysplastic, and carcinomatous tissue, and even more frequent p53 overexpression in multiple primary tumours, the detection of p53 in routine bronchial/transbronchial biopsies could help to identify the patients, especially smokers, with a higher risk for the development of solitary or multiple primary malignancies. In future, p53 could also be considered as a potential target for anticancer drugs.[17]

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Biological behaviour of lung carcinoids
A retrospective analysis of 71 patients

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A retrospective study of 71 patients treated for lung carcinoids during the years 1973–1992 is presented. Beside clinical and pathological data, an inquiry was performed to establish the rates of recurrence of disease and survival of the patients, Lung carcinoids represented 0.6 % of all lung carcinomas. There were 37 male and 34 female patients with age range from 14 to 78 years, and an average age 47.5 years at the time of surgery. The highest incidence of carcinoids (38 patients, 53 %) appeared in the age group 41–60 years. In three patients (4 %), associated clinical syndromes were documented: one patient had typical carcinoid syndrome, while in two others Cushing's syndrome has developed. The most common lobectomy was performed in 45 patients (63 %). Sixty-six (93 %) carcinoids were located centrally, and 5 were peripheral. Histologically, 61 carcinoids (86 %) were evaluated as typical. Two carcinoids (3 %) were composed of spindle cells, 2 had oncocytic areas, and stromal ossification was found in 4 cases (6 %). Out of 64 patients, lymphnode metastases were found in only 3 cases (5 %), and distant metastases in one patient with a recurrent tumour. Nine patients (13 %) have died: 5 (7 %) because of atypical carcinoids and 4 because of other diseases. The second primary malignancy was detected in four patients (5.6 %). Forty-six out of 47 patients (98 %) have survived 5 years, 26/28 (93 %) 10 years, and 13/18 (72 %) have survived even 15 years. The prognosis was good in patients with typical carcinoids but much worse in those with atypical carcinoids; nevertheless, even in the latter, the death occured later than in other lung carcinomas.

Key words: lung neoplasms; carcinoid tumor

Introduction

Bronchopulmonary carcinoids are well differentiated, slowly growing malignant tumours of neuroendocrine origin, rarely metastasizing to the regional lymphnodes.[1, 2] They follow a relatively indolent clinical course for long periods and are therefore amenable to surgical resection. Lung carcinoids represent about 1 % of all long tumours,[3] with usual central localisation in the bronchi. The majority of bronchial carcinoids are without evident clinical syndromes.

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Their localisation leads to nonspecific symptoms such as recurrent cough, hemophthisis and respiratory infections. The tumours are resectable with advocated conservative surgical procedures and thus even curable. Late recurrences may develop. The reported 5- to 10-year survival rates are 80–95 %. The situation is worse with atypical carcinoids. The criteria for the diagnosis of such tumours (celullar and nuclear polymorphism, mitoses, necroses) were set out clearly by Arrigoni[4] and are still used. Because of more malignant behaviour, atypical carcinoids should be treated as truly malignant tumours.[5]

The aim of our study is to evaluatie the experience with our patients in comparison with the data published. This retrospective analysis of 71 patients with carcinoid tumours was performed to establish the incidence of lung carcinoids in Slovenia and to evaluate their clinical behaviour, pathological appearance, surgical treatment and survival data.

Material and methods

The case history records of 71 patients with bronchopulmonary carcinoids surgically treated during the years 1973–1992 were analysed retrospectively. Beside clinical and pathologic data, an inquiry was performed to establish the rate of recurrences of the disease and the survival of patients. Thus, the analysed data comprised symptoms and clinical features, patient age at the time of surgery, tumour size and localization, lymphnode involvement, metastases to distant organs, treatment and survival. The histological diagnosis was based on sections routinely stained with hematoxylin and eosin, and, in recent years, with neuroendocrine markers (neurone specific enolase, chromogranin A, synaptophysin). The original histologic slides were reexamined. Four cases were studied by electron microscopy.

Results

The study group comprised 71 patients. Lung carcinoids represented 0.6 % of all lung carcinomas. There were 37 (52 %) male and 34 (48 %) female patients, in the age range from 14 to 78 years. Their mean age was 47.5 years at the time of surgery; 45.7 years for males, 49.4 years for females. The highest incidence of carcinoids – 38 patients (53 %) – appeared in the age period from 41 to 60 years (Figure 1).

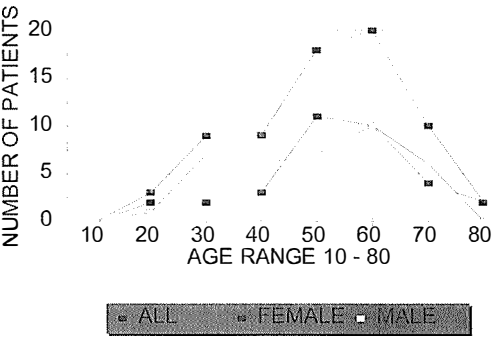

Figure 1. Lung carcinoids (N = 71). Age and sex distribution.

Twenty-nine patients suffered from recurrent or persistent respiratory tract infection, 16 from hemophthisis alone, and 9 patients from hemophthisis with other troubles. Seventeen patients were asymptomatic, their tumours were discovered by chance on chest x-ray.

In 3 patients (4 %), associated clinical syndromes were documented as follows: one patient had typical carcinoid syndrome, while in two others Cushing's syndrome due to ectopic ACTH secretin developed.

The most common lobectomy was performed in 45 (63 %), bilobectomy in 5, pulmectomy in

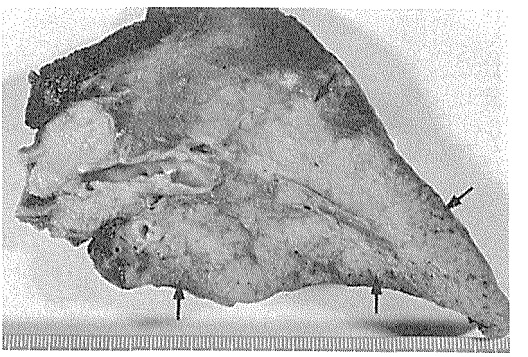

Figure 2. A central bronchial carcinoid with secondary obstructive pneumonitis (arrows).

2, segmentectomy in 8, and minor partial resections in 9 patients. Resection was contraindicated in one patient, while in another there were no exact data about surgical procedure available. Sixty-six (93%) carcinoids were located centrally, and 5 were peripheral. On gross examination, carcinoids appeared as finger-like polypoid intraluminal masses, with 6 to 55 mm in diameter. They could penetrate the bronchial wall and extend in the peribronchial lung tissue with a relatively sharp demarcation line. Endobronchial growth was also a cause of secondary obstructive pneumonitis (Figure 2).

Microscopic picture disclosed solid nests, trabecules and/or glandular structures, separated by a delicate fibrous stroma rich in capillaries. Neoplastic cells were quite uniform, with regular round nuclei. Occasionaly, some variations in cell size and shape were seen. More prominent cellular pleomorphism, together with mitotic figures and areas of tumour necroses were characteristic of atypical carcinoid. Sixty-one (86%) carcinoids were evaluated as typical and 10 (14%) as atypical variant. Ossification of the tumour stroma was found in four cases (Figure 3, 4). Two carcinoids were composed of spindle cells while two had oncocytic areas (Figure 5). In all cases examined for neurone specific enolase, immunohistochemical reaction was positive, it was not constant with chromogranine, and seldom weakly positive with synaptophysin. Electron microscopy disclosed neurosecretory dense-core bodies, characteristic for tumours of neuroendocrine origin (Figure 6).

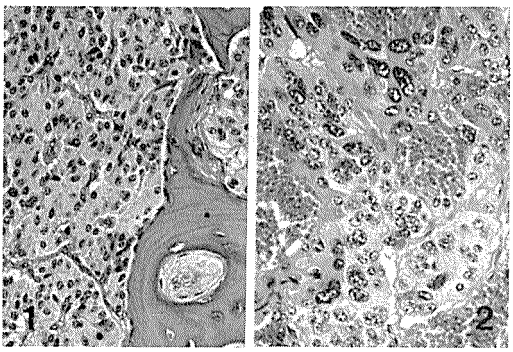

Figure 3. 1. A typical carcinoid with uniform cells and stromal ossification. 2. Prominent cellular and nuclear polymorphism with focal oncocytization in a peripheral atypical carcinoid.

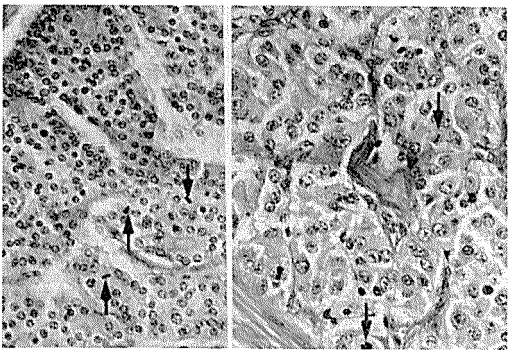

Figure 4. Obvious mitoses in two atypical carcinoids with only slight cellular and nuclear polymorphism.

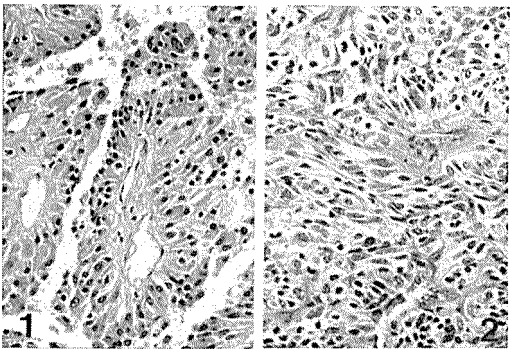

Figure 5. 1. An onocytic carcinoid with abundant cosinophilic cytoplasm of the tumour cells. 2. Peripheral spindle cell carcinoid.

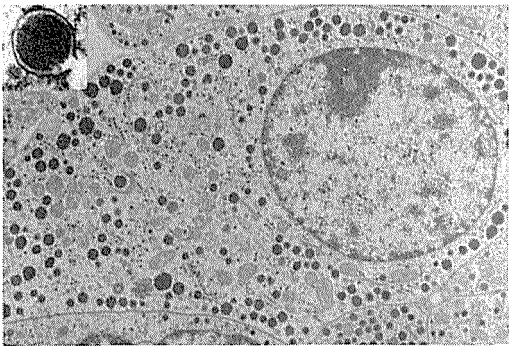

Figure 6. Electron microscopy of a carcinoid in the patient with Cushing's syndrome. Numerous dense-core neurosecretory bodies better visible in the insert.

Out of 64 patients with resected lobar, hilar or other regional lymphnodes, only 3 patients showed evidence of metastatic involvement, this was found patients with Cushing's syndrome. Metastases to distant organs were proven only in one case.

The patients were followed from 1 to 19 years after surgical resection. Carcinoid recidives were documented in 6 patients. Nine patients have died: four of them because of stomach cancer, lung cancer, leukaemia and hypertonic heart disease, respectively. Atypical carcinoid was the cause of death in another 5 patients.

In four (6%) patients with carcinoid, the second primary malignancy was found as follows: lung adenocarcinoma, lung squamous carcinoma, stomach adenocarcinoma, and leukaemia respectively. Excluding mortality from other causes, 46 (98%) out of 47 patients have survived 5 years, 26 (93%) out of 28 10 years, and 13 (72%) out of 18 even 15 years. Patients with atypical carcinoids have died 3, 7, 11, 12 and 13 years respectively after surgical resection. Three patients from our group were living in close vicinity, without any family relationship.

Discussion

Previously, bronchopulmonary carcinoids were inapropriately, classified as "bronchial adenomas" together with mucoepidermoid and adenoid cystic carcinomas. This term is still used,[6–8] but it is inadequate for bronchial carcinoid. Bronchial carcinoid and bronchial adenoma are terms reserved for two biologically and pathologically different and well defined entities.

Also, the term carcinoid could probably be reserved only for tumours secreting 5-hydroxytryptamine and developing classical carcinoid syndrome. It is known that neuroendocrine tumours are the source of various biogenic amines or polypeptides, including ectopically excreted hormones (over 30 different substances were identified up to now), which are associated with other clinical syndromes, different from the classical carcinoid syndrome. But the term "carcinoid" has been already widely known and accepted. Thus we agree with the statement that the term "carcinoid" for these "indolent carcinomas in slow motion" is already so "old, like old soldier, who died hard", that the term "carcinoid" will also survive.[9] Bronchopulmonary carcinoids are neuroendocrine tumours of the bronchopulmonary system.[10–15] They originate from the neuroendocrine Feyrter's cells, which are counterpart of Kulschitzky's cells in gastrointestinal mucosa.[16, 17] Feyrter's cells are found in the basal part of the bronchial epithelium and deeper layers of the bronchial tree (mucous glands).[18] This could explain the most often endobronchial and usual centrally located tumour growth.

The incidence of bronchial carcinoids in Slovenia is comparable with other published data.[19, 20] There is no significant difference in sex distribution. The age range and mean age in our analysis are similar to many previous reports.[19–22]

Many carcinoids remain asymptomatic for long periods of time.[23] The most common symptoms, i.e. respiratory tract infections and/or hemophthisis, are not specific for this tumour, as reported also by others.[24] Bronchopulmonary carcinoids are rarely the cause of clinical syndromes,[25–28] but they account for approximately 2% of all causes of ectopic ACTH production.[29] Both two carcinoids in our study, associated with an ectopic ACTH production and Cushing's syndrome, were classified as typical carcinoids. In both cases lymphnodes were metastatically involved, but until now, surgical treatment is believed to be curative. A carcinoid syndrome found in one patient with atypical carcinoid has developed only after the recurrence with metastases to distant organ.

Peripheral locations of carcinoids are not common, their rate ranging from 2–16%.[5, 22] Out of 5 (7%) peripheral carcinoids in our study, one was composed of spindle cells, while another was defined as an atypical carcinoid.

Most authors regard surgery as the treatment of choice, also successful in the cases of recurrence. They suggested that a pulmonary resec-

tion should be avoided unless there is histologic evidence of the tumour spread in to the lung parencyma or irreverrible inflammatory changes distally from the obstruction. Many new surgical procedures have been introduced, such as parenchyma saving bronchoplastic, procedure, bronchoscopic removal or laser techniques.[5, 22, 30, 31]

Lymphnode involvement is not common in patients with bronchopulmonary carcinoids and bears no relationship with atypical variant.[32] Only in one patient with atypical carcinoid, distant metastases were proved on autopsy. Recurrences of the disease appeared at very different intervals after surgery. Therefore, long follow up is recommended.

The long term results in this study show good survival. Only 5 patients died of carcinoid tumour, all of them with atypical carcinoid. We could also confirm that bronchopulmonary carcinoids follow a very indolent clinical course.[33–35]

The overall prognosis following tumor resection is excellent. It is better in typical carcinoids, and worse in atypical ones.

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Binding capacities to blood-group antigen A, B and H, DNA- and MST measurements, and survival in bronchial carcinoma

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The expression of binding capacities related to blood-group antigens A, B, and H was assessed glycohistochemically in paraffin-embedded samples from 149 lung carcinoma patients. In addition, measurements of integrated optical density (IOD) and syntactic structure analysis (MST) were performed. The material comprised potentially curative excised surgical specimens of 46 epidermoid carcinomas, 42 adenocarcinomas, 26 small cell carcinomas, and 35 large cell anaplastic carcinomas. In about 50% of the carcinomas binding capacities to BLOOD A, B, and H could be demonstrated. No relation to the tumor cell type was found. The measurements of IOD revealed a S-phase-related fraction of 5–18% of tumor cell nuclei and a remarkable fraction of tumor cell nuclei with an IOD > 5C. Patients' survival was strongly related to the number of stem lines, S-phase related fraction, percentage of tumor cells with an IOD > 5C and expression of binding sites to BLOOD A and BLOOD H. The expression of binding sites to blood-group antigens H was associated with decreased cellular heterogeneity as demonstrated by the percentage of tumor cell nuclei with abnormal IOD. The analysed prognostic factors were found to be independent from cell type and tumor stage (TNM).

Key words: bronchial neoplasms-pathology; blood groups; DNA, neoplasm

Introduction

The following study was performed to assess the prognostic importance of blood-group antigens, macrophage inhibitory factor, DNA contents of tumor cell nuclei as defined by the integrated optical density (IOD), and syntactic structure analysis in operated bronchus carcinoma patients. The most important prognostic factors in surgically treated lung cancer patients are in descending order lymph node involvement (pN-stage), tumor size and its localization (pT-stage), inflammatory response of host tissue, and invasion of bronchial cartilage.[1, 2, 3]

Additional factors related to cellular heterogeneity and proliferation (number of stem lines, percentage of proliferating tumor cells), and to the variability of tumor cell textures analyzed by syntactic structure analysis (distance between

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proliferating tumor cells, distance between tumor cells and immunocompetent cells, etc) have been suggested;[4] however, detailed data are still missing. Ligandohistochemistry of bronchial carcinoma revealed a large variety of binding capacities of carbohydrates and significant differences in tumor cells compared to cells of healthy lung parenchyma.[5, 6] Expression of epidermoid growth factor (EGF) and that of corresponding binding sites could be demonstrated in nearly all epidermoid and adenocarcinoma cases.[7] The determinants of ABH blood group antigens are carbohydrate side chains of glycoproteins. Their expression is probably associated with the differentiation of cancer cells.[8, 9] In addition, Lee et al.[10] reported a favourable survival of lung carcinoma patients whose tumors had not lost their blood-group A antigens. Similar data have been published for patients sufering from epidermoid carcinoma of the head and neck.[11] Ligandohistochemistry is a newly developed technique which permits histochemically the demonstration of biologically important binding capacities. This has already been demonstrated by the macrophage inhibitory factor (MIF) , which is a lymphokine able to prevent the migration of macrophages from the capillary tubes in guinea pigs, and probably, a mediator regulating the activity of macrophages in host defense,[12] or sarcolectin (SAR) which is an interferon antagonist, and had been isolated and purified from human placenta.[13] For example, the presence and expression of binding sites to MIF and SAR could be demonstrated in nearly all analysed cases with healthy human lung parenchyma;[14] however in only a minority of human lungs of patients who developed autoimmune-related diseases, such as biliary cirrhosis.[15]

– We have employed the binding capacities of BLOOD A, BLOOD B, BLOOD H in human lung carcinomas, and report their relation to tumor cell type, and survival of the patients. In addition, their relationship to nuclear and structural features is analysed.

Material and methods

This study includes 149 patients who underwent surgery for lung cancer with potentially curative resection at the Thoraxklinik Heidelberg. The tumor size, pTNM stage, and cell types of the resected lobes and lungs were obtained as usual, i.e. the surgical specimens were fixed with bufered formalin, cut into serial sections and analysed as described in detail elsewhere.[5] The antibodies and biotinylated probes were applied to 4–5 um thick histological slides. After deparaffination and rehydration through garded alcohol, and blocking of the endogenous peroxidase by incubation in 0.1 % methanolic hydrogen peroxide for 30 min an equilibration with 0.1 M Tris buffer and treatment with 1 % bovine serum albumin was followed by incubation with biotinylated probes (oligosaccharides bond to biotinylated polyacrylamide) at a concentration 10 μg/ml at room temperature for 60 min.

Visualization of the binding capacities was performed by the application of ABC complex (Camon, Wiesbaden) and development of the chromogenic product from the substrates diaminobenzidinehydrogen peroxide. Finally, the sections were counterstained and mounted. Positive and negative controls were performed as usual, i.e. by parallel performance of positive cases, any by replacement of biotinylated probes with BSA. Cases were considered to have stained positively only if a dark brown staining could be seen in all or in clusters of tumor cells. The survival of patients was assessed by repeated questionnaires to the house physicians or physicians responsible for postsurgical tumor care of patients. The analysis of survival rates was performed by the Kaplan-Meier and log-rank tests.[16] IOD measurements were performed on Feulgen stained histological slides using an automated image analysing system (DIAS, Towersoft, Berlin). The extracted features included IOD, nuclear size, S-phase related fraction as defined $2.75 < \text{IOD} < 3.25$, percentage of tumor cell nuclei with an $\text{IOD} < 5\text{C}$ ($< 5\text{C}$), number of stem lines, 2CV standard deviation, entropy as defined by Stenkvist,[17] and IOD entropy-flouss (current of entropy) as described.[18] The features of syntactic structure analysis were obtained by construction of the minimum

Table 1. Synopsis of material (number of patients)

Feature	Cell Type Epidermoid	Adeno	Large Cell	Small Cell
Men	41	29	27	23
Women	5	13	8	3
T-Stage				
T–1	10	18	7	8
T–2	21	14	22	15
T–3	14	8	3	1
T–4	1	2	2	2
N–Stage				
N–0	17	12	15	8
N–1	12	8	5	7
N–2	11	9	10	8
N–3	6	13	5	3
Total	46	42	35	26

spanning tree, and comprised minimum distance between of centers of all tumor cell nuclei (DMST), proliferating tumor cell nuclei only, tumor cell nuclei with an IOD < 5C only, between tumor cell nuclei and immunocompetent cells, MST entropy and MST entropy-fluss as described originally.[18] The use of external and internal standards provided a reproducibility of measurements as described previously.[19]

Results

A synopsis of patients and tumor cell types included in the study is given in Table 1. All in all, primary bronchial carcinoma of 149 patients (121 men and 28 women) could be analysed. The relation of positive stained cases in respect to the cell type and IOD and MST features is given in Table 2. Expression of blood-group A antigen was seen in 68/149 cases, that of blood-group B antigen in 82/149 cases, and that of blood-group H antigen in 72/149 cases respectively, without any preference to a certain cell type. No association of binding of blood group trisaccharides to tumor stage, cell type, or sex could be established. The median survival rates as defined by Kaplan-Meier estimations for the patients, including the number of deaths, grouped according to the expression of blood-group A antigen, blood-group H antigen, and IOD features (number of stem lines, IOD-entropy, IOD-entropiefluss), structural features (MST-entropy, MST-entropiefluss), are given in Table 3. The differences between the different median values of survival rates marked with an asterisk are at a statistically significant level ($p < 0.05$).

Discussion

Lung function depends on complex interactions between many cell types, their matrix, and organized preserved morphological structures. Development of lung cancer, i.e. the occurence of a new uncontrolled proliferating biological system within the preexisting biological system (lung) may retain, or loose certain cellular properties of the original system, or express new characteristics. Some of these properties may be of advantage for cellular propagation while others may not. It has been demonstrated by various authors that the expression of carbo-

Table 2. Expression of histo blood-group antigenes in relation to IOD and MST features (mean values).

Feature	Histo Blood Group A–	A +	B–	B +	H–	H +
Number of cases	(81)	(68)	(67)	(82)	(77)	(72)
IOD – features						
Stem Lines	2.7	2.9	3.0	2.7	3.1*	2.5
S-Phases (%)	12	12	12	12	13*	11*
Entropy	2.2	2.2	2.2	2.2	2.2	2.2
2CV-Std (%)	11	9	10	10	11	9
5C Exc (%)	7.1	7.6	7.6	7.1	8.1*	6.5*
Structural features (MST)						
Dist Tu-Tu (um)	12	12	12	12	12	12
Dist Pr-Pr (um)	40	38	39	39	39	39
Dist 5C-5C (um)	25*	28*	26	27	26	27
Entropy	11	9	10	10	11	9
Entropy-flow	29	29	28	30	33*	24*

* Statistically significant ($p < 0.05$)

Table 3. Expression of histo blood-group antigens, IOD-, and MST features, and median survival of patients (in months).

Feature	Patients (N)	Deaths (N)	Survival (months)
Blood A–	81	39	12*
Blood A +	68	30	25*
Blood B–	67	32	12
Blood B +	82	37	16
Blood H–	77	41	14*
Blood H +	72	28	23*
1 Stem line	28	4	45*
2 Stem lines	32	6	30*
> 2 Stem lines	89	59	11*
< 5 % S-phases	10	2	53*
5–10 % S-phases	45	3	31*
> 10 % S-phases	94	64	10*
< 10 MST Entropy-flow	94	36	21*
> 10 MST Entropy-flow	55	33	11*
< 10 MST Entropy-flow	50	14	23*
> 10 < 30 Entropy-flow	45	26	12*
> 30 MST Entropy-flow	54	29	11*

* Statistically significant (< 0.05)

hydrate-binding capacities of lung carcinoma cells differs from that of cells of a normal lung in a broad range.[4] Patients with epidermoid carcinoma and adenocarcinoma who have a favourable prognosis compared to small cell or large cell carcinoma patients, commonly express a broad panel of carbohydrate binding capacities in contrast to other cell types.[3, 4] The expression of carbohydrate binding capacities in human lung cells reflects to both injury and differentiation of the corresponding cells.[3] The expression of blood group antigens is closely associated with that of carhobydrate-binding capacities. The loss of blood-group A antigeneity has been reported to be an unfavourable prognostic indicator in various cancer types. In patients suffering from head/neck cancer Wolf and Carey[11] observed a median survival of 8.1 months in tumors with corresponding loss of blood-group A antigens, and a median survival of 38 months in those with retained antigens.[11] Similar observations have been reported by Mijake *et al.*[20] in lung carcinoma patients (expression of blood-group H antigens) and by Lee *et al.*[10] (expression of blood-group A antigens). Lee *et al.*[10] could, however, only demonstrate the prognostic significance of blood group A antigens, and found no influcence of blood group B and blood group H antigens on survival. Our data are in agreement with the previous reports with respect to blood-group A antigen expression: the survival of patients with expression of blood-group A antigens of tumor cells is favourable compared to that of patients without this tumor characteristics.[21] In our material, this observation holds true for both patients with blood type A and those with other blood types. In our material, patients with expression of blood-group H antigens had a prolonged survival compared to those with loss of blood-group H antigens whereas antigeneity of blood-group B had no influence. These data are in accordance with the findings reported by Miyake *et al.*[20] An influence of blood types on survival of patients could not be seen in our material. Miyake *et al.*[22] developed two monoclonal antibodies that recognize migration-inhibitory-related carbohydrate sequences. The authors reported a significantly improved survival of patients whose lung tumors exhibited no detectable binding sites to the antibodies. In accordance with our findings, these data again support the idea, that carbohydrate-related cellular binding capacities may play an important role in tumor propagation and tumor cell interactions with their environment. This hypothesis is supported by the findings that nuclear abnormalities (abnormal chromosome content) is associated with loss of trisaccharide blood A and H binding. The MST entropy-fluss as estimated from the Onsager equation can be assumed to be a stable indicator for the "distance of a thermodynamically open system from its equilibrium", i.e. reflects the amount of heat produced inside the tumor which has to be removed through its surface. Similar to the number of stem lines, S-phase related tumor cell fraction, percentage of tumor cell nuclei > 5C, this factor, as well as blood-group A antigeneity, blood-group H antigeneity, and expression of binding sites to sarcolectin are associated with an improved survival of potentially curable bronchial carcinoma patients treated by surgery, and may thus be added to the list of prognostic factors in lung cancer.

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Methodology and results of bronchopulmonary cancer detection in Slovenia 1970–1992

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The results of bronchopulmonary cancer detection in pneumonology departments represent over 90 % of all microscopically verified cases of bronchopulmonary cancer in Slovenia. The incidence rose from 370 in 1970 to 782 in 1992, with male prevalence (85 %). Passive detection was preferentially used as mass fluoroscopy has been gradually abandoned after 1972. Bronchoscopy was always the main diagnostic method (92.1 % in 1970 and 90.7 in 1992), followed by perthoracic fine neddle aspiration biopsy (3.8 % and 4, 5 %). Other methods (sputum cytology, mediastinoscopy, thoracoscopy, thoracotomy) accounted for 4.1 and 4.8 % respectively. There is a slight predominance of central type (53.7 vs. 46.3 % in 1992). Planocellular type was predominating (68.9 % in 1970, 39.8 % in 1992), followed by small-cell (10.1 and 19.2 %), adeno- (8 and 16.5 %), and large-cell (7 and 13.6 %) carcinomas. In 1992 surgery was the therapy of choice in 26,3 %, chemotherapy in 15 % and radiotherapy in 22,5 % of newly detected cases.

Key words: lung neoplasms-diagnosis; Slovenia

Introduction

Today, bronchopulmonary carcinoma is the most prevalent type of cancer, and is responsible for more cancer-related deaths than any other tumour in man. In some countries in the world it has surpassed breast carcinoma in women as the most lethal tumour. [1]

These facts stress the importance of research into the modalities and results of lung cancer detection in every country facing rise in the incidence of bronchopulmonary carcinoma, in order to find the way to detect and properly diagnose lung carcinoma as early as possible, and to institute adequate therapy.

In Slovenia, in contrast to some other countries, diagnosis and partly also therapy of bronchopulmonary cancer is almost exclusively carried out in the pneumonology departments and out-patient clinics. Our aim was, therefore, to investigate methodology and evaluate the results of lung cancer detection in these units in the period from 1970 to 1992.

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Material and methods

The data from annual Golnik Epidemiology Reports were used as a source, together with

the data from individual pneumonology departments of regional hospitals in Slovenia.

Statistical evaluation was performed by means of SAS software.

Results

Figures 1a and 1b present newly detected patients with lung cancer by age and sex. There

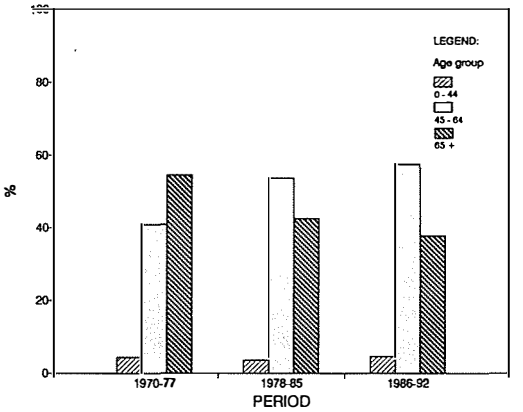


Figure 1a. Distribution of newly detected male patients with lung cancer according to age (1970–92).

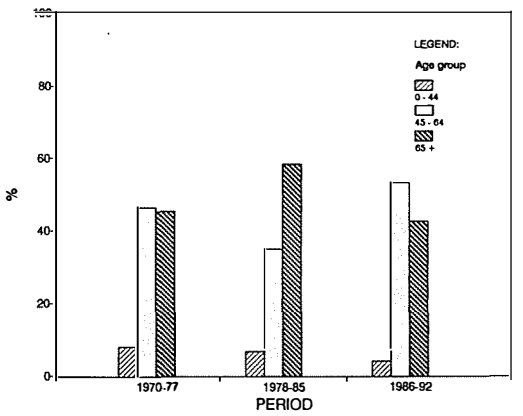
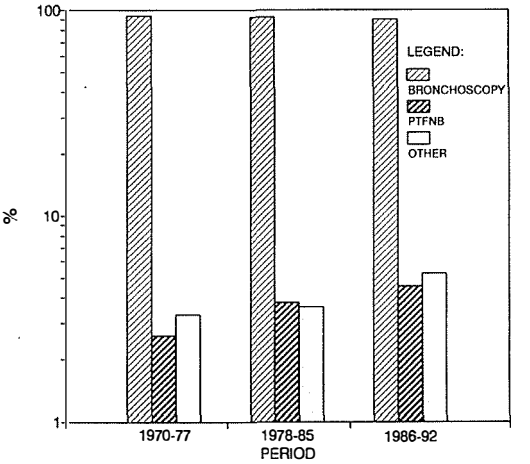


Figure 1b. Distribution of newly detected female patients with lung cancer according to age (1970–92).

is an obvious increase in the number of patients, especially in the 45–64 year age group in both males and females.

Passive detection was the most frequently used mode of detection throughout the observed period: 82.3 % in 1970–77 and 93.4 % in 1986–92 period. Mass X-ray method made an important contribution (14.7 %) in the period 1970–77 only; after 1972 it has been gradually abandoned because of a high cost-benefit ratio in tuberculosis detection.

Diagnostic methods were not grossly changed in the observed period, with bronchoscopy leading and others (perthoracal fine needle biopsy, sputum cytology, mediastinoscopy, thoracoscopy, thoracotomy) contributing less than 10 % (Figure 2).



PTFNB = Perthoracic fine needle biopsy.

Figure 2. Diagnostic methods for verification of lung cancer.

Cytology alone or in combination with histology was the most frequent method of cancer verification. In 1970–77, cytology alone was used in 60 % of cases, with gradual decrease to 51 % in 1986–92. In the same periods both cytology and histology were used in 35 % and 46 % of cases respectively.

Histologic type of the detected carcinomas (Figure 3) significantly changed over time, with a decrease in squamous and an increase in adeno- and partly also small- and macrocellular types.

The detection of carcinoma required adequate therapy. The progress in therapeutic decision making in 1970–92 period is shown in Figure 4.

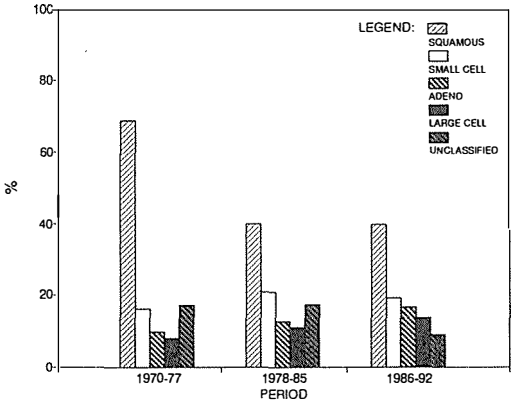


Figure 3. Distribution of detected lung cancer according to histologic type in %.

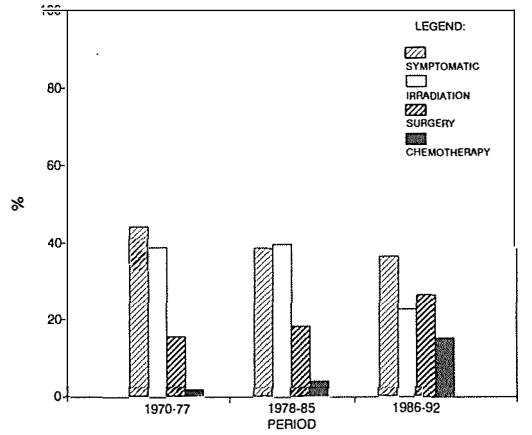


Figure 4. Modes of therapy in newly detected patients.

Discussion

Growing trends in lung cancer incidence are characteristic for industrial developed countries.[2] It is quite sad that by this standard Slovenia is a well developed, industrial country. The incidence of lung cancer in the age group 45–64 years increased by almost 50%, mostly in men, but with an important contribution of female population in the last third of the observed period. Smoking could be blamed for 90% of causes in males but only for 73% in female population as observed also by others.[3]

It is clear from our data that the increase in lung cancer incidence could not be ascribed to a better or modified mode of detection. Also in the period of mass X-ray, more than 50% of detected patients already had symptoms of the disease.

Changes in bronchoscopy, with prevalent use of flexible instruments have dramatically changed the distribution of lung cancer histology. As more peripheral tumours were being diagnosed, the percentage of squamous type steadily decreased and of adeno increased. This pattern was observed also by others.[4,5] The increase in large and small cell types was less significant and mostly due to better classification.[6]

In contrast to other authors, we used cytology more frequently as the only method of cancer verification.[7] This was mostly due to a better access to this type of service. In the last observation period both methods have been used with more balanced use of different therapies, with only a small proportion of patients being treated only symptomatically. It is most promising that the increase is greatest in surgery and chemotherapy as these two methods contribute most to the survival of lung cancer patient.[8]

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Epidemiological features of lung cancer in Slovenia

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Lung cancer is the most frequent cancer in the world with wide geographical variations in risk. In Europe its incidence trends in men are decreasing in the most affected countries such as Scotland and Finland, increasing moderately in Eastern Europe, and increasing steeply in Southern Europe. The incidence trends in women are increasing everywhere. Many risk factors have been identified, and the overwhelming role of tobacco smoking has been repeatedly demonstrated. According to the data of the Cancer Registry of Slovenia in the time period 1961–1990, the incidence of lung cancer in Slovenia was increasing. In the 80's the increase was moderate in men and steep in women. The cumulative rates in men were in the middle of those established for selected European states and regions while the rates in women were at the bottom. The results of the birth cohort analysis indicated a stabilisation of the rates in men and further increase of the rates in women. About 25 % of cases in both sexes were diagnosed in a localised stage. In men the percentage of the localised stage was increasing by age which was explained by a decreasing percentage of the more aggressive small cell carcinoma. More squamous cell carcinomas were registered in men, and more adenocarcinomas in women. The observed survival of lung cancer patients was around 7 % for men and 6 % for women, and has not changed since 1970. In 1989, 42 % of adult men and 24 % of adult women in Slovenia were smokers. In the period 1975–1994, the percentage of smokers was decreasing in men, and increasing in women. These results are a challenge for more efficient antismoking campaigns, especially among women.

Key words: lung neoplasm-epidemiology; Slovenia

Introduction

Lung cancer is now the most frequent cancer in the world. Pisani, Parkin and Ferlay estimated that in the year 1985 the world burden had been: 896 000 new lung cancer cases (677 000 in men and 219 000 in women) and 785 000 deaths due to lung cancer (600000 in men, and 185 000 in women).[1]

There are wide geographical variations in the risk. In Europe alone the crude incidence rates are varying from 180–45/100 000 in men, and from 55–5/100 000 in women.[2] In men the time-trends in incidence are different. They are decreasing in most affected countries such as Scotland, England and Finland, increasing moderately in Eastern Europe, and increasing steeply in Southern Europe. In women the trends are increasing everywhere.[3]

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Study of the epidemiology of lung cancer has been one of the most rewarding aspects of medical research in the past 40 years. It has been shown how a disease that has become the most common type of cancer throughout the world can be made to become relatively rare.[4] Many risk factors have been identified: tobacco smoking, atmospheric pollution, occupational hazards, ionising radiation, some familial, genetic and other host factors as well as the protective role of diet rich in fruit and vegetable. The overwhelming role of tobacco smoking in the causation of lung cancer has been repeatedly demonstrated.[4,5]

The aim of our study was to analyse lung cancer incidence in Slovenia in depth and to compare the obtained results with the available data on Slovenian smoking habits.

Material and methods

Lung cancer incidence and survival data were drawn from the data base of the Cancer Registry of Slovenia. This Registry was established in 1950 at the Institute of Oncology as a population-based cancer registry. Data from the period 1961–1990 were analysed.

Data on smoking habits have been gathered regularly within the framework of Slovenian public opinion survey on a random sample of 2093 adult men and women since 1975.[6] These data were kindly supplied by the Faculty of Social Sciences.

Standard methods in descriptive epidemiology were used.[7] Crude incidence rate has been defined as the rate of total annual number of new cases per 100 000 population in the relevant year. Comulative incidence rate is a special age-standardised rate. It is the sum over each year of age of the age-specific incidence rates taken from birth to age 74. It can be interpreted either as a directly age standardised rate with the same population size in each age-group, or as an approximation to the cumulative risk.

Staging was based on the international cancer registries regulation. According to this regulation, all investigation methods including surgery are considered in stage determination of solid tumours. In the case that patient was not treated previously, the autopsy report is considered as well. The lung cancer cases were coded as localised when tumour was confined to the same site of the lung and no nodes or distant metastasis were present.

Results

Lung cancer incidence and survival

In Slovenia the incidence of lung cancer was increasing in both sexes (Figure 1). In men the increase was steep in the sixties and seventies, and moderate in the eighties, while in women the increase was steeper in the eighties than before.

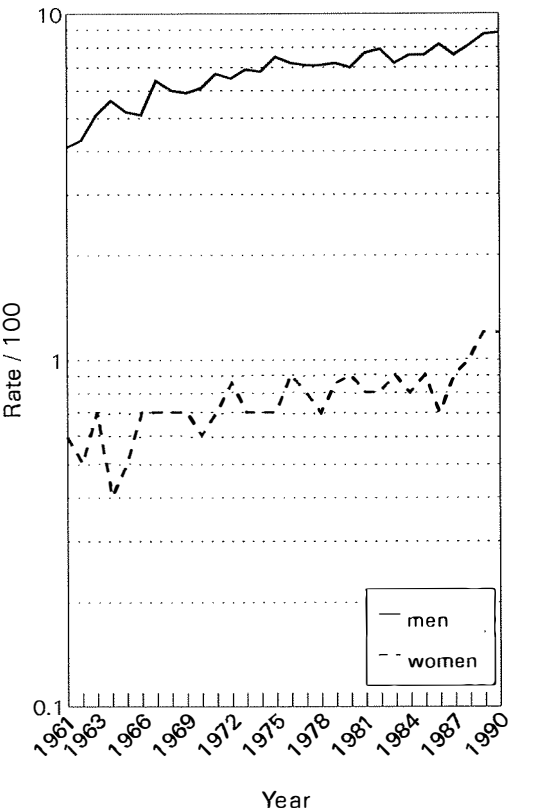

Figure 1. Crude annual lung cancer incidence rates by sex, Slovenia 1961–90.

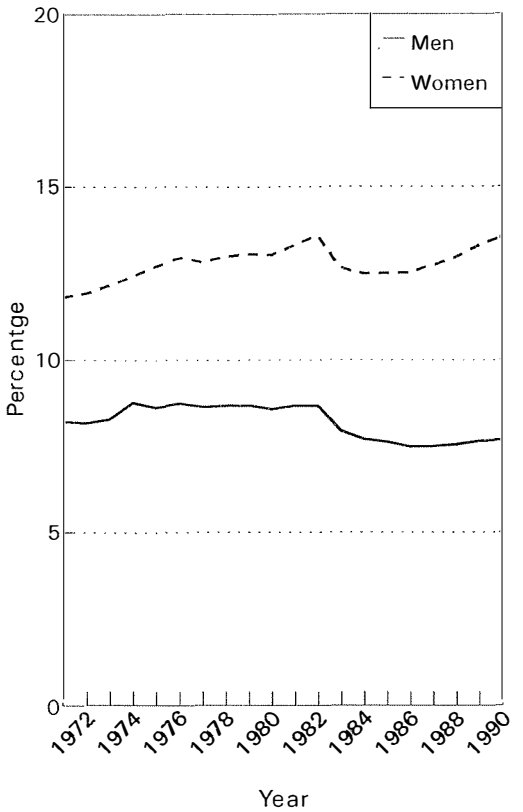

Figure 2. Percentage of elderly population by sex, Slovenia 1971–90.

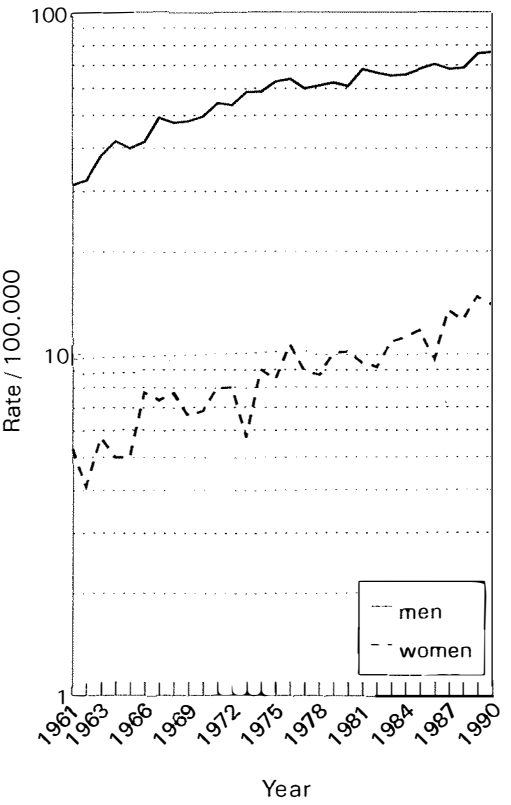

Figure 3. Cumulative annual lung cancer incidence rates by sex, Slovenia 1961–90.

In this long time period the population tree of Slovenia changed.[8] The percentage of the elderly population was growing till 1982 to be temporarily stabilised in the eighties (Figure 2). We have to take this changing age distribution into account and look at the age standardized cumulative rates, at the risk of getting lung cancer till the age of 75 years (Figure 3). In men a steeper increase in the risk to get lung cancer in the sixties and at the beginning of seventies, and in women a steady increase in the eighties was confirmed.

These cumulative rates in men place Slovenia in the middle of the rank order of selected European states and regions (Figure 4). In Slovenia the risk of getting lung cancer in a man till the age of 75 years was almost 8/100, in comparison to the Netherlands and Lower Silesia in Poland where it was about 11/100, and with Norway and Sweden where the rates were the lowest 3-4/100. With the cumulative rates in women (0.9/100), Slovenia was placed at the bottom, very close to different regions of Germany (Figure 5).

In Slovenia itself, the cumulative rates varied. In men high rates were found in industrial and mining settlements, while in women they were found in the capital region of Slovenia.[9] In the commune of Idrija stable high rates were found in both sexes.

To predict properly further trends of lung cancer in Slovenia a detailed analysis on trends in the incidence of specific age-groups by time periods (Figure 6a, b) and by birth cohorts was needed (Figure 7a, b). In men the peak of the rates plotted by time periods shifted to the left and a stabilisation in the eighties was observed.

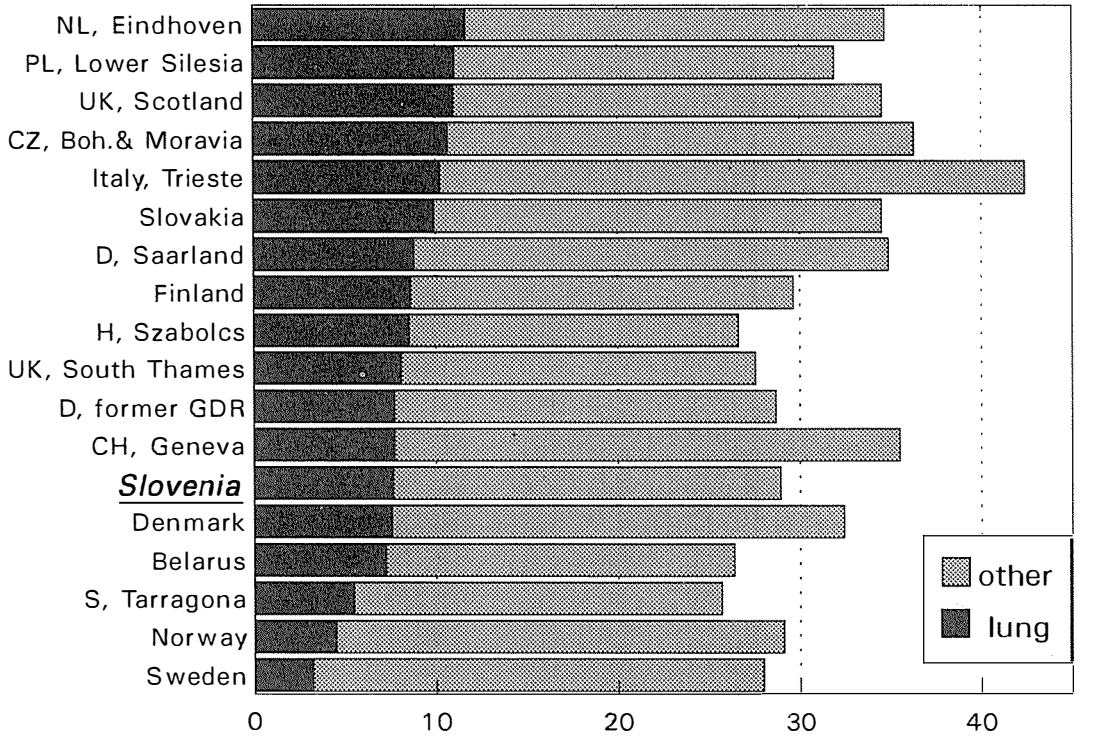

Figure 4. Cumulative average annual lung cancer incidence rates in men, Europe 1983–87.

In women the peak remained in the oldest age groups and the curve was higher in each subsequent time period. We tried to explain such a different behaviour by sex with a birth cohort analysis. In the birth cohort analysis (Figure 7) we presented the same data in a different way. The rates were plotted by birth cohorts, by the year of birth of newly diagnosed lung cancer patients. There was a clear cohort effect in both sexes. An encouraging one in men with lower rates in younger generations, born around 1931 and later, and a warning one in women, with higher rates in younger generations in all age groups.

In the period 1981–90 in Slovenia about 25 % of patients of both sexes were diagnosed in the localised stage (Figures 8 and 9). The stage distribution differed by age however. In men only, a growing percentage of the localised stage in the elderly was obvious. To explain this observation, we analysed the histologic types of lung cancer in Slovenia by age in men and women (Figure 10a, b). The distribution differed by sex. More adenocarcinomas were registered in women, and more squamous cell carcinomas in men, while approximately the same percentage of carcinomas were nonspecified or microscopically non verified. The percentage of small cell carcinoma decreased by age in both sexes.

Population survival of lung cancer patients in Slovenia did not change in the period 1970–1989. The observed five year survival rate of patients aged 0–74 years was around 7 % for men and around 6 % for women.

Smoking habits

In 1989, 42 % of adult men and 24 % of adult women in Slovenia were smokers. With these data Slovenia was placed in the middle of the EC countries. In men the highest percentage

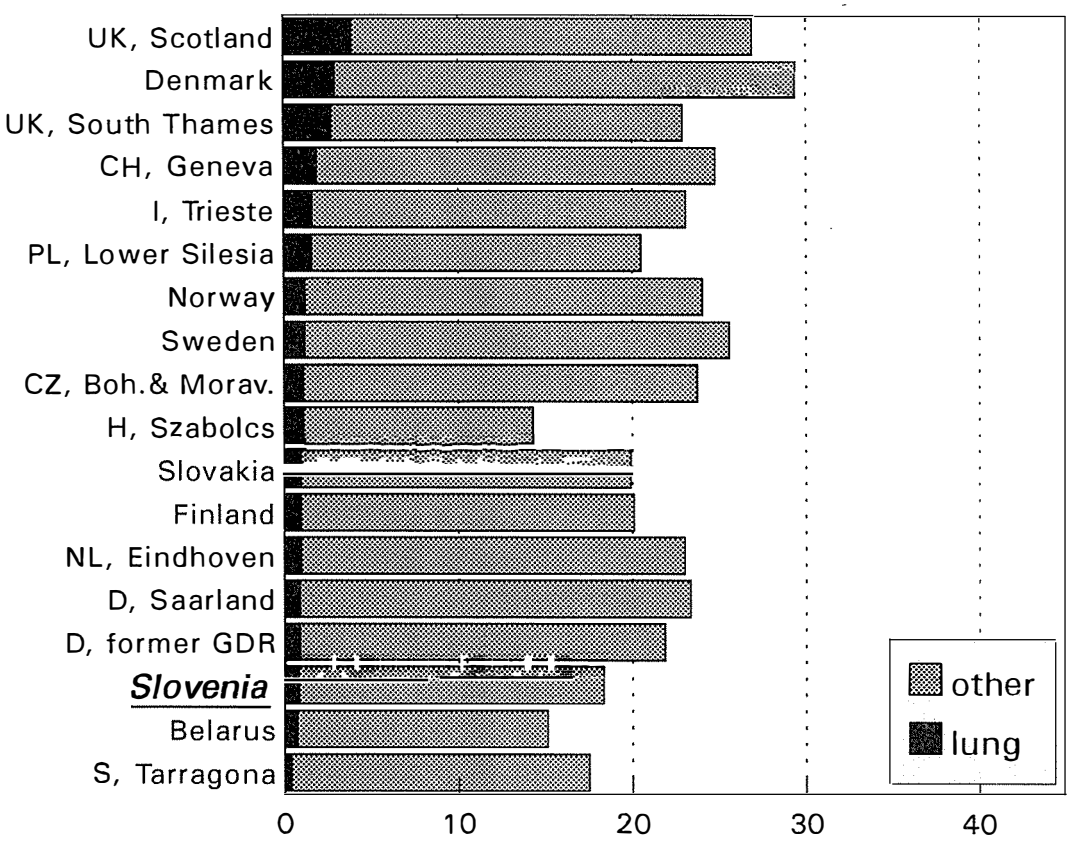

Figure 5. Cumulative average annual lung cancer incidence rates in women, Europe 1983–87.

of smokers was seen in the age group 31–40 years while in women it was in the age group 26–30 years. The percentage of ex-smokers was higher in men in all age groups after the age of 25. Smoking habits differed by education. The highest percentages were seen in men with elementary and professional education, and they were highest in women with professional and middle education. In the time-period 1975–1994, the percentage of smokers among men was decreasing whereas among women it was increasing (Figure 11). The decrease in men was observed in all age groups after the age of 26, while the increase in women was observed till the age of 61.

Smoking habits differed by communes of Slovenia. In 1989, more smokers were found in industrial and mining settlements.[9] Unfortunately, an analysis by sex was not performed.

Discussion and conclusion

In the time period 1961–1990 the incidence of lung cancer in Slovenia was increasing. In the eighties the increase was moderate in men and steep in women. The cumulative rates in men were in the middle of those established for selected European states and regions, while the rates in women were at the bottom. The results of the birth cohort analysis indicate a stabilisation of the rates in men and further increase of the rates in women in the near future.

About 25% of cases in both sexes were diagnosed in the localised stage. In men, the stage distribution differed by age, however. The localised stage was increasing with age. With age also the percentage of more aggressive small cell carcinoma was decreasing. A similar observation was reported by Teeter and coworkers in 1990.[10]

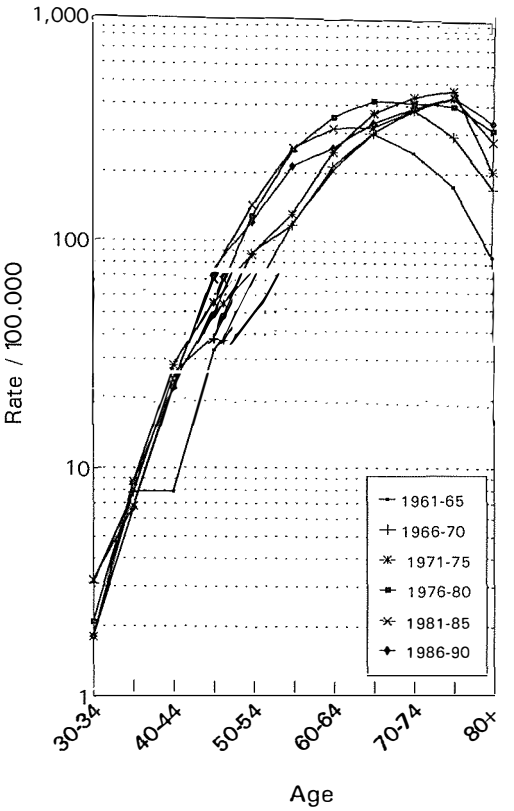

Figure 6a. Age-specific lung cancer incidence rates in men by time periods, Slovenia 1961–90.

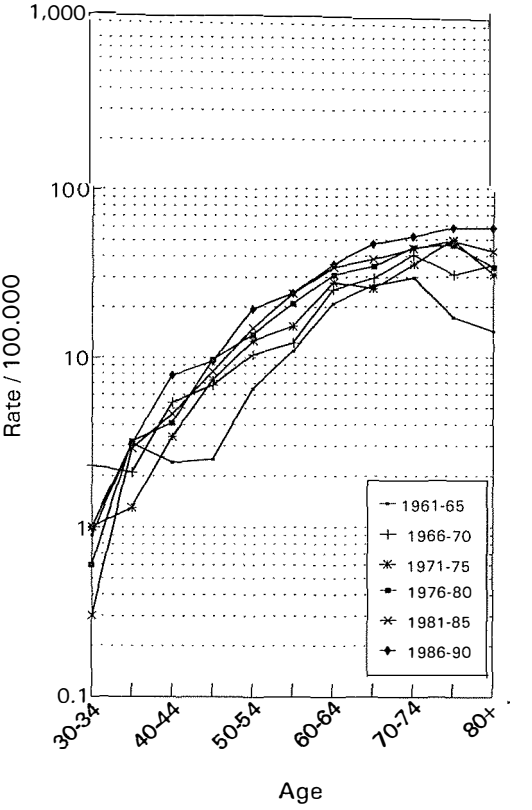

Figure 6b. Age-specific lung cancer incidence rates in women by time periods, Slovenia 1961–90.

More squamous cell carcinomas were registered in men, and more adenocarcinomas in women. Such results were expected according to other reports in the literature.[11]

The observed survival of lung cancer patients was around 7 % for men and 6 % for women, and has not changed since 1970. This statement is a challenge not only for clinicians in their search for additional pieces to the unresolved puzzle of a more efficient treatment, but first of all for health educators and general practitioners in their attempt to develop more efficient antismoking campaigns, especially among women. According to the described smoking habits in 1989 in Slovenia, (42 % of adult men and 24 % of adult women were smokers), and the fact that by eliminating tobacco smoking, the worldwide potential to reduce the incidence of lung cancer would reach 80–90 % for men and 60–80 % for women,[12] a lot of work still waits to be done in the future.

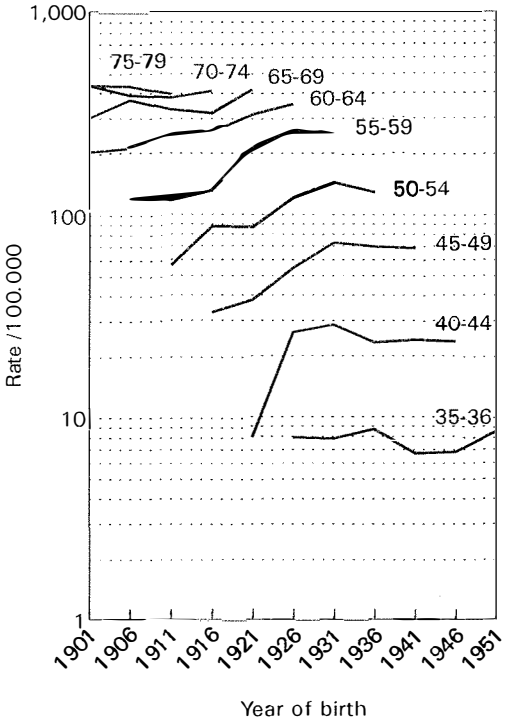

Figure 7a. Age-specific lung cancer incidence rates in men by birth cohorts, Slovenia 1961–90.

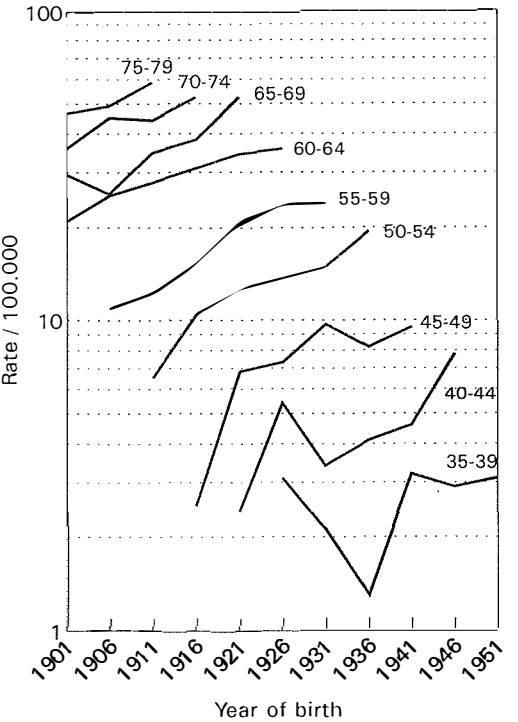

Figure 7b. Age-specific lung cancer incidence rates in women by birth cohots, Slovenia 1961–90.

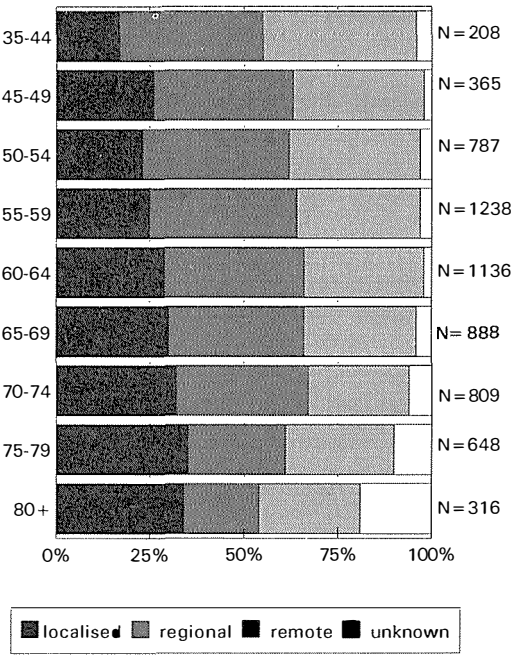

Figure 8. Stage distribution of lung cancer in men by age, Slovenia 1981–90.

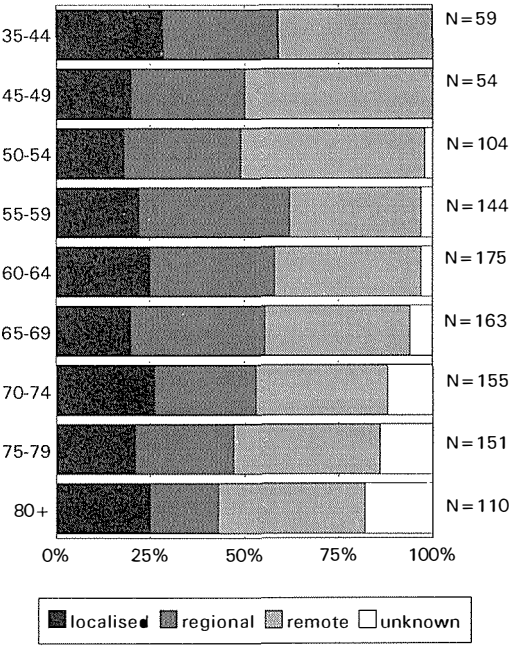

Figure 9. Stage distribution of lung cancer in women by age, Slovenia 1983–90.

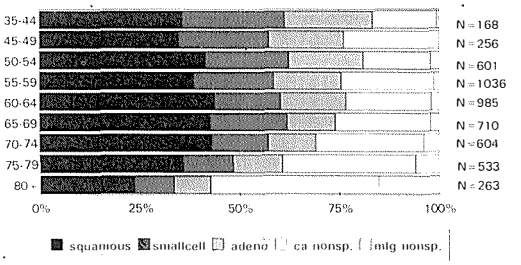

Figure 10a. Histologic types of lung cancer in men by age Slovenia 1983–90.

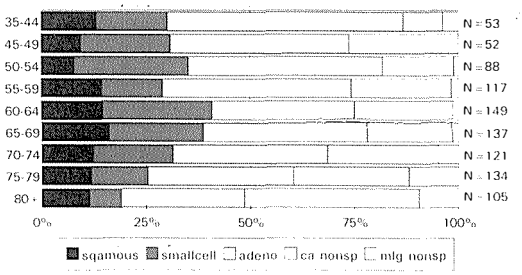

Figure 10b. Histologic types of lung cancer in women by age, Slovenia 1983–90.

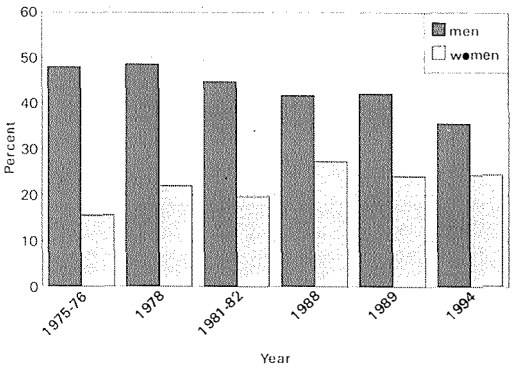

Figure 11. Percentages of smokers by sex, Slovenia 1975–94.

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Epidemiologic data of lung cancer during 1984–1993 in Albania

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Since we cannot attain greatness, let us have our revenge by railing at it.
(Montaigne)

During the last ten years in Albania, the incidence of lung cancer was 10 per 100.000 inhabitant. The diagnosis was based on conventional examinations, biopsy taken through fiberbronchoscopy, or by using other invasive methods. In 75 % of cases the histopathologic examination has determined the cytologic type; 45 % of cases belong to the 55–64 year age group, and 27.1 % of those were over 65 years old. According to the place of living, there were 50.9 % of cases from urban areas, and 49.1 % from rural areas. Considering that the greatest part of Albanian population lives in rural areas, the frequency of lung cancer is greater in urban areas. The smoking is the main risk factor, accounting for 88 % of cases. Radical surgical treatment was done only in 9 % of cases and palliative surgical treatment was performed in 3.5 % of cases as the patients seek medical help in too advanced stages of diseases.

Key words: lung neoplasms-epidemiology; Albania

Introduction

Many epidemiologic studies have concluded that lung cancer is a disease the prevalence of which has increased after the turn of the century, especially after 1950.[1-4] Many attempts have been made to stop this disease of modern times. Though medicine have failed to cure this disease, it is railing by hundred and thousand attempts to treat it as easily as is treating tuberculosis.

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Among these efforts, the epidemiologic ones take the first place, being the starting point of all others.

Material and methods

In our country, the diagnostic methods of lung cancer have been as follow: X-ray examination; cytologic examination of sputum; fiberoptic bronchoscopy; bronchial biopsy; diagnostic thoracotomy. This study is the first one in the epidemiology of lung cancer in Albania. We have studied some of the main epidemiologic characteristics of lung cancer in the last ten years (1984–1993), such as incidence, incidence by sex; by age; incidence rates in urban and

rural areas, smoking-specific, male-female ratio and the percentage of cases treated by radical and palliative resection.

During the studied period, 3000 lung cancer cases were diagnosed. A geographic variation study in occurrence of lung cancer was carried out.

Results and discussion

The incidence of lung cancer during this period was 10, and has not been found to vary not any evident by years (Figure 1). Lung cancer

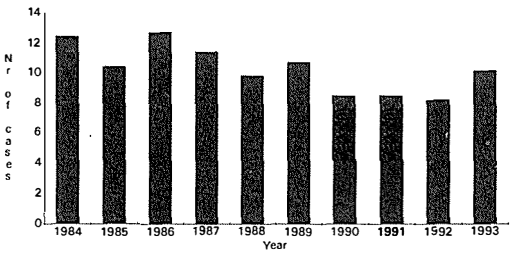


Figure 1. Lung cancer incidence rates (per 100000).

in our cases is more frequent in males, (8.7 per 100000) than in females (1.23 per 100000) (Figure 2).

Figure 2. Lung cancer incidence by sex (per 100000).

Different epidemiologic studies have pointed out the predominance of lung cancer in urban areas compared with rural ones.[5] Our data, do not show any great difference between urban and rural areas: 5.1 per 100000 of cases are in towns and 4.9 per 100000 in villages (Figure 3).

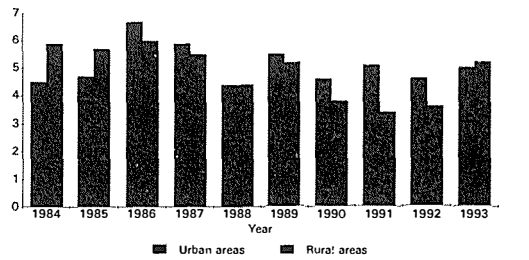


Figure 3. Lung cancer incidence rates in urban and rural areas.

In fact people that live in rural areas represent 65% of population in our country. Thus our data are consistent with those of others studies. It is difficult to attribute this effect to air pollution rather than increased cigarette smoking and occupational exposures in urban residents. The data of last year (1993) draw attention because the number of cases in rural areas is greater than that in urban areas. It seems as if there is a tendency of equal spreading of lung cancer in urban and rural areas in that year. This phenomenon can be explained by employment of villagers in urban areas.

There is a predominance of lung cancer in ages above 55 years. In last years, lung cancer incidence has shown tendency to decrease among middle aged people and those above 65 years of age (Figure 4).

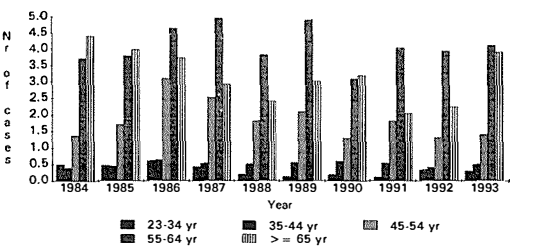


Figure 4. Lung cancer incidence rates by age, (per 100000).

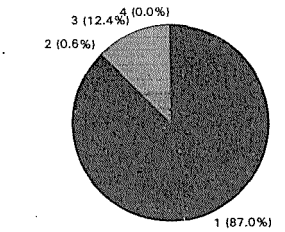
Within Albania, the geographic variation in the frequency of lung cancer is as follows: the disease is more frequent in Tirana, Elbasan, Durres and in north districts than in South areas. This is explained by the fact that in

Tirana, Elbasan and North districts there is mineral and metal Industry and mines.

Risk factors for lung cancer

A lot of former facts can be explained by risk factors. Since Adler[6] in 1912 first suggested a relationship between smoking and lung cancer, there are many studies which have provided evidence that is now regarded as conclusive in establishing the causal link between cigarette smoking and lung cancer.

The cigarette smoking as a risk factor encompas multiple aspects of smoking behaviour, including age at start the number of cigarettes smoked, the product smoked, and inhaling pattern. In our study, 57 % of cases were male smokers, 0.6 % female smokers, 0 % male non-smokers and 12.4 % female non-smokers (Figure 5).



1 – Male smokers, 2 – Female smokers, 3 – Female nonsmokers, 4 – Male nonsmokers

Figure 5. Smoking and lung cancer. Specific male-female.

Almost all women in our cases with lung cancer were non-smokers but there was a family history of smoking.

Besides smoking as an important risk factor in lung cancer, there are other non-smoking risk factors, such as asbestos, radon, and other exposures, diet, hormone, acquired host characteristics and genetic factors.[3,6-8]

From 3000 cases with lung cancer, only 9 % have been treated by surgical resection and 3.5 % by palliative surgical procedures.

These results can be explained by a single reason: These late diagnosis of the disease.

The histological types of lung cancer in our patient have been as follow: Epidermoid 47 %; adenocarcinoma 13 %; small-cell lung cancer 7 %; large-cell lung cancer 5 %; carcinoid 1 %; secondary malignant versament 3 %. In 24 % of cases there is no data on the histologic type.

Conclusions

During the last ten years, the incidence of lung cancer has remained unchanged being 10. per. 100 000 population.

This incidence shows a tendency to decline in the middle-aged and those above 65 years old. The cigarette smoking is a main risk factor of lung cancer, accounting for the majority of lung cancers in our country.

The male-to-female ratio of incidence was 7:1. The predominance of lung cancer in men can be explained by the fact that all of them were smokers.

As a result of late diagnosis only 9 % of lung cancer cases were treated by surgical resection and 3.5 % by palliative interventions.

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Prognostic factors in non-small cell lung cancer

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The literature on prognostic factors evaluated in multivariate analyses in patients with non-small cell lung cancer (NSCLC) was reviewed. Twenty studies including a total of 3500 resected patients revealed that definite prognostic variables in the resectable patient group were performance status, stage, category of tumor size and location (T), and category of lymph node involvement (N). Fourteen studies including a total of 5875 patients with inoperable NSCLC, included in chemotherapy trials with or without radiotherapy, revealed that solely performance status and stage were definite prognostic variables in this non-resectable patient group. Possible predictors of long survival were low LDH, female gender, and high plasma albumin level, while weight loss, histology, and age were of minor importance. A large part of the variation in survival outlook remains unexplained, calling for further studies on the prognostic influence of biological features of the tumors.

Key words: carcinoma, non-small cell lung; lung neoplasms; prognosis

Introduction

The current treatment results for non-small cell lung cancer (NSCLC) clearly call for improved therapy and also for careful selection of patients for the treatment options from which they are most likely to benefit. A detailed knowledge of prognostic factors, meaning variables with a well-established relation to the prognosis, is important for achieving these goals. Any clinical trial must therefore include as assessment of the possible influence of these prognostic factors on the therapeutic results.

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The endpoints against which the prognostic variables are tested are usually disease-free survival and overall survival for surgically treated patient populations, and response rate and survival for non-resectable patients. Analyses with response duration or quality of life as endpoints have been infrequently compared with prognostic variables. This is especially the case for quality of life, which for this reason will not be dealt with in the following.

The ideal prognostic test divides the patients into two or more groups with very different outlook and, accordingly, without any overlaps. However, this situation is relatively uncommon in clinical practice and a more likely situation is using a prognostic test which is able to divide the patients into "high-risk" and "low-risk" subgroups with significant differences in outlook. However, there is still a high degree of

uncertainty, since not all the "high-risk" patients will recur and not all the "low-risk" patients escape the bad outcome. If such test results were used to decide treatment, many patients would receive an appropriate therapy, but not without the occurrence of some over-treatment and some under-treatment.

One way to overcome this obstacle and make a more accurate prediction of outcome is to consider a number of predictors simultaneously.[1] This theme was dealt with in a consensus report on prognostic factors in NSCLC in Bruges in 1993.[2] Besides stressing the importance of different, specific variables on prognosis, the report also emphasized the need for multivariate analyses to determine independent significant predictors of prognosis. Having defined which prognostic factors are the most useful and reproducible, it then becomes possible to generate a prognostic index for individual patients. Such an index would combine all accepted prognostic factors into a single statement of outcome. It is recognized that, in spite of multivariate evaluations, the current variables describing anatomic stage, clinical, histological, and clinical chemistry features do not competely predict the prognosis and a large fraction of the variability remains unexplained.[1]

One possible explanation for this phenomenon is that the most frequently used prognostic variables are in reality epiphonomena of the true cellular and molecular characteristics of the disease, and little is known about the biological model of the disease itself. Thus, more knowledge on these cellular and molecular characteristics is needed.

The objective of the following is to provide an update on the current knowledge of prognostic variables in NSCLC which have been established through multivariate analyses, and which have a documented impact on endpoints.

Material and methods

An update on the current knowledge of prognostic variables in NSCLC which have been established through multivariate analyses is given in the following. Studies are reviewed provided that they are describing prognostic factors for survival solely in NSCLC patients and provide clear descriptions of the variables included in the multivariate analyses. The studies are divided according to whether the study populations consisted of resectable patients or non-resectable patients. Results presented in abstracts are not included.

Results

Multivariate analyses of prognostic factors for survival in resectable NSCLC

Twenty studies[3–22] including a total of 3500 patients with resected NSCLC are summarized in Table 1. It is apparent that none of the variables have been evaluated in all 20 studies. Definite prognostic factors for long survival include good performance status, low stage, and low lymph node category (N). Also low tumor category (T) was a major predictor of survival in many trials, but the variables describing T and N were not independent, significant predictors of survival in all studies evaluating these factors. This observation might be explained by the phenomenon that T and N categories may be less important in Cox multivariate regression analysis when stage of disease is included in the analyses as well. In most studies including these variables, there was a significant prediction by either T and N or by stage.

Possible prognostic factors in Table 1 include variables which have not been evaluated extensively, but have been atributed an independent impact on survival in half or more of the studies. This is the case for postoperative infections, perioperative blood transfusions, and DNA ploidy.

The impact of infections, including empyema, pneumonia, or wound infection in the postoperative period was evaluated by Gail et al.[3] while Deslauriers et al.[7] included patients with major postoperative complications, such as pleurapneumonia, bronchopleural fistulas and respiratory failure into one group. Both trials reported

a significant deterioration of survival outlook, a finding which, however, most probably is less associated with the biological characteristics of the malignant disease than with the treatment.

The effect of perioperative blood transfusion has been a significant prognostic variable in two studies.[8, 18] Both studies included exclusively stage I patients and observed 5-year survival rates of 53 % and 62 % for patients with blood transfusion and 81 % and 76 % for patients without, respectively. Thus, any perioperative transfusions significantly worsens the patients prognosis. This association may be due to an adverse effect of the transfusion itself, or may serve as a marker for another, yet undetermined, risk factor.

The ploidy status of the deoxyribonucleic acid (DNA) has been investigated in five studies[13, 17, 19, 21, 22] and was an independent predictor of survival in three studies.[17, 19, 22] Survival was poorest in patients with DNA aneuploid tumors, and the same pattern, though not significant, was observed in one of two negative studies[21] but not in the other.[13]

A number of variables have been relatively intensively evaluated and shown to be of importance in only few of the studies. These variables may thus be of minor importance as predictors of survival in resected NSCLC patients and are outlined in Table 1. This was the case for variables describing age, gender, histology, histologic degree of differentiation, and extent of

Table 1. Prognostic factors in 20 multivariate analyses including a total of 3500 resected NSCLC patients.

Prognostic factor	No. of positive studies total no. of studies evaluated
Definite	
Performance status	3/3
Stage	9/9
T	5/13
N	5/8
Possible	
Postoperative infection	2/2
Perioperative blood transfusion	2/2
DNA ploidy	3/5
Minor importance	
Age	1/8
Gender	1/9
Histology	3/12
Differentiation	1/4
Extent of resection	3/9
Preliminary	
Tumor giant cells	1/1
Plasma cell infiltration	1/1
Solid ACL/other ACL subtypes	1/1
Satellite pulmonary nodules	1/1
FEV_1	1/1
WBC	1/3
Hemoglobin level preoperatively	1/1
Intratumoral blood vessel invasion	1/2
Ras mutation	1/1
p53 mutation	1/1
p53 protein expression	1/1
Tumor-associated antigen 43-9F	1/1
Proliferative activity	1/2
Cell line stablishment	1/1

Abbreviations: ACL, adenocarcinoma of the lung; FEV_1, forced expiratory volume; WBC, white blood cell count.

surgery (usually evaluated as lobectomy against larger resection).

With respect to histology, both Gail et al.[3] and Deslaurier et al.[7] observed an independent and significant prediction for long survival among patients with squamous cell carcinoma as opposed to patients with non-squamous histology, while these observations were not confirmed in a study by Lipford et al.[4] However, the latter study revealed a significantly worse prognosis for patients having large cell carcinoma. In contrast, 9 studies[9, 13–15, 17–20, 22] did not find any independent prognostic impact of histology. Overall, these 12 studies suggest that the influence of different histologic types of resected NSCLC is only minor when also other variables are taken into consideration.

Other less frequently evaluated prognostic factors are outlined in Table 1. Being evaluated in one trial only, or being positive in one trial only, none of these can be claimed to be established prognostic factors, but should be further evaluated for confirmation or rejection as predictors for survival in this group of patients.

Multivariate analyses of prognostic factors for survival in non-resectable NSCLC

Fourteen studies[23–63] including a total of 5875 patients with inoperable NSCLC included in chemotherapy trials with or without radiotherapy have reported data on multivariate analyses of variables predicting survival. The prognostic variables carrying significant and independent information are outlined in Table 2. Included in this table is also a large recent study evaluating independent prognostic factors among 1565 patients treated with radiotherapy in four clinical trials.[37] Solely performance status has been evaluated in all 15 studies in Table 2 and was significant in 14 studies, indicating that performance status is still the best documented prognostic variable in this patient group.

The new international staging system, as described by Mountain[38] has been evaluated in six multivariate analyses, of which it carried independent and additional significant information on survival outlook in five.[30, 34–37] Thus, the importance of the new staging system has now been firmly documented as an independent prognostic factor for survival both among resected patients and among non-recetable patients receiving other treatment modalities.

Other variables, which may be possible predictors of good prognosis, though evaluated less intensively, are low LDH, female gender, and normal plasma albumin level (Table 2). Variables having minor importance, as indicated by lack of significant influence in the majority of studies in which they are evaluated, include weight loss, histology, and age (Table 2).

The relative importance of other potential variables should be further explored in non-resectable patients. This holds true for a number of biochemical variables, such as white blood cell count (WBC), aspartic aminotransferase (AST), hemoglobin, and calcium. However, these variables may have a less logical theoretical background for having a prognostic impact than the anatomical stage of the disease has. The impact of chemotherapy as opposed to best supportive care and of cisplatin-based chemotherapy against cytostatic treatment without cisplatin has been evaluated by Rapp et al.[28] and by Albain et al.[31] respectively. The Canadian multicenter study by Rapp et al. showed both an enhanced survival for patients receiving chemotherapy and, in addition, that chemotherapy – as opposed to best supportive care only – was an indepent predictor of survival among the 137 patients evaluated in the study.[28] Albain et al. analysed data of 2531 patients with inoperable NSCLC from the Southwest Oncology Group treated from 1974 to 1988.[31] The use of cisplatin was an additional independent predictor of improved outcome in multivariate analyses after adjustments for year of accrual and all other prognostic variables. Although the effect of cisplatin was modest, the data allow the conclusion that it is real and not due to concurrent occurrence of other favourable prognostic variables. These data allow a cautious optimism regarding the development of more effective

Table 2. Prognostic factors in multivariate analyses of non-resectable NSCLC including 14 studies with a total of 5875 patient treated with chemotherapy or chemotherapy plus radiotherapy and one study including 1565 patients treated with radiotherapy alone.

Prognostic factor	No. of positive studies/total no. of studies evaluated	
	Chemotherapy ± radiotherapy (n = 5875)	Radiotherapy alone (n = 1565)
Definite		
Performance status	13/14	1/1
New international staging	4/5	1/1
Possible		
LDH	4/8	
Gender	7/11	1/1
Albumin	2/4	
Minor importance		
Weight loss	3/11	1/1
Histology	2/7	
Age	1/9	1/1
Preliminary		
T stage	1/1	1/1
N stage		1/1
Metastases to		
Liver	3/7	
Bone	2/6	
Subcutaneous	1/1	
0/1 extrathoracic metastasis	1/1	
WBC	1/2	
AST		1/2
Hemoglobin	1/2	
Calcium	1/1	
Chemotherapy/BSC	1/1	
Cisplatin/no cisplatin	1/1	

Abbreviations: LDH – lactate dehydrogenase; WBC – white blood cell count; BSC – best supportive care.

chemotherapy against this disease, but the issue should also be further elucidated.

Biological characteristics

In addition to stage of disease and performance status of the patient, many other factors are important for predicting the prognosis in NSCLC. These factors include the biological properties inherent in the tumor cells themselves (Table 3). The majority of these factors are at present preliminary as they have usually not been evaluated against other variables in multivariate testing. However, the literature is rapidly expanding in this field, as recently outlined by Szabo and Mulshine.[39] These biological characteristics should be subjected to further evaluation in multivariate settings for assessment of prognostic impact.

Discussion

Based on a review of 20 multivariate studies including a total of 3500 patients with complete resected NSCLC it appears that definite prognostic factors in the resectable patient group are performance status and stage. Also T and N status are important, though less so when stage is included in the analysis, serving as a summarizing variable. The two former variables are also the most important among patients with non resectable disease based on a review of 14 studies including a total of 5875 patients. Variables describing age, histology, gender, and

Table 3. Biological characteristics attributed prognostic impact among NSCLC patients in univariate analysis.

Variables
Neuroendocrine differentiation
Oncogenes
K-ras mutation
p53 mutation
L-myc mutation
Oncogene products
p53 protein
c-erb B-2 protein
p 185^{neu} protein
DNA ploidy
Carbohydrate antigens
ABH blood group
Le^y and Le^b antigenes
Le^x antigen (4C9 antigen)
Dolichos biflorus agglutinin (DBA) binding site
Growth factors
Epidermal growth factor receptor (EGFr)
Proliferative activity
Ki67 related antigen

weight loss have been confined with a prognostic impact in fewer studies than performance status and stage.

A large number of variables describing biological features of the tumors have been confined with a prognostic impact among NSCLC patients in univariate analyses. This is the case for variables such as neuroendocrine differentiation, oncogenes, and oncogene products, DNA-ploidy status, presence of carbohydrate antigens, growth factors, and proliferative activity of the tumors. Further studies are warranted in order to further document the value of these variables in order to more accurately predict the prognosis of the patients with NSCLC.

In conclusion, several prognostic variables have been indentified to have an impact on the endpoints for clinical studies of NSCLC. However, a large part of the variability in the prognosis among patients still remains to be explained. The results from studies on the cellular and molecular characteristics of the tumors open prospects for scientifically well-founded forms of therapy in the future, which may in time lead to a better therapy for patients with an otherwise poor prognosis.

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Transbronchial needle aspiration with fiberoptic and rigid bronchoscope in the diagnosis and staging of lung cancer

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In the prospective study from May 1992 till March 1994, the sensitivity of transbronchial needle aspiration (TBNA) performed means of Olympus flexible NA-2C and Storz rigid 10436 or 10438 needles was compared. Fourty patients were included into the study, 14 with already confirmed central lung cancer for the purpose of staging, and 26 patients because central lung cancer had been suspected.

Thirty patients had lung cancer and five had metastases of extrapulmonary malignant tumours to the lung and mediastinal lymph nodes. In 5 patients no cancer was found. TBNA of the carina was performed 30 times, of the trachea 7 times and of the right upper lobe bifurcation 8 times. In five patients, minor bleeding occurred after TBNA with a rigid needle.

The sensitivity of TBNA for cancer with Storz needle was 64 % (21 positive out of 33) and 45 % with the Olympus needle (15 positive out of 33). The difference between the two needles was statistically not significant. In 12 patients the TBNA was false negative.

A satisfactory histological sample was obtained in 18 patients with Storz needle. In 6 patients the histologic diagnosis was carcinoma; in 4 nonspecific inflammation and in one patient tuberculosis. TBNA with a rigid needle gives some additional information in comparison with a flexible one. TBNA helps establishing the diagnosis and staging of central lung cancer and improves the bronchoscopic diagnosis. Its sensitivity is satisfactory and complications are few.

Key words: lung neoplasms-diagnosis; biopsy, needle-methods, bronchoscopy; neoplasms staging

Introduction

The transbronchial needle aspiration biopsy (TBNA) of mediastinal lymph nodes was first described by Schieppati.[1] The method was further developed and introduced into practice in the USA[2] and Europe.[3] It became commonly used with the introduction of flexible needles suitable for TBNA through fiberoptic bronchoscope.[4] The fiberoptic bronchoscope has largely replaced the rigid one and only a few authors still report cytological[5,6] or histological[7] examinations of TBNA by rigid bronchoscope. The efficiency of TBNA with fiberoptic broncho-

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scope is comparable with the results that had been previously obtained by the rigid instrument.[8]

TBNA can often replace the surgical methods of staging, i.e. cervical mediastinoscopy and anterior mediastinoscopy in patients with lung cancer. In general, it is agreed that those patients, in whom malignant cells are found on TBNA are considered to be inoperable.[6,9,10] The patient is certainly inoperable if the metastasis has overgrown the capsule, if the metastases are multiple or are present on the contralateral side of the mediastinum.[11-13] If only one micrometastasis into a mediastinal lymph node is present, the prognosis of patients who underwent surgery is better.[9]

TBNA is used also in the diagnostics of necrotic endobronchial tumours in whom frequently only necrosis is obtained by forceps biopsy.[14] In submucously growing bronchial tumours TBNA is successful as well.[15-16] Good results were obtained also in the diagnostics of peripheral tumours.[17] Even better results in the diagnostics of peripheral tumours were obtained by the use of needle brush.[18] TBNA is successful also in the diagnostics of pulmonary metastases from extrapulmonary malignant tumours.[19]

False positive results of TBNA are rare; they may be due to the aspiration of malignant cells from bronchial secretion.[20,21] Transtracheal needle aspiration biopsy of a tumour of the right upper lobe has been described.[2,23] Complications such as pneumothorax after TBNA of peripheral lesions,[17] haemomediastinum,[24] bacteriemia[25] or smaller bleedings into the bronchi[26] are rare.[27]

The frequent false negative findings represent the greatest problem of TBNA.[28]

In our study we tried to establish the sensitivity of TBNA with both a flexible and a rigid needle. We wanted to find out which of them provides better results, and whether TBNA improves the bronchoscopic diagnostics and staging of patients with central lung cancer and metastases of extrapulmonary malignant tumours into the lungs and mediastinal lymph nodes. TBNA related complications were studied as well.

Material and methods

The prospective study of TBNA was approved by the ethic commission of the Institute for Respiratory Diseases Golnik.

From May 1992 till March 1994, 40 patients were included into the study. In 26 patients clinically and roentgenologically a central lung cancer was suspected (tumour visible by fiberoptic bronchoscope), while in 14 patients with comfirmed central lung cancer staging was necessary prior to the plonned surgical intervention. Thirty-two males and 8 females with the mean age of 53 years were included into the study.

Prior to bronchoscopy, posteroanterior and lateral X-rays of the thorax were performed. In patients, candidates for surgical treatment, computed tomography (CT) of the thorax was performed as well, mostly after bronchoscopy.

Bronchoscopy was performed with a fiberoptic bronchoscope Olympus 20 D and a Storz bronchoscope No. 8. Premedication was Atropini sulphas 1 mg subcutaneously. We used local anaesthesia with Xylocain 4 % 5 ml in drops or transtracheally, together with the application of narcotic analgetic fentanyl citrate 0,1 mg intravenously. In 16 patients, diazepam was given intravenously as an additional premedication. During the procedure, up to 20 ml of 2 % Xylocain was added through the working channel of the bronchoscope, and the patient received 3 L of oxygen min by nasal catheter.

Fiberoptic bronchoscope was introduced through the nose, through the mouth with an orotracheal tubus or through the channel of a rigid bronchoscope. TBNA was performed first with an Olympus NA-2C flexible needle. This 21 gauge, needle is 13 mm in length, with a side hole. In every site of aspiration biopsy the needle was introduced three times to the area of 1 to 2 cm. Afterwards aspiration biopsy of the same sites was performed also by a rigid straight needle 10436 of by a curved needle Storz 10438. This needle is of 22 mm length with 17 gauge. The carina was aspirated with the straight needle, and the trachea and the right upper lobe bifurcation with the curved

needle. The flexible needle was introduced by a shaft through the working channel. When we had seen the top of the shaft, the needle was protruded from the shaft and advanced by a quick thrust between two cartilages. Sometimes the patient helped the advancing of the needle by coughing. Even if this manoeuvre had not been successful, the needle was fixed on the upper part of the working channel of the bronchoscope, and both the needle and the bronchoscope were advanced.

The rigid needle was thrusted into the wall between two cartilages and to the shaft. We aspirated by a 20ccm syringe. TBNA was technically easier with the rigid needle. Then we examined the entire tracheobronchial system and obtained the forceps biopsy and brushing. The patients were monitored for 24 hours after bronchoscopy for possible complications. X-ray was not made routinely.

The first and the second aspirations were expelled from the needle on to a glass slide. The third aspiration was rinsed in Haemacell (Hoechst) and the smears from Haemacell were prepared by cytocentrifuge (Shandon Cytospin II). The smears were stained by May Grünwald Giemsa and Papanicolau. The aspirations in which the elements of lymph nodes were found together with a few epithelial cells were considered as satisfactory. This criterion was suggested by Baker.[29] All three aspirations obtained by one needle were considered as a single result. The particles of the tissue obtained by the rigid needle, were fixed in the 10% formalin and examined by standard histological methods.

The sensitivity was calculated as the quotient of the number of TBNA with malignant cells in all patients with metastases in the mediastinal lymph nodes. The sensitivity of TBNA with both flexible and rigid needle was compared by Chi square test.

Results

From May 1992 till March 1994 TBNA was performed in 40 patients by fiberoptic and rigid bronchoscopy. Thirty patients had primary lung cancer, while 5 had metastases of extrapulmonary malignant tumours into the lungs and mediastinal lymph nodes (Table 1). In 5 patients nonmalignant lung diseases were found as follows: tuberculosis, sarcoidosis and connective tissue disease, and pneumonia in two patients, but no cancer.

Table 1. Diagnoses of patients with malignant tumours included into the TBNA study.

Lung cancer		Metastatic lung lesions	
Small cell	7	Adenocarcinoma-breast	1
Large cell	4	Adenocarcinoma-pancreas	1
Adenocarcinoma	7	Adenocarcinoma-unknown	
Squamous cell	12	origin	1
		Hodgkin's Disease	2
Total	30	Total	5

The site of the aspiration biopsy was the main carina in 30 patients, the carina of the right upper lobe in 8 and the trachea in 7 patients. In 3 patients the TBNA was done both through the main carina and through the trachea, and in two patients through the main carina and through the carina of the right upper lobe.

TBNA with a Storz needle was positive in 60% (21 of 35) and with an Olympus needle, at the same sites, in 43% of patients (15 of 35). One of the aspirations obtained by the Olympus needle was cytologically suspicious. In the assessment of sensitivity it was included among the negative findings. There were no statistically significant differences between the sensitivity of TBNA performed with either Storz or Olympus needles. In 6 patients, malignant cells were found in TBNA by the Storz needle only. In no case the malignant infiltration of mediastinal lymph nodes was confirmed by the Olympus needle alone (Table 2).

Table 2. Comparison of Storz and Olympus needle TBNA results in 33 patients with metastatic mediastinal lymph nodes.

		Storz Needle	
		+	−
Olympus needle	+	15	0
	−	6	12

The sensitivity of TBNA in patients with lung cancer and extrapulmonary malignant tumours with metastatic mediastinal lymph nodes is presented in Table 3.

Table 3. Sensitivity of TBNA in lung cancer and extrapulmonary malignant tumours with metastatic mediastinal lymph nodes.

Tumour	Positive TBNA	Sensitivity (%)
Small cell	6 of 7	86
Large cell	3 of 4	75
Adenocarcinoma	5 of 7	71
Squamous cell	5 of 10	50
Lung cancer – total	19 of 28	68
Extrapulmonary malignant tumours	2 of 5	40
Total	21 of 23	64 %

In the bronchoscopic diagnostics, the forceps biopsy and brushing were used. The sensitivity was 77 % (27 of 35). In two patients with small cell lung cancer and in one patient with adenocarcinoma, TBNA was the only bronchoscopic method confirming the malignoma and increasing the sensitivity of bronchoscopic methods to 86 %.

In 7 patients with no mediastinal involvement TBNA was negative. There were no false positive findings, the specificity being 100 %.

Among the patients with positive TBNA, 17 had bronchoscopic signs of extrinsic pressure on the trachea, carina or on the right upper lobe bifurcation at the site of TBNA. Only 4 patients had a normal bronchoscopic finding in the site of TBNA (Table 4).

Table 4. Frequency of positive TBNA in relation to bronchial extrinsic compression.

	TBNA positive	TBNA negative
Extrinsic compression	71 % (17 of 24)	29 % (7 of 24)
Without compression	36 % (4 of 11)	64 % (7 of 11)
Total	60 % (21 of 25)	40 % (14 of 35)

Tissue for histological examination was obtained by Storz needle only in 40 % of patients (14 of 35) with malignant lung tumours. In 6 patients histology confirmed metastases while in 8 patients it was negative. The histological and cytological type of malignoma were consistent in 5 cases; in one patient the histological diagnosis was large cell carcinoma while the cytological one was adenocarcinoma. In three TBNA with histological signs of inflammation, malignant cells were found only cytologicaly.

Histologically, five patients had TBNA with no malignant tissue and aspiration with no malignant cells. In these patients, cartilage and other parts of bronchial wall were found histologically. These samples were deemed unsatisfactory.

In 14 patients TBNA was without malignant cells. In 6 of these, the mediastinal node metastases were not found on surgery in 2.

Other 12 (34 %) cases were considered to have false negative TBNA.

Mediastinal lymph node metastases were found in 4 patients; in 2 by pneumonectomy, in one by explorative thoracotomy and in one by left lower lobectomy. In two of them, the affected lymph nodes had not been accessible by TBNA: one in paraesophageal – N_8 and the other in the lymph nodes of pulmonary ligament – N_9.

In 8 patients, metastases in the mediastinal lymph nodes were confirmed: once by transthoracic needle aspiration and twice by mediastinoscopy. In 5 patients we indirectly estimated metastatic involvement of the mediastinal lymph nodes, which were roentgenologically enlarged. Two patients had Hodgkin's disease, one patient had small cell lung cancer and two patients had distant metastases in the brain and parietal pleura.

In one patient, right pneumonectomy was performed even though TBNA of the right upper lobe bifurcation revealed malignant cells. TBNA of the main carina was not performed. Metastases in the carinal lymph nodes were found on pneumonectomy.

In patients with benign lung diseases in 4 cases (80 %) tissue was obtained by a Storz needle. In one patient tuberculous lymphadenitis and in the other nonspecific inflammation was found. In the third patient the cytological

examination showed epitheloid cells and lymphocytes. In this patient transbronchial lung biopsy showed nonnecrotising granulomas, which was consistent with the diagnosis of sarcoidosis.

After TBNA with a Storz needle in 5 patients, minor bleeding was observed which ceased spontaneously. Hemorrhage was observed 4 times after TBNA of the main carina and once after TBNA of the right upper lobe bifurcation. Twenty-four hours after the intervention no other complications were observed.

Discussion

In our study the efficiency of TBNA (64 %) is similar to that obtained by other authors: 34 %,[8] 46 %,[26] 71 %.[16] We consider that, in addition to the technical performance of TBNA, the selection of patients is of great importance. In our patients the sensitivity was established only in those patients who had central lung cancer visible by fiberoptic bronchoscope, and in whom roentgenograms showed enlarged lymph nodes in the mediastinum where metastases were confirmed or strongly suspected. The sensitivity in our study is therefore approaching that achieved by Shure and Fedullo,[16] whose criterion for inclusion into the study was submucous growth or peribronchial tumour. Even greater sensitivity may be reached if the presence and site of enlarged lymph nodes in the mediastinum were proved by computed tomography.[22] According to the success in our patients, CT is not considered to be essential prior to TBNA. Other authors are of the same opinion.[31] Malignant cells were most frequently found in TBNA in patients with signs of external pressure on the bronchi. This finding was in agreement with those of other authors confirming malignant cells in TBNA of such patients in 33 %,[8] 53 %[31] or even 62 %.[26] The lowest sensitivity of TBNA, only 7 %, was described by British authors,[32] probably because TBNA was applied during routine bronchoscopies and performed by a needle for sclerosation; only samples with abundant malignant cells were considered positive.

We found that TBNA increased the bronchoscopic diagnosis of lung cancer by almost 9 % (3 of 35). TBNA showed a similar improvement of bronchoscopic diagnosis also in other authors: by 7 %,[31] 14 %[33] or even 18 %.[34] TBNA significantly improves the bronchoscopic diagnostics by forceps biopsy, brushing and washing.[35] The sensitivity of TBNA with Storz needle was insignificantly higher from that with Olympus needle. Despite that, in 6 patients malignant cells were confirmed by aspiration with Storz needle only.

We think that TBNA with a rigid bronchoscope has been abandoned because it requires general anaesthesia, while local anaesthesia is considered more inconvenient for the patient,[36] and not because it would be less efficient. The results of TBNA with rigid and fiberoptic bronchoscope were comparable.[3,8] We had similar results. By application of sedatives and modern narcotic analgetics, the patient can tolerate bronchoscopy either with a rigid or flexible instrument.

We find it important that in 40 % of patients also samples of tissue for histological examination were obtained by Storz needle which enabled the diagnosis of malignoma in 6, and of nonmalignant disease in 2 patients. The sensitivity of 20 % (8 out of 40) cannot be compared with that to new flexible needles for histological examination: 72 %,[37] 80 %[38] or even 85.5 %.[39] The histological examination of the tissue in TBNA enables the differentiation of bronchial wall or peribronchial tissues involvement, especially lymph nodes. Possibly, rare false positive results could be excluded as well.

We are not quite sure that there were no false positive results among our TBNA findings because the involvement of mediastinal lymph nodes in TBNA positive patients was not verified by the most reliable methods of surgical staging,[9] the final test being the follow up. To prevent possible aspiration of malignant cells from the bronchial secretion, we have followed the principles of other authors[33] and performed TBNA first, and only afterwards on examination of the bronchial system and forceps biopsy were performed together with brushing. Since

false positive TBNA are rare, this method often allows omission of surgical staging.[39]

However, the greatest problem is encountered with patients who have had negative finding of TBNA; there were 14 (40%) such cases among our patients. In these patients, surgical staging is necessary if they are potential candidates for resection.

By obtaining six aspirations from the same site, in each patient the efficacy of the method was improved. The expelling of the sample on a glass slide had been used as recommended by Ndukwu.[40] According to our experience, washing of the needle with Haemacell is equally or even more efficient; namely in the third aspiration we frequently found malignant cells and they were more abundant. Due to technical reasons, the cytologist was unable to examine the material immediately so that in the case of negative aspiration the bronchoscopist might repeat TBNA immediately as it had been recommended by Davenport.[41]

Mediastinal metastases were found by TBNA most frequently in patients with small-cell lung cancer, followed in descending order, by those with large cell, adenocarcinoma and squamous cell lung cancer. This is in agreement with most other studies.[31]

As was found by other authors,[6,31,33] also in our patients only minor bleedings during TBNA occured. They were more abundant after aspiration biopsy by Storz needle, as it had been expected since this needle is longer and broader. We avoided aspiration biopsies of the posterior tracheal wall and the right main bronchus since the biopsy in these sites is more hazardous.[42]

The sensitivity of TBNA by Olympus needle is satisfactory and comparable with TBNA performed by Storz needle. Histological diagnosis of malignant and benign diseases is sometimes possible by Storz needle. TBNA improves the bronchoscopic diagnosis of pulmonary malignant tumours and in many patients enables the staging of lung cancer in an easy, cost-effective and safe way.

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Carcinoembryonic antigen (CEA) levels in pleural effusion and serum in differentiation of malignant and benign pleural effusion

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We determined CEA levels in pleural effusion (CEAP) and in serum (CEAS) of 67 patients. Thirty-eight patients had histologically and/or cytologically proven malignant effusion (Group I) and 29 patients had benign effusion (Group II). The obtained data were analysed using multifactorial Kruskal-Wallis test, Bayesian theorema and Spearman rank correlations.
Results: 1) There was a significant difference between the levels of CEAP in Groups I and II ($p < 0.001$), 2) there was no significant difference between the levels of CEAS in Groups I nad II, 3) there was satisfactory sensitivity, specificity and predictive value of CEAP in the diagnosis of malignant pleural effusion, 4) combined measurement of CEAS-CEAP in the diagnosis of malignant pleural effusion by cut-off levels 10 ng/ml – 7 ng/ml had a positive predictive value of 0.95.

Key words: pleural effusion carcinoembryonic antigen, pleural effusion, malignant

Introduction

Carcinoembryonic antigen (CEA), first described by Gold and Fredman in 1965, has been an extensively used serologic marker. Increased levels are detected in carcinoma of the large intestine, anus, pancreas, liver, stomach, esophagus, pharynx, ovaries, breast, lung, thyroid gland, some hemoblastoses and sarcomas as well as in some benign diseases: bronchitis, pulmonary emphysema, tuberculosis, hepatic cirrhosis, hepatitis, ureamia, or in heavy smokers.[1]

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CEA determined in serum, may be used in monitoring the course of disease or as a prognostic factor in patients with some types of cancer, whereas CEA serum determination for diagnostic purposes[1–3] is less effective.

CEA levels in pleural effusion have been investigated by several authors to distinguish malignant effusion from benign.[4–7] However, the diagnostic usefulness of CEA measurement in pleural effusion is still unexplained.

The aim of the present study was to determine and compare CEA levels in pleural effusions (CEAP) and in sera (CEAS) of patients with malignant and benign pleural effusion and to determine the value of CEAP and CEAS in differentiation between malignant and benign pleural effusion.

Patients and methods

Patients

67 patients with pleural effusion were enroled into this study. 38 patients (Group I) had histologically and/or cytologically proven malignant effusion: in 23 patients by lung cancer, in 10 patients by breast cancer, in 3 patients by other types of cancer, in 2 patients by disseminated cancers of unknown origin. 29 patients (Group II) had benign effusion: in 18 patients by tuberculosis, in 8 patients by TB-unrelated pneumonia, in 3 patients by ischemic heart disease.

In Group I were 20 men, 18 women, age-median: 62 years (range: 42–82), in Group II were 16 men, 13 women, age-median: 60 years (range 16–91).

CEA determination

The samples of pleural fluid and sera were obtained on the same day in each patient. CEA was measured with commercially available radioimmunoassay kits.

Statistical analysis

For the statistical analysis the multifactorial Kruskal-Wallis test, Bayesian theorema, and Spearman rank correlations were used.[8, 9]

Results

Table 1 shows the median CEA levels in pleural fluid and sera of patients with malignant (Group I) and bening (Group II) pleural effusion.

In Group I CEAP levels exceeded the cut-off levels of 5 ng/ml in 28 patients, 7 ng/ml in 27 patients, and 10 ng/ml in 23 patients. In Group II the CEAP levels exceeding the above-mentioned cut-off levels were found in 6, 5, and 4 patients respectively.

CEAS levels exceeding the cut-off level of 5 ng/ml were found in 31 patients, 7 ng/ml in 26 patients, and 10 ng/ml in 23 patients of Group I. In Group II the cut-off levels were exceeded only in 18, 10, and 5 patients respectively.

There was a correlation between the levels of CEAS and CEAP in Group I: $r = 0.88$, $p = 0.0000$ (+ + +).

Significant correlation (but still less strong) between the levels of CEAS and CEAP was found also in Group II: $r = 0.41$, $p = 0.25$ (+).

The comparison of CEAP and CEAS levels in Group I and Group II is shown in Figure 1.

Table 1. CEA levels in pleural effusions (CEAP) and serum (CEAS).

Median (xl – xn)	CEAP (ng/ml)	CEAS (ng/ml)
I Malignant effusion (n = 38)	20.0 (0.1 – 360.0)	15.0 (0.9 > 80.0)
II Benign effusion (n = 29)	3.75 (0.1 > 7.0)	5.55 (2.0 > 14.0)

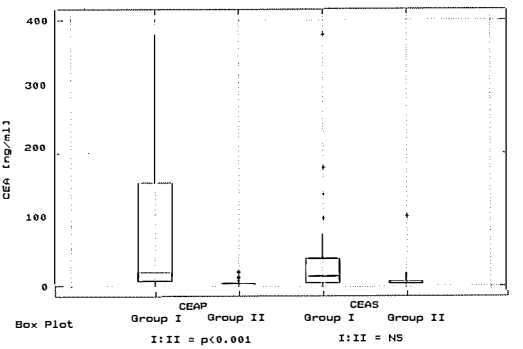

Figure 1. Comparison of CEAP and CEAS in patients with malignant (Group I) and benign (Group II) pleural effusion.

There was a significant difference between the levels of CEAP in Groups I and II ($p < 0.001$), but the difference between the levels of CEAS in Groups I and II was not significant.

The sensitivity, specificity, and predictive value (positive and negative) of different CEA cut-off levels in the diagnosis of malignant pleural effusion are shown in Table 2.

Positive predictive value of different combined CEAS – CEAP cut-off levels in the diagnosis of malignant pleural effusion is shown in Table 3.

Discussion

Elevated levels of CEAP were found to correlate with malignancy at sensitivities ranging

Table 2. Sensitivity, specificity, and predictive value (positive and negative) of different CEA cut-off levels in the diagnostic of malignant pleural effusion.

CEA	Cut-off (ng/ml)	Sensitivity (%)	Specificity (%)	Predictive value Positive	Predictive value Negative
Pleural effusion	5	72.05	78.57	0.83	0.65
	7	71.05	82.71	0.86	0.67
	10	60.53	85.71	0.87	0.59
Serum	5	76.05	40.11	0.65	0.52
	7	63.00	66.00	0.73	0.54
	10	56.01	83.00	0.83	0.65

Table 3. Positive predictive value of different combined CEAS – CEAP cut-off levels in the diagnostic of malignant pleural effusion.

CEAS (ng/ml)	–	CEAP (ng/ml)	Test results and predictive value			
Cut-off level			1–1	1–0	0–1	0–0
5	–	5	0.86	0.40	0.74	0.24
5	–	7	0.88	0.39	0.78	0.23
5	–	10	0.89	0.46	0.79	0.28
7	–	5	0.90	0.49	0.73	0.23
7	–	7	0.92	0.49	0.77	0.22
7	–	10	0.93	0.62	0.61	0.33
10	–	5	0.94	0.63	0.72	0.22
10	–	7	0.95	0.63	0.76	0.21
10	–	10	0.95	0.69	0.77	0.26

Tests results: 1 – positive, 0 – negative

from 25 % to approximately 70 % using different cut-off levels from 5ng/ml to 15ng/ml.[4, 10, 11] By using lower cut-off levels, it has been impossible to detect a significant difference between benign and malignant effusion.[12]

In our study the cut-off level of CEAP 10 ng/ml has yielded a sensitivity of 60.53 %, specificity of 85.71 %, and positive predictive value of 0.87. The combined measurement of CEAP and CEAS has further enhanced the positive predictive value.

In other words, the probability of malignant etiology by elevated levels of CEA both in serum and pleural effusion over 5 ng/ml is 86 %, over 7 ng/ml – 92 %. In the presence of CEA levels in serum exceeding 10 ng/ml, and CEA levels in pleural effusion exceeding 7 ng/ml the probability of malignancy is 95 %.

Nevertheless, these probabilities are influenced by the studied group of patients referred to our institute. The prevalence of malignant effusion in this group of patients was 0.6. By changing prevalence, according to the situation in other institutions, different probabilities may be expected.

In conclusion, the measurement of CEA levels in pleural effusion, together with the measurement of CEA levels in serum, in addition to cytology, pathology, and other studies, may contribute to the diagnostic evaluation of patients with pleural effusion.

For the institutions dealing with differential diagnosis of pleural effusion in larger groups of patients we would recommend the statistical analysis which would take into account the local situation – prevalence of the malignant pleural effusion – before choosing the optimal values of CEAP and CEAS for diagnostic purposes.

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Tumor markers and hormones as a diagnostic and prognostic test in lung cancer

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A study of the blood-levels of carcinoembrionic antigen (CEA), alfa-fetoprotein, ferritin, ACTH, cortisol, triiodothyronin (T_3) and thyroxin (t_4) carried out by means of radioimmunoassay in 61 patients with lung cancer, 57 patients with lung tuberculosis and in 12 healthy controls has shown that the levels of CEA, ferritin and cortisol in patients with lung cancer exceed the levels in patients with lung tuberculosis ($p < 0.05$) and the controls ($p < 0.05$). Low levels of T_3 and T_4 were found in more than 70 % of lung cancer patients ($p > 0.05$). The highest level of ACTH was noted in patients with adenocarcinoma (20.68 nmol/L) and distant metastases (21.12 nmol/L). There was no correlation between the clinical stage of the disease, the histological pattern of tumor and the levels of tumor markers. These data can be used as a diagnostic and prognostic test.

Key words: lung neoplasms-diagnosis; tumor markers, biological; hormones; prognosis

Introduction

A study of the blood-levels of tumor markers and hormones has been recently widely used as a diagnostic and prognostic test in lung cancer simultaneously with other routine methods.[1–4] The aim of our work was to determine the blood-levels of some tumor markers and some hormones for initial diagnosis and differential diagnosis of cancer and tuberculosis of the lung.

Material and methods

The blood-levels of carcinoembryonic antigen (CEA), cortisol, triiodothyronim (T_3), thyroxin (T_4) (made by means of a standard kit produced in the former Soviet Union) and alfa-fetoprotein, ferritin, ACTH (of the French firm CIS) were measured by means of radioimmunoassay in 61 patients with lung cancer (group 1), 57 patients with tuberculosis of the lung (group 2) and in 12 healthy coontrols (the control group 3). The blood was taken on an empty stomach in the morning. The serum was kept in a refrigerator at –20° C not more than 1–2 months. The obtained data underwent statistical analysis. Forty-seven man and 14 women formed the first group of patients, aged 46–72. 22 patients had the second stage of cancer. The third stage was diagnosed in 23 cases while 16 patients had the fourth stage of the disease. All the cases were histologically or cytologically verified. Fourteen had adenocarcinoma and 27 squamous cell carcinoma. Small-cell lung cancer was diagnosed in 20 patients. In 38 cases it was

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necessary to conduct differential diagnosis between the infiltrative form of tuberculosis and the central cancer of the upper lobar bronchus with atelectasis or hypoventilation. Twenty-three patients had a peripheral tumor of the upper lobe which was difficult to differ from tuberculoma or the rounded shape of infiltrate. Group 2 comprised 46 men and 11 women, ranging in age form 25 to 67 year. The infiltrative form of tuberculosis was present in 28 patients and the cavity phase of tuberculosis in 29 patients. Since in all the examined patients there has not been established a distinct dependence of tumor markers and hormones upon age, sex, stages of cancer, different forms of tuberculosis, etc., the data in Table 1 are given for all groups together.

Table 1. The blood levels of tumor markers and some hormones in the group observed.

Tumor markers, hormones (nmol/)	Control group (n = 12), M ± m	Group 1 (n = 61), M ± m	Group 2 n = 57), M ± m
CEA	0.04 ± 0.01 (0.01 – 0.06)	0.17 ± 0.015*,** (0.10 – 0.19)	0.081 ± 0.015* (0.04 – 0.10)
Ferritin	0.10 ± 0.026 (0.08 – 0.13)	0.668 ± 0.52* (0.52 – 0.86)	0.486 ± 0.44** (0.10 – 0.61)
ACTH	11.52 ± 0.73 (9.22 – 13.41)	16.97 ± 1.6* (11.0 – 18.33)	11. 96 ± 1 .32 (10.28 – 13.0)
Cortisol	182.87 ± 33.68 (146.4–20.27)	652.10 ± 60. 3*.** 594.0 – 730.0)	330.15 ± 46.9* (290.0 – 400.0)
T_3	2.26 ± 0.12 (2.13–3.0)	1.33 ± 0.03 (0.96 – 2.30)	1. 23 ± 0.35 (0.88 – 2.20)
T_4	67.9 ± 9.9 (57.9 – 78.0)	59.15 ± 3.5 (50.1 – 68.0)	83. 5 ± 7.5** (72.4 – 93.0)

* Significantly higher ($p < 0.05$) than the control.
** Statistically significant diference ($p < 0.05$) between the first and the second groups.
The limits of the levels variation of the substances studied, are given in parentheses.

Results and discussion

As evident from Table 1 in patients with lung cancer much higher blood levels of CEA, ferritin and cortisol were found than in the control group (the lowest blood-levels of these substances in group 1 were higher than the highest ones in group 3.) The inter group comparison revealed significan differences ($p < 0.05$). The excess of ACTH was found in 70% of lung cancer patients (more than 13.5 nmol/ L). The excess was significant ($p < 0.05$). Lower levels of T_3 and T_4 were found in more than 70% of lung cancer patients. The difference was not statistically significant. The blood levels of CEA and cortisol in patients with lung cancer were significantly higher ($p < 0.05$) than those in patients with tuberculosis. The same substances and ferritin in patients with tuberculosis were significantly higher ($p < 0.05$) than those of the controls.

This phenomenon is difficult to explain. It is still harder to explain the significantly higher ($p < 0.05$) blood levels of thyroxin in patients with tuberculosis than in the by can group. The correlational analysis demonstrated a high positive Pearson r (r_1 in r_2 more than 0.8) between the levels of ACTH, cortisol and the levels of ACEA. There was no correlation between the clinical stage of the disease, the hystological pattern of tumour and the level of CEA found, although there was a two-threefold excess in individual cases. The blood-levels of CEA, for

example, in the individual patients with a central cancer of the lung stages III-IV reached 1.075–1.525 nmol/L. The average levels of CEA in patients with small-cell lung cancer was 0.335 ± 0.02 nmol/L and two-threefold higher in patients with squamous cancer and adenocarcinoma (0.007 ± 0.01 and 0.126 ± 0.01 nmol/L) respectively. The highest level of ACTH is found in patients with adenocarcionoma (20.68 nmol/L) and with distant metastases (21.12 nmol/L). As a rule, an increase in the level of ACTH associated with an increase in the level of cortisol.

These data, which are hard to explain, can be used as a diagnostic and prognostic test. In conclusion it is necessary to say that the most valuable information for the primary diagnosis and the differential diagnosis of lung cancer can be obtained from CEA, cortisol and ferritin. Our data are consistent with literary data.[5]

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Adrenocorticotropic hormone and cortisol levels depending on the outcome of non-small cell lung cancer treatment

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The comparative analysis of adrenocorticotropic hormone (ACTH) and cortisol serum levels was performed in 25 patients with non-small cell lung cancer, surviring 5 and more years after radical surgery and in 220 patients who died due to tumor progress in the first years of observation. The aim of our study was to determine (the) additional criteria for the assessment of disease prognosis. The important differences distinctions in the hormone concentrations in blood serum, which depended on the stage of disease and patients survival have been shown as well. A statistically significant increase in ACTH and cortisol levels was found in lung cancer patients as well as in controls. The ACTH serum level decreased with an advanced tumor stage.

Key words: carcinoma, non-small cell lung; adrenocorticotropic hormone; cortisol; treatment outcome

Introduction

The efficiency of lung cancer treatment in influenced primarily by the extent of tumor involvement. However, the existing examination methods fail to diagnose subclinical metastases. So it is necessary to search for additional criteria to estimate the extent of lung cancer involvement.

Differences in the hormonal profile of lung cancer patients are of both theoretical and practical interest as they can be used for accurate diagnosis as well as for monitoring of the disease and follow up of treatment results.

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The aim of our investigation is to study adrenocorticotropic hormone (ACTH) and cortisol serum levels depending on the extent of tumor growth and the outcome of lung cancer treatment, as well as to estimate the possibility of using these hormone levels as additional criteria of prognosis.

Materials and methods

Blood sera from 220 patients (209 men, 11 women) at an age of 44–64 years, with morphologically confirmed non-small cell lung cancer were studied. The control group included 25 healthy volonteers at an age of 40–58 yrs examined according to the contract. Stage I tumor (T1-2 NO MO) was established in 32 patients while 66 patients had Stage II (T1- 1N 1MO) and 91 patients stage III of the disease (T1-3

N2 MO). Distant metastases were found in 31 patients. All patients were divided into 2 groups depending on the treatment outcome. Group I included 45 patients who had survived with 60 months and more with no evidence of tumor progression. Group II included 175 patients who died of disease progression within 24 months from the beginning of therapy.

Commercial kits such ans ACTHK -PR, Steron – K – 1251 were used for determining the concentration of hormones studied. The investigation was perfomed before the special treatment was studied. The blood was drawn in the morning from 8.30 a.m. to 9.00 a.m. in patients on an empty stomach. A singl blood sample of 10.0 ml was collected into a test-tube containing 30 μg of ethylenediaminetetraacetat and 50 μl. of hordox. After centrifugation at a speed of 2000 rpm for 10 minutes, the blood serum was dripped into plastic test-tubes in a dasage required for the analysis (25, 50, 100, 200 μl). The analysis methods were perfomed according to the enclosed instructions. The calllibration as well as all estimated samples were paired. The result were not taken into account in the case when the analysis error between the pairs exceeded 20%. The measurements of hormone concentrations and the guality control were performed according to the special programmes using intralaboratory control sera. The mean rate in the group of healthy volunteers was taken as cut-off value (for 6.23 ± 0.726 pmol/l, for ACTH and 364.6 ± 27.40 nmol/l for cortisol).

Results

The comparative analysis of hormone levels in patients with lunc cancer and in healthy volunteers showed a statistically significant increase in ACTH and cortisol levels in patients with lung cancer. ACTH and cortisol levels in patients with lung cancer exeeded those of the control group in 78.8% and 73.5% of patients, respectively. The mean levels of hormones studied are given in Table 1. Despite the elevated ACTH levels in the blood serum of patients with lung cancer there were no clinical manifestations typical for Itsenko-Kushing syndrome in any case.

The analysis of ACTH and cortisol levels revealed the correlation of these markers with both the tumor stage and the treatment outcome. A statistically significant increase in ACTH and cortisole levels in lung cancer patients was found as compared to the hormons levels in the control group. Taking into account the tumor stage and the outcome of treatment in patients with good treatment results the evalution of the ACTH level showed a clear inverse dependence: the hormon levels decreased by higher tumor stage. The highest ACTH levels were observed in patients with stage I lung cancer (19.1 ± 3.22 pmol/l) with a gradual decrease in its level at stage III (12.9 ± 1.52 pmol/l) and stage IV (12.9 ± 2.11 pmol/l). ACTH concentration in patients with unfavourable treatment outcome was found to be practically unchangedable) irrespective of the stage. The rates of ACTH level in patients with a favourable treatment outcome at stage I and II lung cancer were significantly higher than in the group with soor treatment results (Figure 1).

No statistically significant differences in the cortisol levels were found between the groups with stages II, III and IV. There was a tendency

Table 1. Mean levels of markers in healthy persons and in patients with lung cancer.

Hormones	Healthy persons		Patients with carcinoma	
	N	M ± m	N	M ± m
ACTH pmol/l	25	6,23 ± 0,726	203	12, 0 ± 0,88*
Hydrocortisone nmol/l	25	364,6 ± 27,40	218	445, 4 ± 14,20*

Notes: * – statistically significant difference between groups ($p < 0,05$)

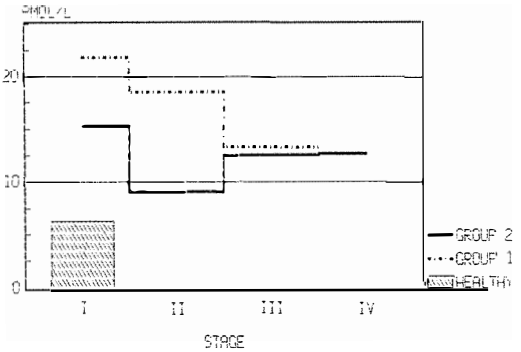

Figure 1. ACTH level in patients with carcinoma of the lung according to the stage of disease and treatment results.

to the hormone level decrease in patients with stage II and stage IV. At the same time when studying the cortisol levels with regard to treatment results, it was found that the patients who had died of tumor progression within the first 2 years of folow-up showed a tendency contrary to the ACTH level. The hormon concentrations increased by higher stage of lung cancer. In the group with favourable results, the changes in cortisol levels followed the same trend as the changes in ACTH levels i.e. they decreased progressively from stage I (485.6 ± 21.72 nmol/l) to stage III (411.0 ± 44.09 nmol/l). The difference in long-term treatment results between the groups with stage II and stage III disease was statistically significant. (Figure 2).

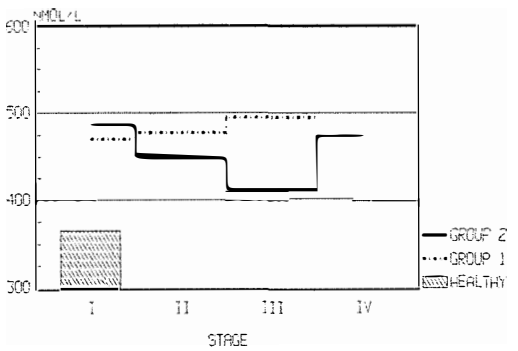

Figure 2. Cortisol level in patients with carcinoma of the lung according to the stage of disease and treatment results.

Discussion

One of the main links in the realization of adaptation organism responses is the change in the hypothalamo – hypophyseal – adrenal system. The study of ACTH and cortisol levels which are directly involved in realization of the mechanisms of adaptation and immunoreactivity of a human organism is of great importance for determining the criteria for the assessment of distant metastases in lung cancer patients.[1,2]

The ACTH level increase in patients with carcinoma of the lung was marked long ago, but a mechanism that would explain these changes has not bean found yet. Many investigators connect the increase in ACTH and cortisol levels with ectopic secretion of the hormone by the cells of APUD system which are found practically in all morphologic forms of carcinoma of the lung.[3–5] At the same time the obtained results of our examination inolicate that the mechanism of ACTH increase in the blood serum of patients with carcinoma of the lung is more complex. Some factors likely to influence ACTH level rise in patients with carcinoma of the lung are as follows: the ectopic secretion of the hormone and its precursors by the cells of the diffuse neuroendocrine system; the increase in hormonal disadaptation mechanisms and the rise of hypothalamic sensitivity threshold to the inhibitory level of hormone concentration in the blood serum of patients, which is marked more clearly as more the extent of tumor involvement. A long – term stress, which Causes homeostasis in cancer patients, plays an important role in increasing the level of hormones that result in the immunodepression enhancement. The results of studying the hormone levels in Correlation with the survival rate of patients with lung cancer, as well as with the extent of tumor involvement, have show that the greate the tumor extent, the more distinctive the changes and the disbalance in the system of hormonal homeostasis. The quantitative changes in patients with stage IV of the disease are comparable with those in the group of patients who died of tumor pro-

gression within the first years of follow-up, i.e. in patients with subclinical metastases.

Thus, the ACTH and cortisol levels correlate with both the stage of disease and the treatment results. The present changes in the hormone levels can be used as additional criteria for the evaluation of the extent of tumor involvement and the disease prognosis.

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Mediastinal changes after mediastinoscopy: CT findings

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Mediastinoscopy is a diagnostic method more and more frequently employed for the staging of bronchogenic carcinoma. The agressiveness of this method depends upon the traumatism of the mediastinoscope as it passes through the soft tissue of the mediastinum, and upon bioptic manoevres, and can be the cause, even if rather rarely, of important iatrogenic complications. Howeve, we do not consider these unusual occurrences. The aim of our work is the evaluation of mediastinal changes in patients who underwent mediastinoscopy. With this intent, chest CT scans performed in 16 patients at an interval ranging from 48h to 28 days after mediastinoscopy were reviewed. None of the patients had had clinically relevant complications after mediastinoscopy nor had gone chemotherapy or radiotherapy in the period between mediastinoscopy and chest CT. The first finding was the presence of air in the soft tissues of the mediastinum and neck. The second finding was a diffuse increase in the density of mediastinal fat. This increased density is probably associated with an asymptomatic bleeding from small mediastinal vessels, which could be the cause of a fibrotic outcome and constitute a handycap to repeat mediastinoscopy. These tomodensitometric changes are very important for the CT diagnosis too. In fact, normal tissue planes between vascular structures and lymph nodes can be shaded off, thus rendering CT less reliable for the follow-up of these patients.

Key words: mediastinoscopy-adverse effects

Introduction

Mediastinoscopy is an aggressive method that thoracic surgeons use more and more frequently particularly for the staging of bronchogenic carcinoma.

Major complications such as rupture of a major vascular structure or of the tracheobronchial tree, as well as lacerations of the pleura and pericardium, are well known and may require urgent surgical intervention.[1, 2]

Apart from these unusual occurrences, mediastinoscopy always gives rise to asymptomatic changes in the mediastinal fat already known to endoscopists, because they may represent a controindication to repeated mediastinoscopy.

The aim of our work is to point out and to evaluate tomodensitometric changes of the mediastinum, which may be misinterpreted and, in oneway or the other, always cause difficulties at the evaluation of mediastinal structures on the follow-up CT scans.

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Material and methods

Our series include 16 patients with bronchogenic carcinoma and CT findings of enlarged lymph nodes, who underwent mediastinoscopy for staging purposes. The patients were followed up by CT at an interval ranging from 48h to 28 days after mediastinoscopy in order to assess whether the enlarged lymph nodes seen on CT scans had been really removed or sampled. All accessible lymph nodes were sampled and mapped according to the American Thoracic Society's recommendations for "Clinical staging of primary cancer of the lung".[3, 4] Minimum three and maximum six biopsies were performed in each patient. The results of this comparison will be the subject of another work.

Some important mediastinal changes were observed by the radiologists in the repeated scans, and these constitute the point of our work.

Our series included 14 men and two women, their age ranging from 47 to 71 years. None of the patients had had clinically relevant complications after mediastinoscopy nor had undergone chemotherapy or radiotherapy in the period between mediastinoscopy and CT.

The CT technique was standardized both in the first CT scan (before mediastinoscopy) and in the repeated scans. CT was performed after rapid infusion of a contrast medium with sequential slices of 8 mm from the base of the neck to the carina.

In all cases, a significant increase in the density of the soft mediastinal tissues was found. These tomodensitometric changes have been also numerically valued in post-mediastinoscopy chest CT scans. With this aim we defined rectangular Reactive oxygene intermediates (ROIS) and set them in the retrosternal fat space. The CT numbers of pixel included in the ROIS, with the size of 153 mm^2 (correspondig to 200 pixels), were calculated.

The pixel mapping was displayed and the mean CT numbers calculated.

Mean CT numbers were then compared. Three cases were excluded from these measurements: two cases because the CT performed soon after mediastinoscopy (48h) showed a great amount of air in the anterior mediastinum that would have altered the measurements, the third one because retrosternal fat, poorly represented, did not allow to set the ROI correctly.

Results

All 16 patients in whom CT was performed after an uncomplicated mediastinoscopy, showed significant changes of tomodensitometric values of the mediastinum in comparison with the first CT.

At least in those examinations performed within three days from mediastinoscopy the first finding to be pointed out is the presence or air disposed anteriorly as a "stripe" in the soft tissues of the neck and in the superior mediastinum (Figure 1a, b).

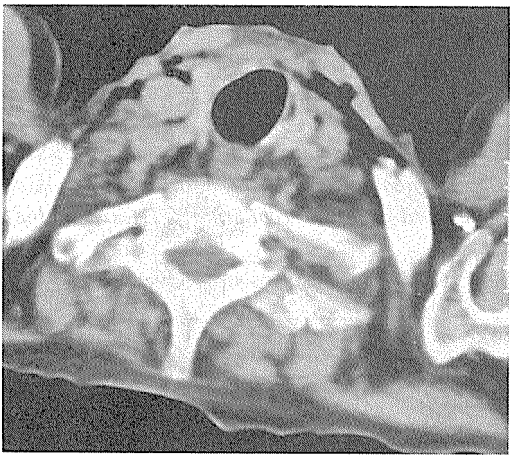

Figure 1a. CT scans performed soon after mediastinoscopy. At the base of the neck a great amount of air is disposed anteriorly as a "stripe".

This finding, which is an obvious consequence of the mediastinoscopic opening allowing the air to come in from the outside, ceased to be of any value in CT examinations performed later, because air was rapidly reabsorbed.

The second finding found in all 16 patients was the notable increase of density of the mediastinal fat as compared with the first CT

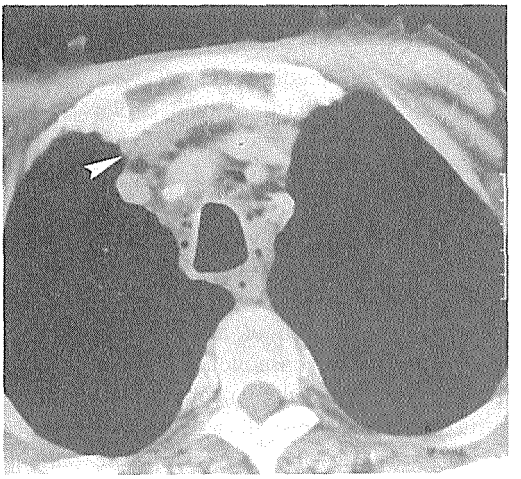

Figure 1b. Bubbles of air are shown in the soft tissue of the superior mediastinum. A band of increased density (blood) is well seen in the retrosternal space (arrow).

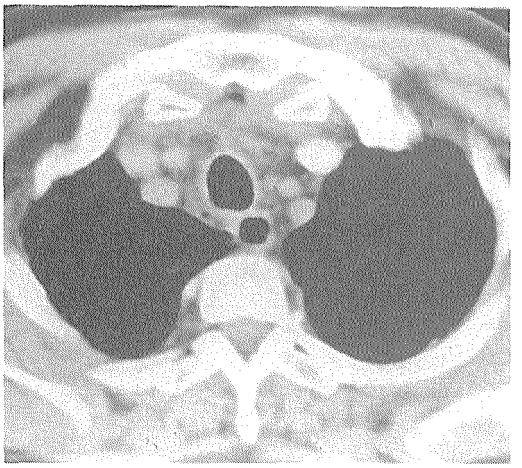

Figure 2. CT scan on the level of the superior mediastinum shows a notable increase in the density of retrosternal mediastinal fat.

(Figure 2). This increased density appeared as a *disomogeneous* blurring of the mediastinal fat.

To have an objective criterion for the evaluation of fat tissue density, the average CT numbers in the ROIS situated in the retrosternal fat space were calculated (Figure 3). In the 13 patients in whom these measurements were possible, the mean CT density in the retrosternal space ranged from −6 and + 18 UH. When compared with CT performed before mediastinoscopy, the lowest increase noticed was 74 UH, and the highest 138 UH.

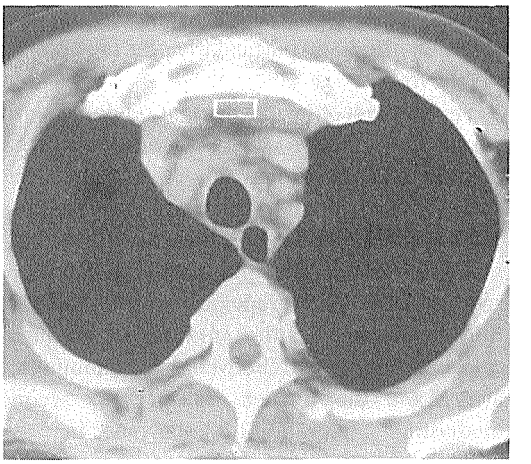

Figure 3. To have an objective criterion for the evaluation of fat tissue density, a rectangular ROI of 153 mm^2 (200 pixels) was defined and set in the retrosternal fat space.

Discussion

Nowadays mediastinoscopy is considered a diagnostic procedure of primary importance, particularly for the staging of N parameter in bronchogenic carcinoma: in fact, it enables sample taking from most mediastinal lymph node centres, without a recourse to thoracotomy.[5]

Major complications of this procedure such as major vascular or tracheobronchial injuries, lacerations of the pleura and pericardium, or, as already reported in the literature, a more severe esophageal disruption, are unusual occurrences that often require an immediate surgical intervention.[1] Such injuries have been reported to occur in up to 2% of patients undergoing this diagnostic procedure.[2]

Actually, most of the patients do not develop complications nor have any *objectivness*.

Anyhow, it is certain that mediastinoscopy causes a trauma to mediastinal structures and microscopic bleeding, which however, does not

require a therapeutic intervention; this is a common finding particularly during bioptic manoevres.[6]

The softness of mediastinal fat renders mediastinoscopy a safe procedure devoid of technical difficulties if performed for the first time; the situation is different if the procedure has to be repeated.

According to certain authors, mediastinoscopy should not be repeated because a severe fibrosis develops in the pretracheal and paratracheal spaces and between the innominate artery and the trachea, so that the second mediastinal exploration often becomes impossible or controindicated because of the difficulty to visualize and avoid great mediastinal vessels like the innominate artery.[7, 8]

The authors of later series[9, 10] stated that mediastinoscopy should be repeated only whenever it could crucially contribute to the diagnosis. Others[6] recommend that repeated mediastinoscopy should be performed by experienced surgeons following the left lateral wall of the trachea, thus avoiding the critical area of severe fibrosis.

Actually, when compared with the first CT, all CT scans in our series performed after mediastinoscopy showed, a diffuse, disomogeneous increase in the density of mediastinal fat, together with the presence of multiple air bubbles spread in the superior mediastinum in the CT examinations performed early after mediastinoscopy. This last finding, which is of minor clinical importance, is always noticed in the examinations performed within three days from mediastinoscopy, but it ceases to be relevant a few days later because air is rapidly reabsorbed.

The diffuse increase in tomodensitometric CT values in the mediastinal fat found in all patients of our series, with increased values ranging from 74 UH to 138 UH, is a certain consequence of mediastinal bleeding which results in a fibrosis.

This microscopic bleeding is an unavoidable consequence of bioptic manoevres, but is probably also associated with disruption of small mediastinal vessels by the mediastinoscope.

In conclusion, as already reported with reference to technical difficulties of re-mediastinoscopy because of the severe fibrosis that always develops in the mediastinum, CT scans performed after a mediastinoscopic exploration always show tomodensitometric changes of mediastinal fat, which should be recognized and paid proper consideration. Mediastinal fibrosis that is, more or less, always present in CT scans performed after mediastinoscopy, must be considered an unavoidable occurrence associated with the traumatism of mediastinoscopic manoeuvres, whose consequence in terms of diagnosis is more difficult evaluation of mediastinal structures and, above all, a less reliable staging of N parameter. Therefore, in these patients CT is associated with greater diagnostic difficulties, particularly in the identification of mediastinal nodes which are no longer surrounded by normal hypodense fat tissue, but are blurred in the mediastinal fibrous tissue (Figure 4).

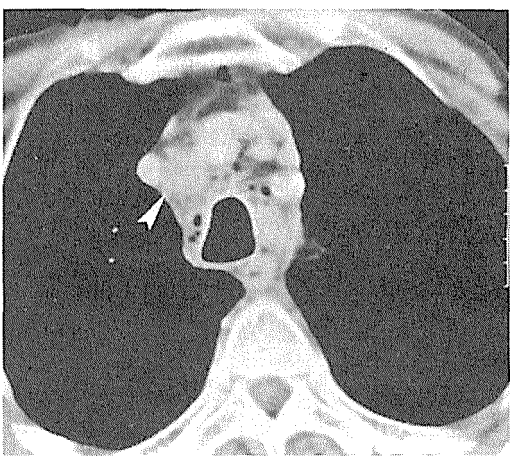

Figure 4. CT scan on the level of the superior mediastinum. A large lymph node in the right paratracheal space is not clearly distinguishable, shaded in the high tissue density of mediastinal hemorrhage (arrow). Small bubbles of air are still demonstrated.

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Value of perfusion lung scan in predicting unresectability of bronchial carcinoma

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We analyzed retrospectively the value of perfusion lung scanning in 88 cases with primary bronchial carcinoma regarding preoperative suggestion of unresectability. Twenty-four of the examined patients were operated on, and 11 of them had an exploratory thoracotomy only. In most of these 11 patients other noninvasive diagnostic methods (X-ray and CT) did not indicate inoperability. Only the perfusion lung scan demonstrated defects near the ipsilateral hilum and/or an enlargement of the mediastinum. At thoracotomy we found an involvement of hilar vessels and the mediastinum by the tumor or by "bulky" nodal metastases. A sensitivity of 91 %, a specificity of 50 % and an accuracy of 76 % were established for perfusion lung scanning data. These findings show that in some patients with bronchial carcinoma the perihilar defect and/or the enlargement of the mediastinum in the perfusion scan image can suggest a potential unresectability and requires a more extensive staging like mediastinoscopy or thoracoscopy.

Key words: bronchial neoplasms-surgery; lung neoplasms-radionuclide imaging; surgery, operative-contraindications

Introduction

Surgical resection of non-small cell lung cancer (NSCLC) remains the most effective form of treatment of the disease when feasible. Thus, the determination of resectability and operability is the principal problem in evaluating patients with NSCLC for treatment. A great contribution toward resolving this problem has been made by the application of the New International Staging System for Lung Cancer.[1] In the last years a number of studies pointed out the possibilities of different noninvasive and invasive procedures for lung cancer staging. According to the general view, the data from noninvasive procedures must set indications for invasive staging. The X-ray imaging and computed tomography (CT) are known as the most accurate noninvasive methods. Additional information is provided by fiberoptic bronchoscopy. As for patients with radiologically suspected stage III disease, the differentiation of T 3 from T 4 and N 2 from N 3 is required. The possibilities of noninvasive procedures concerning this differentiation are limited and usually the diag-

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nosis involves invasive methods such as mediastinoscopy and thoracoscopy.

Some information to predict the inoperability (presence of T 4 or N 3) is obtained by precise interpretation of perfusion lung scintigraphy performed before the invasive staging. In most cases, the perfusion lung scan demonstrates a picture consistent with the data from other noninvasive imaging procedures.

The role of pulmonary perfusion scanning as determinant of inoperability is discussed in many communications.[2–6] We undertook our study with the assumption that more detailed information about the tumor spread and potential unresectability is of great importance for indicating invasive staging and surgery. In our serie of operated lung cancer patients we found a strong correlation between perfusion scan data suggesting unresectability and the number of exploratory thoracotomies.

Material and methods

We analyzed retrospectively 88 consecutive cases with primary lung carcinoma treated in our departments. Every patient was subjected to a standard postero-anterior and lateral chest X-ray and fiberoptic bronchoscopy. Most of them had a chest CT-scan performed. There were 76 men and 12 women so that the male to female ratio was 6.3 to 1. The age range was from 35 to 76 years with a median age of 55.6. The tumor was located in the right lung in 48 patients and in the left lung in the remaining 40 cases. Pulmonary perfusion scintigraphy was performed in all patients. The method makes use of 99mTc – human albumin microspheres with a particle size of 23–45 μm (kit Sferotec – Sorin, Biomedica – Italy). The injection was applied in supine position, intravenously in bolus, 1 ml at an activity of 55–74 MBq. The period of examination was between the 15th min and the 2nd hour after injection, at least at anterior and posterior detection, but more frequently we used polyposition detection (lateral and 45°), (Picker Dyna Camera 4 Scintillation Camera System – Picker Corporation Nuclear and Ultrasound, USA).

We considered 4 pathological criteria for interpretation of perfusion lung scanning:

1. Absent or minimal perfusion of the affected lung or a perfusion defect in more than 2/3 of the affected lung.
2. Perfusion defect and enlargement of the hilum of the affected lung.
3. Enlargement and displacement of the mediastinum in anterior or posterior detection.
4. Perfusion defect in the contralateral hilum.

From 88 patients, 64 were not considered for surgery because of different reasons: histology (SCLC); advanced stages – III B and IV; functional inoperability and patientss refusal of surgery.

The remaining 24 patients were submitted to surgery as follows: 13 of them underwent curative resections – 5 pneumonectomies, 7 lobectomies and 1 sleeve resection. Only exploratory thoracotomy was done in 11 patients. An invasive staging (mediastinoscopy or thoracoscopy) before thoracotomy was not performed in our diagnostic programme.

Results

We were not able to examine the real accuracy of perfusion lung scanning for predicting inoperability in 64 patients who were not operated on because of lacking verification on thoracotomy. However, we analyzed the data from perfusion lung scanning in the operated 24 patients. Table 1 shows the characteristics of the operated patients with curative resections and Table 2 presents the operated patients with exploratory thoracotomies. In the group with curative resections 3 of the patients were estimated as stage I, 4 as stage II and 6 as stage III. The definitive staging was based on the characteristics of the primary tumor and on the lymph node sampling by mediastinal lymph node dissection, performed in every patient. There was 1 patient with SCLC, who presented with a radiologically evident peripheral solitary pulmonary nodule and negative fiberbronchoscopy. At thoracotomy, the frozen section histological

Table 1. Patients with curative resection.

Patients N°	Stage	Site	Age	Histology	Karnofsky index	Type of surgery
1.	II	L	54	Adeno	70– 80	LUL
2.	I	R	48	SCLC	90–100	RUL
3.	III A	L	56	Adeno	70– 80	LP
4.	II	L	57	Squamous	90–100	LP
5.	II	L	51	Adeno	70– 80	LLL
6.	III A	L	49	Adeno	70– 80	LP
7.	II	L	64	Squamous	50– 60	LLL
8.	III A	R	61	Bronchiolo-alveolar	70– 80	RP
9.	III A	R	62	Squamous	70– 80	RLL
10.	III A	R	39	Squamous	90–100	RLL
11.	I	R	42	Squamous	90–100	RP
12.	I	R	55	Squamous	90–100	RUL
13.	III A	R	54	Squamous	70– 80	RLL

L – left, R – right, LP and RP – left and right pneumonectomy, UL and LL – upper and lower lobectomy

Table 2. Patients with exploratory thoracotomy.

Patients N°	Stage	Site	Age	Histology	Karnofsky index	Type of surgery
1.	III A	R	55	Adeno	70–80	ET
2.	III B	R	60	Squamous	70–80	ET
3.	III B	R	61	Adeno	70–80	ET
4.	III B	R	52	Squamous	70–80	ET
5.	III B	R	52	Squamous	70–80	ET
6.	III B	R	54	Squamous	70–80	ET
7.	III B	R	58	Squamous	70–80	ET
8.	III B	R	54	Squamous	50–60	ET
9.	III B	L	62	Squamous	70–80	ET
10.	III B	R	55	Squamous	70–80	ET
11.	III B	R	66	Squamous	70–80	ET

ET – exploratory thoracotomy

examination revealed SCLC stage I that led to a right upper lobectomy and consequent adjuvant treatment. In all other patients NSCLC was found.

We examined retrospectively the perfusion lung scanning images of the resected patients especially those with III A postoperative stage. They are comparable to the patients of the second group (with exploratory thoracotomy) by stage III, presence of NSCLC histology, age and performance status (Karnofsky index = 70–80). In 3 of these 6 resected patients the perfusion lung scan data suggested inoperability due to ipsilateral perihilar defects and enlarged mediastinum. These results were interpreted as false positive. In the other 3 patients we had only a parenchymal perfusion defect lower than 2/3 of the entire lung which was not considered as a sign of unresectability.

The second group of patients (those with exploratory thoracotomy) was staged preoperatively by noninvasive procedures at stages II – III A. The perfusion lung scan demonstrated an enlarged mediastinum and ipsilateral perihilar defects in 10 patients. No patient with parenchymal defect involing more than 2/3 of the affected lung, a sign indicating unresectability, was found.[5] In one patient perfusion lung scanning of the hilum and mediastinum was normal. All 11 patients were operated on, the

most frequent finding on thoracotomy was invasion of the mediastinum by the tumor (T 4) or a tumor with "bulky" nodal metastases in hilar and mediastinal lymph nodes. There were 2 patients with invasion of the vena cava superior (without clinically demonstrated VCS-syndrome). All patients were staged as III B stage and the operation consisted of exploration only.

Retrospectively, we accepted the perfusion lung scanning findings as true positive in 10 patients and as false negative in 1 patient.

According to these results, the characteristics of perfusion lung scanning, in terms of unresectability prediction, were evaluated. The examination of the group of patients with stage III (A and B together) showed 3 true negative and 3 false positive images in the "resected" group, and 10 true positive and 1 false negative in the "exploratory thoracotomy" group. This yielded a sensitivity of 91%, a specificity of 50% and an accuracy of 76%.

Because of a small number of patients these data can not be statistically evaluated. Nevertheless they coincide with the reported data presenting the perfusion lung scanning as a noninvasive diagnostic method with a good sensitivity and a low specificity.

Discussion

Perfusion lung scanning was defined as a sensitive determinant of inoperability by several authors. The possibilities of this procedure in detecting the tumoral spread were studied in the 70's.

Secker-Walker et al.[2] concluded from their series that when more than 2/3 of the lung had diminished or absent perfusion the tumor was unresectable. Maynard and Cowan[3] compared the perfusion scan and X-ray images in 25 patients undergoing exploratory thoracotomy alone, and found in all of them scan changes equal to or greater than those seen on X-ray. None of these patients had a normal scan and all were judged unresectable on thoracotomy. In these two studies, the hilar defect and enlargement of the mediastinum in perfusion scan were not discussed.

Ernst et al.[4] analyzed 138 cases with malignant pulmonary tumors, 120 of them with hilar and 18 with peripheral lesions. In all cases with hilar location of the tumor the lung scan showed significant perfusion abnormalities.

Fletcher et al.[5] reported that lesions which were hilar in location generally produced larger perfusion defects than peripheral lesions. In addition, some patients had normal scans despite abnormal chest radiographs.

All these authors consider the perfusion lung scanning as mere supplement to the diagnostic process in evaluating lung cancer. Of greater importance is the nonspecificity of the perfusion defect. There is no characteristic pattern to distinguish benign from malignant neoplasms or neoplastic disease from other forms of pulmonary disease.

Before the introduction of the New International Staging System for lung cancer in 1987, a predominant role in the diagnosis was assigned to noninvasive procedures, especially to CT. An increase in the percentage of exploratory thoracotomies was marked.[6] Few thoracic surgical units insisted on and performed regularly invasive diagnostic procedures.

The introduction of T 3 and T 4, N 2 and N 3 categories in the New Staging System has shown that the enthusiasm about the noninvasive staging had been premature.

Würsten and Vock[7] reported a limited specificity of CT to evaluate T 4 – 63%. Similar results have been communicated by other investigators.[8–11]

The increased possibilities of the neoadjuvent therapy of lung cancer require a histological verification of N 2 disease before treatment.

All these facts caused a shift towards a more aggressive staging of lung cancer in the last years. Now the majority of thoracic surgeons and oncologists recommend invasive staging procedures such as mediastinoscopy and thoracoscopy before surgery and perform them regularly. Regardless of this concept, there is no controversy about the complete application of all available noninvasive procedures before resorting to the invasive diagnosis. Nowadays the great merit of perfusion lung scanning in pulmo-

nary oncology is the precise evaluation of pulmonary function and prediction of functional inoperability.

Our experience with perfusion lung scanning shows that an additional information concerning the tumor spread can be obtained from this noninvasive imaging method.

The assessment of perfusion defects close to the ipsilateral hilum and enlargement of the mediastinum can suggest the presence of T 4 and a potential unresectability. Our observations are in agreement with all cited authors, that the method is of low specificity and can not be used alone to determine T 4. But every patient with the above noted pathological findings of perfusion lung scan must be considered for detailed invasive staging. Recently Landreneau et al.[12] and Lewis et al.[13] reported on greater possibilities of video-assisted thoracoscopy for lung cancer staging. Several months ago we started to perform video-assisted thoracoscopic surgery in our clinic. We hope that the data from perfusion lung scan will be useful for indicating the need of a video thoracoscopic examination. We hope to obtain more adequate staging of lung cancer and to reduce the number of exploratory thoracotomies.

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Accordance of clinical versus pathological stage (pTNM) in patients with surgically treated non-small cell lung cancer

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In a group of 350 patients with non-small cell carcinoma of the lung, who were subjected to operation during the period from May 1983 to June 1987 at our institution, the agreement between the preoperative, the intraoperative and the pathological TNM stage (4th ed.) was examined. The preoperative stage was identical with the pathological classification in only 46% of patients, underestimated in 47% and overestimated in 7%. With regard to the staging of intrapulmonary lymph nodes involvement (N1), the agreement between the intraoperative and the pathological classification reached 68%. In this group we overestimated the lymph nodes involvement in 23% and underestimated it in 9%. The accordance between the intraoperative and the pathological stage of mediastinal lymph nodes (N 2) was in 70%, in 26% mediastinal lymph node metastasis was suspicious, but the result was negative and in 4% the evaluation of these nodes was underestimated. We can conclude that the preoperative and the intraoperative staging of lung cancer is very inaccurate, and doubts, concerning the actual degree of the tumour extension, especially in the lymph nodes, can ultimately be solved in most cases only by thoracotomy, node dissection and pathological examination.

Key words: lung neoplasms-surgery; neoplasms staging, TNM classification

Introduction

Survival of patients with non-small cell lung cancer is related to the stage of disease at the time of diagnosis. Stage I and II of the disease have a favorable prognosis and are best treated by pulmonary resection when cardiopulmonary status allows it. Locally aggresive disease (stage IIIa and stage IIIb) and distant metastatic disease (stage IV) are advanced stages for which survival rates are poor.[1] Once metastatic disease has been ruled out, the search for locally advanced cancer should be undertaken.[2]

The exact preoperative staging is a prerequisite for establishing an adequate treatment plan for patients. The preoperative staging of bronchial carcinoma is mainly based on plain chest x-ray examination, bronchoscopy, CT scan of the chest, mediastinoscopy and mediastinotomy.[3]

The aim of our retrospective study was to evaluate the accuracy of preoperative and intraoperative staging, compared with the defini-

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tive pathological stage. Special attention was devoted to the ability to identify macroscopically intrapulmonary and mediastinal metastatic lymph nodes.

Patients and methods

In the period from May 1983 to June 1987 we operated 350 patients with non-small cell carcinoma of the lung (NSCLC) in our institution. We included in the study only those patients for which we determined, after preoperative clinical investigation, that they were clinical stage I and II of the TNM classification (4^{th} ed.).

In that period the determination of clinical stage consisted of a detailed examination of the patient, chest x ray, bronchoscopy, ultrasound of the abdomen and bone scan in patients with pains. In patients with enlarged hilus, suggestively abnormal mediastinal shadow or when either structure was obscured by overlying tumour or parenchymal disease, a CT scan was done. When nodes were 1 cm or larger, the preoperative exploration was performed with cervical mediastinoscopy and/or anterior mediastinotomy. In the beginning of that period we used CT scan very rarely, but later more and more frequently. It was the same with mediastinoscopy and mediastinotomy. In the whole group, we have performed CT scan in 24%, cervical mediastinoscopy in 11% and anterior mediastinotomy in 9% of patients. At thoracotomy the surgeon determined the intraoperative TNM stage and recorded it in the operative protocol. At that time we did not perform radical mediastinal lymphadenectomy routinely, but carried out the excision of all enlarged and visible lymph nodes (sampling).

The presence or absence of tumour in nodes and pathological staging was made by Dr. T. Rott at the Institute of Pathology in Ljubljana.

Results

The results of definitive (pathological) stage of our patients are in Table 1.

Table 1. Pathological stage of 350 patients with NSCLC of the lung.

STAGE	No. of patients	%
Stage 0	1	0.3
Stage I	134	38
Stage II	87	25
Stage III a	90	26
Stage III b	29	8
Stage IV	9	3
	350	100

There is only one patient in our group with carcinoma in situ and stage 0. In 119 patients (37%) the pathological stage was higher than determined preoperatively (stage III a, III b and IV). The preoperative stage was identical with the pathological classification in only 46% of patients, underestimated in 47% and overstimated in 7%. In 58 patients (16%) the preoperative stage was underestimated due to tumour invasion in the surrounding organs of the chest, and only in 9 patients (3%) we discovered metastases during the thoracotomy. The disagreement between the clinical and the pathological classification was mainly due to the misinterpretation of intrathoracic lymph nodes.

Table 2. Agreement between intraoperative and pathological classification of intrapulmonary lymph nodes (N 1).

N 1 intraop. – pathol.	No. of patients	%
Identical	216	62
Underestimated	50	14
Overestimated	74	21
Unknown	10	3
	350	100

In table 2 we have evaluated intrapulmonary lymph nodes, not only N 1 disease; important was only the correct classification. Unknown are cases in which we did not examine nodes due to inoperability or for other reasons.

We did not achieve good results in patients with N 1 disease.

Table 3. Intraoperative classification of lymph nodes in patients with N 1 disease.

I. / op. classification	No. of patients	%
N 1	28	26
N 0	47	43
N 2	33	31
	108	100

The correct classification was only in 26 %, in 43 % the macroscopic appearance was normal and in 31 % we suspected mediastinal lymph nodes metastatic involvement. In patients with normal intrapulmonary lymph nodes our macroscopic classification was correct in 50 %.

Table 4. Intraoperative classification of lymph nodes in patients with N 0 disease.

I. / op. classification	No. of patients	%
N 0	81	50
N 2	49	31
N 1	29	19
	159	100

The accordance between the intraoperative and the pathological stage of mediastinal lymph nodes was in 73 %; in 22 % mediastinal lymph nodes were suspicious, but the result was negative, and in 2 % the evaluation of these nodes was underestimated.

Table 5. Agreement between intraoperative and pathological classification of extrapulmonary lymph nodes (N 2).

N 2 intraop. – pathol.	No. of patients	%
Identical	254	73
Overestimated	78	22
Underestimated	10	3
Unknown	8	2
	350	100

More accurate staging was effected for malignant lymph nodes, where the accordance between macroscopic and pathological evaluation was in 92 %, underestimated in 5 % (N 0) and 2 % (N 1).

Discussion

Surgery is the treatment of choice in NSCLC for stage I and II. Unfortunately, when the diagnosis is established, slightly less than one fourth of the patients are in these two stages, one fourth have stage III a and III b, and half have the disseminated stage IV disease.[4] From our results we can conclude that the preoperative and macroscopic intraoperative staging is very inaccurate, especially that of lymph nodes.

It is unacceptable that we operated 128 patients (37 %) with preoperative stage I or II, but later established that they were in stage III a or higher. This can be partially explained with the fact that at that time the CT scan was not in routine use, and especially at the beginning of our study, only a small proportion of the patients was examined by this method. The average preoperative underestimation of the N stage in recent literature is about 25 %.[5, 6] For the best selection of patients who can benefit from operation, in many institutions the mediastinal exploration is the standard preoperative method of evaluating the status of mediastinal lymph nodes.[2, 7, 8, 9] On the other hand, 10 to 20 % of patients with positive nodes may have resectable lesions, with a good 5 years survival.[10, 11, 12, 13] The incidence of patients with microscopic involvement of mediastinal lymph nodes was 29 %, and the survival rate was higher than that of patients with gross involvement of these nodes.[10] We now agree with a selective approach and perform CT scan in any potential surgical candidate, and when nodes are 1 cm or larger, a preoperative exploration of mediastinum is done. If biopsy proves metastatic mediastinal node disease this contraindicates surgery.[1, 14, 15] Due to inaccuracy of surgical staging and because metastases are found in approximately 30 % of lymph nodes smaller than 1 % cm, routine systematic radical lymphadenectomy of all lymph node regions that are surgically accessible is mandatory for exact staging, better survival and proper selection of patients for adjuvant therapy.[16]

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Complete resection for unsuspected N_2 non-small cell lung cancer (Stage IIIA)

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Between 1975 and 1985, 111 patients with non-small cell lung cancer (NSCLC) without clinically evident N2 status were finally classified as Stage IIIA with N_2 discovered invasively at mediastinoscopy or at thoracotomy; 95 patients underwent mediastinoscopy mainly because of a central localization of the tumor. In 32 patients the removed lymphnodes were not involved while in 63 they were; the latter patients were considered inoperable, their 3- and 5-year actuarial survival being 5% and 0% respectively. For the non-operated patients, no favourable prognostic factors could be detected. The 32 patients without involved lymphnodes at mediastinoscopy, and 16 patients in whom no mediastinoscopy was performed because of a peripheral localization of the tumor, were operated ($n = 48$). They underwent complete tumor resection and ipsilateral mediastinal lymphadenectomy, but unsuspected N_2 disease was found on surgery in those 48 patients. Their 3- and 5-year survival was 19% and 10%. The better survival rate in the operated group was statistically significant ($P = 0.001$), mainly due to a better survival of the lobectomy group ($p < 0.001$). Univariate analysis of prognostic factors in the operated patients showed worse prognosis for pneumonectomy, peripheral tumor, non-squamous cell carcinoma and extracapsular lymph node invasion. Multivariate analysis showed a significantly better prognosis for lobectomy and central location of the tumor, whereas histology, level and number of involved lymphnode stations and capsular invasion were not significant. Using multivariate regression analysis, the 5-year survival was 39% vs. 14% after lobectomy for central vs. peripheral tumor, and 5% vs. 0% after pneumonectomy for central vs. peripheral tumor. We conclude that stage IIIA NSCLC patients with unsuspectedly discovered N_2 disease at thoracotomy benefit from complete tumor resection and mediastinal lymphadenectomy, especially if the resection can be limited to lobectomy for a central tumor. Preoperative accurate staging with CT-scan and mediastinoscopy is necessary.

Key words: carcinoma, non-small cell lung-surgery; survival analysis

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Introduction

Schields [1-3] divided the patients with N_2 disease in two broad categories: those with clinically evident N_2 disease, generally non-resectable,

and those with N_2 disease discovered by an invasive procedure (mediastinoscopy, thoracotomy). Patients with mediastinal lymph node metastases of non-small cell lung cancer (NSCLC) are usually not primary surgical candidates.

We studied retrospectively the prognosis of patients with NSCLC and N_2 disease discovered at thoracotomy (Stage IIIA), who underwent complete tumor resection and ipsilateral lymphadenectomy with or without preoperative mediastinoscopy, in order to identify the subgroup of patients with N_2 disease that may benefit from resection. Their survival was also compared with that of non-operated patients with mediastinal lymph nodes involvement discovered on mediastinoscopy.

Patients and methods

A retrospective analysis was performed in a series of 111 patients with NSCLC without clinically evident N_2 disease but discovered invasively or by mediastinoscopy or during thoracotomy. The patients were candidates from surgery in the period 1975 to 1985, before the routine use of CT-scan and before the use of MRI on indication.

Of the 111 patients, 95 underwent mediastinoscopy for preoperative staging. In 63 patients the mediastinal lymphnodes were involved by tumor (positive mediastinoscopy) and those patients were not operated on. In 32 patients the mediastinal lymphnodes were not involved by tumor (negative mediastinoscopy) and those patients underwent thoracotomy. In 16 patients no preoperative mediastinoscopy was performed, mainly because of peripheral localization of the tumor and those patients also underwent thoracotomy. In total, 48/111 patients (43 %) without clinical evidence of N_2 disease, underwent complete tumor resection and ipsilateral lymphadenectomy, and unsuspected N_2 disease was discovered on surgery.

Survival of the three groups (non-operated, lobectomy, pneumonectomy) was calculated by the Kaplan-Meier method. The influence of several variables on the survival was studied in univariate und multivariate regression analysis:

- Age: 60 years or less versus over 60 years
- Tumor
  - histology: squamous cell carcinoma versus other types
  - size: T_1 versus larger than T_1
  - localization: central versus peripheral
- Lymphnodes
  - number of involved stations by tumor: one versus more.
  - involvement: intra- versus (also) extracapsular
- Adjuvant therapy: chemotherapy or radiotherapy versus no adjuvant therapy.

Results

32 patients had a negative preoperative mediastinoscopy but on surgery mediastinal lymph node involvement was discovered. In 4 patients the mediastinoscopic exploration was incomplete as only cervical mediastinoscopy and no left parasternal mediastinoscopy was performed for a left upper lobe tumor; in 11 patients lympnodes accessible by a mediastinoscope were not detected and the lymphnodes were false negative; and in 17 patients the involved mediastinal lymphnodes detected on surgery were not accessible by a mediastinoscope. Of the 16 patients with no preoperative mediastinoscopy, but with mediastinal lymphnode involvement, 14 presented with lymphnodes accessible by a mediastinoscope.

For the non-operated group of 63 patients with N_2 disease discovered at mediastinoscopy, the mean survival was 15 months, the actuarial survival was 5 % at 3 years and 0 % at 5 years.

For the operated group of 48 patients with N_2 disease discovered at thoracotomy and who underwent complete resection and ipsilateral lymphadenectomy, the hospital mortality was

10.4 % (5 patients) or 5.5 % (one of 18 patients) after lobectomy and 13.3 % (4 of 30 patients) after pneumonectomy. The actuarial 3-year survival was 19 % and the 5-year survival was 10 %. For the lobectomy and pneumonectomy subgroups the 3-year survival was 28 % and 13 %, the 5-year survival was 17 % and 7 %. The survival rate of the operated patients was significantly better than of the non-operated patients ($p = 0.001$), mainly due to those who underwent lobectomy ($p < 0.001$), whereas the pneumonectomy group had a nearly significantly better survival rate than the non-operated group ($p = 0.08$).

The influence of each variable on the survival rate of the non-operated and operated patients was investigated by univariate analysis. For the non-operated patients no favourable prognostic factor could be detected, but the number of stations with positive lymph nodes was negatively associated with the survival rate ($p = 0.06$). For the operated patients a worse prognosis was found for pneumonectomy ($p = 0.03$), peripheral tumors ($p = 0.03$), non-squamous cell carcinoma ($p = 0.02$) and extracapsular lymph node invasion ($p = 0.05$).

With multivariate stepwise regression analysis the prognosis was better for lobectomy ($p = 0.004$) and central tumor ($p = 0.05$). No significance could be established for tumor histology; level, number and capsular invasion of the lymphnodes. The corresponding calculated survival with respect to surgical procedure and tumor location according to the proportional hazard model discloses a 3-year and 5-year survival of 51 % and 39 % respectively for lobectomy-central tumor, 25 % and 14 % for lobectomy-peripheral tumor, 13 % and 5 % for pneumonectomy-central tumor, 1 % and 0 % for pneumonectomy-peripheral tumor.

Discussion

Patients with NSCLC and contralateral lymph node metastases (N_3) are generally not accepted for surgery. The treatment of patients with ipsilateral lymph node metastases (N_2) is intensively studied at present.[4–14] Patients with symptomatic N_2 disease almost always have non-resectable lesions, while patients without clinical evidence of N_2 disease are investigated for possible complete surgical resection.[1–3]

Pearson and associaties[15] studied the significance of positive superior mediastinal lymphnodes identified at mediastinoscopy or at thoracotomy in 141 patients who underwent thoracotomy for a presumably operable NSCLC. Of the 141 patients, the first group of 79 patients had a preoperative positive mediastinoscopy and the involvement of the lymphnodes was ipsilateral and intracapsular, 67 (85 %) underwent a resection; which was complete in 51 (65 %) with a 15 % 5-year survival; incomplete in 16 (20 %) with no 5-year survival. The surgical mortality was 16 % in this first group and the overall 5-year survival was 9 %. The second group of 62 patients had a negative preoperative mediastinoscopy but involved mediastinal lymphnodes (N_2) were discovered on surgery. 57 (92 %) underwent a resection which was complete in 25 (40 %) with a 41 % 5-year survival and incomplete in 32 (5 %) with a 14 % 5-year survival. The surgical mortality was 8 % in this second group, and the overall 5-year survival was 24 %. Pearson and associates[15] found that the subgroup of patients with mediastinoscopically positive N_2 disease, who might benefit from thoracotomy consisted of patients with only one involved lymph node station, without extracapsular invasion and situated low paratracheally, tracheobronchially, subcarinally or in the aortic window.

In our group of non-operated patients with mediastinoscopic positive N_2 disease, no such more favourable subgroup could be detected in whom surgery could have been advised. The usefullness of surgery is still questionable if N_2 disease is found on mediastinoscopy.[16]

Recently Ginsberg[4] mentioned a 5-year survival after surgical resection for N_2 NSCLC going up to 30 %, and to 38.5 % for squamous cell carcinoma in the series of Martini.[6]

In our series of 111 patients with NSCLC without clinically evident N_2 disease who were candidates for surgery, 48 underwent complete

tumor resection and ipsilateral mediastinal lymph node disssection and had unsuspected N_2 disease. The mortality was 10.4 %, and was higher for pneumonectomy than for lobectomy. The 5-year survival was 10 %, including surgical deaths, and is lower than the rates of 15 % to 30 % reported in the literature.[6,10,14]

In univariate analysis of the prognostic factors, pneumonectomy, peripheral tumor, non-squamous cell carcinoma and extra capsular lymphnode invasion had a significantly worse prognosis. This is in agreement with other studies[4–14] in which, moreover, the level and number of involved lymph node stations were significant. In multivariate analysis a significantly better prognosis was found for lobectomy and central tumor. Patients with a limited resection such as lobectomy and bi-lobectomy had a better overall survival. Pneumonectomy is required in more advanced situations with worse prognosis. The better prognosis of a central tumor in our series was due to the fact that 14 of the 16 patients with a peripheral tumor and no preoperative mediastinoscopy presented with involved mediastinal lymphnodes accessible by a mediastinoscope or located high mediastinally. In those patients the contralateral lymph node status was unknown as only ipsilateral lymphadenectomy had been performed. Finally, most of these patients had a non-squamous cell carcinoma on the final histology.

After multivariate analysis Roeslin and associates[11] found that microscopic blood vessel invasion correlated with a significantly worse prognosis. We did not analyze this factor.

The conclusions of our study were:

1. The survival of patients with NSCLC and N_2 disease discovered operatively and having undergone complete resection and ipsilateral lymphadenectomy is better than the survival of patients with N_2 disease discovered on mediastinoscopy and not undergoing surgery.

2. A subgroup of patients with N_2 disease discovered on thoracotomy and benefiting from complete tumor resection and lymphadenectomy is identified as the group with negative preoperative mediastinoscopy and a resection limited to lobectomy for a central tumor.

3. A preoperative staging with CT-scan and complete mediastinoscopy is necessary. We still perform mediastinoscopy for all central tumors, for all non-squamous cell carcinomas and for peripheral tumors with suspected lymphnodes on the CT-scan. After a positive mediastinoscopy we will consider surgery if only one ipsilateral lymphnode station is involved intracapsularly by a squamous cell carcinoma.

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Surgical treatment of multiple primary lung cancers

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From 1970 to 1990, 1287 patients (pts) underwent resection for primary lung cancer. 55 pts (4.3%) had a second primary lung cancer, being synchronous in 15 (1.2%) and metachronous in 40 pts (3.1%). The 15 pts with synchronous cancers underwent surgery, 10 in a two-stage and 5 in a one-stage procedure. There were 3 postoperative deaths (20%). The 3- and 5-year actuarial survival was 26% and 15%. Of the 40 pts with metachronous cancers the mean interval between treatment of the first and second cancer was 5 years and 11 months and was longer for the pts having a bilateral location (7 years) than for the pts having an ipsilateral location (4 years). We did not find a significantly different mean interval for those having an epidermoid carcinoma twice and an adenocarcinoma twice, but we found a longer mean interval (6 years and 8 months) for those having cancers of a different histological type. At the time of the second cancer 7 pts were treated by chemo- and/or radiotherapy and 33 pts by surgery. There were 5 postoperative deaths (15.2%). The 3- and 5-year actuarial survival was 33% and 18%. For 25 pts with stage I or II second cancer these rates were 42% and 27%; all 8 pts with stage III second cancer died within 14 months. Survival was positively affected by a difference in histological type between both cancers, an interval of more than 3 years, a bilateral location and a mild smoking habit. But the only significant factor for longer survival was a stage I or II for the second cancer.

Key words: lung neoplasms-surgery; neoplasms, multiple primary

Introduction

Multiple primary lung cancers can develop in the same patient either synchronously or metachronously. In this retrospective study of our patients with multiple primary lung cancers the prevalence and the prognostic factors influencing the survival, such as interval between operations, tumor histology, localization and stage, and finally, the smoking habit of the patient were analysed.

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Patients and methods

From 1970 to 1990, 1287 patients underwent resection for a primary lung cancer. Of this group 55 (4.3%) presented with a second primary lung cancer, synchronous in 15 (1.2%) and metachronous in 40 (3.1%). The criteria

of Martini[1] were followed for the diagnosis. *Synchronous cancers* were distinct and separated. The histology was different or the same; in the latter case the tumor was localised in a different segment, lobe or lung, originating from carcinoma in situ, without carcinoma in common lymphatics or metastasis. In *metachronous cancers* the histology was different or the same; in the latter case with a cancer free interval of at least 2 years, tumor originating from carcinoma in situ, or localised in a different lobe or lung, without carcinoma in common lymphatics, or metastasis.

The group of 55 patients consisted of 53 men and 2 women. The age at first resection was from 39 to 77 years, mean 58.9 years. Until the first resection, 43 patients were smokers, 5 patients never smoked while in 7 patients the data on smoking habit were not available. After the first operation 23 patients stopped smoking and 20 patients continued. Before each surgery, staging was performed including mediastinoscopy for all central lung cancers and on indication for peripheral cancers. For cancers of the left upper lobe or left main bronchus cervical and eventually left parasternal mediastinoscopy was performed.

Of the 15 patients with a synchronous lung cancer the synchronous cancer was found on chest X-ray in 11 cases, on histological examination of the resection specimen in 2 cases, during surgery in one case and during postoperative bronchoscopy in another case. Of the 40 patients with a metachronous lung cancer, 4 patients were symptomatic without abnormality on chest X-ray whereas in 36 patients the second primary was discovered on a routine control chest X-ray, 11 patients being asymptomatic. The symptoms were cough, sputum production, eventually with blood and dyspnea.

In 14 patients (35%) the metachronous cancer was discovered within 3 years and in 26 patients (65%) after 3 years. In 6 patients (15%) the interval was more than 10 years. The mean interval between the first and second treatment was 5 years and 11 months, ranging from 0.5 month to 24 years and 3 months. The mean interval was 5 years and 7.6 months for twice a squamous cell carcinoma (23 patients), 5 years and 6 months for twice an adenocarcinoma (4 patients) and 6 years and 7.7 months for a different histologic type (12 patients). The mean interval was 4 years and 5.9 months for tumors in the same lung and 7 years and 2.5 months for bilateral tumors. The interval for the group of patients who stopped smoking and the group who continued smoking after the first surgery did not show a significant difference.

The 15 patients with synchronous lung cancers were all treated surgically, 10 patients in two stages and 5 patients in one stage. The postoperative histology was different in 4 patients and the same in 11 patients. The 40 patients with metachronous lung cancer underwent surgical resection for the first tumor: 35 lobectomies, 3 bilobectomies and 2 pneumonectomies. A second operation was not performed in 7 patients: one patient presented with mediastinal lymphnode invasion on mediastinoscopy, and another one with respiratory insufficiency; one 83 year old patient refused reoperation and 4 patients presented with a small-cell lung carcinoma treated by chemo- and/or radiotherapy. The remaining 33 patients (82.5%) with metachronous lung cancer underwent a second resection: 2 wedge resections, 4 segmentectomies, 10 lobectomies, one pneumonectomy and 16 completion pneumonectomies. The postoperative histology was different in 12 patients and the same in 21. Twenty-five patients had stage I or II and 8 patients had stage III second lung cancer. After resection, all patients had yearly follow up with general examination and chest X-ray. The data on survival were obtained from the general practitioner. Survival probabilities were calculated by the Kaplan-Meier method.

Results

The postoperative mortality including all deaths within 30 days was 3 out of 15 (20%) for patients with a synchronous lung cancer, and 5 out of 33 (15.2%) for those with a metachronous lung cancer. The causes of death for patients with synchronous cancers were arrhyth-

mia (1) and respiratory insufficiency; (2) with metachronous cancers: sepsis, (1) aspiration pneumonia, (1) respiratory failure (2) and respiratory distress syndrome. (11)

In both groups together 30 patients died during the follow-up, 17 due to malignancy. Of the 4 patients treated by chemo- and/ or radiotherapy, 3 have died and one is still alive after 4 years and 6 months.

The 3 and 5 year actuarial survival was 26 % and 15 % respectively for the patients with a synchronous lung cancer; for the patients with a metachronous lung cancer these rates were 83 % and 53 % after the first resection and 32 % and 18 % after the second resection respectively.

The 31 patients with a metachronous lung cancer without mediastinal lymphnode involvement (stage I and II) had a 3 and 5 year survival of 42 % and 27 %, whereas the 2 patients with mediastinal lymphnode involvement (stage III) died within 14 months. The survival was not significantly different for patients with squamous cell carcinoma, adenocarcinoma or different histology. For patients with a metachronous lung cancer and an interval of 3 years and longer between the two cancers, the 3 and 5 year survival was 55 % and 32 % respectively; when the interval was shorter than 3 years, the 3 year survival was only 11 %.

There was no difference between the survival of patients with metachronous cancer who stopped smoking and those who continued after the first resection.

Discussion

In the literature,[2] the incidence of multiple primary lung cancers is 0.5 % to 3.9 %, mean 1.6 %, for all lung cancers. For metachronous lung cancers the incidence varies from 0.5 % to 10 % and more for the long-term survivors.[3, 4] In a series of 145 patients with a previous sleeve resection for lung cancer, the incidence was 7.6 %.[5] The low incidence generally reported in the literature is due to the unfavourable prognosis of most patients with lung cancer, to the fact that many metachronous lung cancers are not discovered, to different criteria for a metachronous cancer and finally to the follow-up time after the first operation.[2, 4–7] The variability in incidence reported in the literature is probably due to the confusion between primary, metastatic and recurrent cancers.[6–9] In our series the incidence of multiple primary lung cancers was 4.3 %: 1.2 % for synchronous and 3.1 % for metachronous cancers.

The male predominance at 96 % found in our series, as compared to the rate of 76 %[9] to 100 %,[2, 7] reported in the literature, is probably attributable to the smoking habits of males.

The mean age of patients with synchronous or metachronous lung cancers was 58.9 years in our series and is not different from the mean age reported in the literature[6, 10] and not different from the mean age for other primary lung cancers.[7]

The mean interval between the first and the second lung cancer in our series was 5 years and 11 months, and was longer for different histologic types and for contralateral localization, which is in accordance with the literature.[10, 11] In 15 % of our cases the metachronous cancer was discovered after 10 years, in the series of Ribet[7] in 17 % of his cases.

All our patients with synchronous lung cancers were treated surgically for both cancers while of our patients with a metachronous lung cancer 33 (82.5 %) underwent resection. This reoperation percentage for metachronous cancers is high compared to 31 %,[7] 40 %[12] and 52 %[6] reported in the literature; Martini in his series, however, reports on 74 %.[9] Nevertheless, in our series 31 patients (93 %) were in stage I or II and only 2 patients (6.1 %) in stage III at the postoperative staging.

The extent of resection is still controversial in the literature. Jensik et al.[13] found similar survival and recurrence rates after limited resections as segmentectomies compared with lobectomies and pneumonectomies for stage I lung cancer. Others[9, 11] found better survival rates and less local recurrences after more extended resections. As lobectomy was most frequently

performed on the first surgical intervention in our series, comparison is not possible. A sleeve lobectomy is performed instead of pneumonectomy whenever possible in order to save lung tissue and lung function, allowing further resection in the case of metachronous cancer.

The operative mortality in our series was high: 20% for synchronous and 15.2% for metachronous lung cancers. In the literature, the operative mortality for metachronous cancers varies from 0%[12] to 26%[1] with a mean of 8.9%.[10, 14–16] Completion pneumonectomy for lung cancer entails a higher risk than primary resection, with a mortality to 12.5% in the literature.[17] In our series, completion pneumonectomy was necessary at the second operation in 4 patients of the 15 with synchronous lung cancers, and in 16 patients of the 33 with metachronous lung cancers.

The prognosis of patients with a synchronous lung cancer is worse than that of patients with a metachronous lung cancer,[2, 4, 7, 10, 16] which was also found in our series. The difference between synchronous and metachronous cancer is arbitrary as it refers to the moment of diagnosis and not to the moment of tumor development.[7] Consequently, like other authors,[10] we found a worse prognosis when the interval between both tumors was shorter than 3 years. Although only 11% 3-year survival has been found in those cases, complete surgical resection remains the only treatment for the non-small cell lung cancer. An unfavourable group is the group with cancer involvement of the mediastinal lymphnodes. In the preoperative staging and selection of patients we used mediastinoscopy, cervical and sometimes left parasternal for cancers of the left upper lobe or left main bronchus to assess the mediastinal lymph node status and to exclude surgery in patients with extensive lymph node involvement.[8, 18] Unfortunately, only a limited part of the mediastinum is accessible by a mediastinoscope. When unsuspected mediastinal lymph node invasion was discovered on surgery, we tried to perform complete resection with mediastinal lymphadenectomy.[19] But in stage III metachronous lung cancer we obtained poor results, which is consistent with the literature.[4]

Our series is too small to find a prognostic difference between the patients who stopped and those who continued smoking.

Conclusions

When a second primary lung cancer appears, reoperation is the treatment of choice in the absence of metastasis or other contraindications. In most cases a complete curative resection is possible.

Careful follow-up of all patients operated for lung cancer is necessary, even after more than 10 years.

The incidence of metachronous lung cancer is probably higher than generally reported.

Pulmonary resections have to be as conservative as possible, but complete.

The prognosis of a metachronous lung cancer seems positively affected by different histological types of both tumors, an interval of more than 3 years, bilateral localization, mild smoking habit, and by a complete resection without mediastinal lymph node involvement.

On the discovery of the initial lung cancer, patients are advised to stop smoking although in our small series the benefit of that has not been proved.

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Importance of surgery in the multimodality treatment for small cell lung cancer (SCLC)

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Until November 1990 186 unselected patients received first surgery for cure at 23 cooperating departments of thoracic surgery in 9 different countries. All patients had improved SCLC with clinical stage $T_{1,2}N_{0,1}M_0$ and were postoperatively randomized to aggressive standard chemotherapy (cyclophosphamide, doxorubicin, vinblastin) or to alternating chemotherapy which went on for 6 months. Thereafter they recieved prophylactic cranial irradiation (PCI) according to the prospective ISC protocols I and II.

Since December 1990, more than 90 additional patients received surgery and postoperative adjuvant chemotherapy according to the simplified, still on going, ISC protocol VIVI at the above mentioned and 8 additional departments.

In February 1994 the preliminary evaluation showed that, after 28–30 months after the surgery, the curves indicating long-time survivals (cures) takes a plateau-like shape. The survival rate 30 months after the surgery is 61 % (45 patients) for stage $pT_{1-3}N_0M_0$ and 37 % (27 patients) for stage $pT_{1-3}N_2R_0M_0$.

We would like to conclude that a preference should be given to the surgery with the curative intent as the first step of multimodality treatment. A complete resection is indicated for SCLC as for the other nonsmall cell subtypes of lung cancer, even if mediastinal lymphonodes are involved, provided they can still be resected completely according to the Naruke's system. Based on the feasibility of the aggressive chemotherapy used, we suggest to further engaged thoracic surgeons to perform similar studies, using first surgery for SCLC followed by aggressive postoperative chemotherapy.

Key words: lung neoplasms-surgery, surgery with curative intent; small-cell lung cancer (SCLC); combined modality therapy, postoperative adjuvant chemotherapy

Introduction

The differences of efficacy of adjuvant chemotherapy after surgery for cure on patients with SCLC versus patients with non-small cell lung cancer (NSCLC) were discussed in Paris in 1979.[1] Consequently, we discontinued chemotherapy for NSCLC and made preparations for, together with Stjernswaerd, cooperative immunotherapeutical studies. At the time of surgery the immunostimulation was made by intrapleural applications of coryne-bacterium parvum by

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patients with NSCLC at early stages.[2] At the same time we continued cooperative trials, using the agressive combined adjuvant chemotherapy after surgery for patients with SCLC at early stages. The results of this latter randomized studies were discussed at the 13th International Congress of Chemotherapy (I.C.C.) in Vienna.[3,4] With the help of Prof. Orel, these discussions led to the further enlargement of the multinational cooperation; we formed the International Society of Chemotherapy – Lung Cancer Study Group (ISC – LCSG).[5] The 2nd Central European Conference on Lung Cancer in Ljubljana is dedicated to the 40ieth anniversary of the Austrian Cancer Research Institute in Vienna, whose first director, the late surgeon Prof. Wolfgang Denk, started on adjuvant chemotherapy for lung cancer in 1954.[6,7] The results have stagnated during the last decade despite of new and more intensive treatment regiments. Moreover, the duration of chemotherapy and the integration of radiotherapy and surgery in the multimodality management of SCLC are still controversial.[8–10] One of the most important controversies is related to the indication for radical surgery with curative intent: (a) Indication for surgery treatment is the same as in NSCLC. It is the first choice for treatment – as long as the chance for the complete resection of the primary tumour (T), together with its lymph drainage area (N), seems possible. It works when the stage $pTNR_0$ is set up. (b) Indications for surgery treatment are only small peripheral coin lesions. (c) Chemotherapy is the first option for the beginning of the treatment, regardless, of the stage, eventually followed by adjuvant surgery.

Material and methods

Until 1990 the ISC-LCSG conducted 4 prospective randomized multinational cooperative ISC Studies for the optimum of the treatment of SCLC regarding their different stages.

ISC Study I for operable patients with SCLC at clinical stages I or II ($cT_{1,2}N_0N_{0,1}M_0$).

ISC Study II for patients with received surgical resection for an underfined lung tumour. After the resection, the patho histological examination of the operation specimen defined the histological sub-type of a SCLC.

ISC Study III for patients with SCLC at N_2 stage to receive preoperative neoadjuvant chemotherapy followed by surgery with a curative intent.

ISC Study IV for inoperable patients with palliative chemotherapy

All patients were randomized to receive the standard chemotherapy CAV or another combination of chemotherapy. The standard chemotherapy consisted of Cyclophosphamid 1000 mg/m^2, Adriamycin 50 mg/m^2 and Vincristin 1.4 mg/m^2. It was administered in 500 ml saline per i.v. infusion on the day of the onset of the chemotherapy, 1-2 weeks after the surgery and again at 3 weeks interval for a total of 8 such cycles within the first half of postoperative year. Another sequential chemotherapies (combination A, B, C) consisted of 3 different drug-combinations, given intermittetly in a timing as the former mentioned chemotherapy.

Combination A: Cyclophosphamid 1500 mg/m^2, CCNU 100 mg/m^2 and MTX 15 mg/m^2.
Combination B: Cyclophosphamid 1000 mg/m^2, Adriamycin 40 mg/m^2 and Vincristin 1 mg/m^2.
Combination C: Ifosfamide 1600 mg/m^2, Mesna 400 mg and VP-16 120 mg/m^2.

The above mentioned chemotherapy was given at 4 intervals, so that 6 cycles were administered within the first half year after the surgery.

Four weeks after the end of chemotherapy the prophylactic cranial irradiation (PCI) was performed by patients without the symptoms of brain metastases in Study I and II. Tumour dose was 30 Gy in 10 fractions and 36 Gy in 18 fractions.

The input of patients for the Study I and II was closed in November 1990. Since December 1990 the consequent continuation is still going on as ISC-Studies V and VI with simplified protocols: All patients undergo the same chemotherapy, using first a new combination A: Adriamycin 50 mg/m^2 on day 1; Ifosfamide 2 g/m^2 on day 1 and 4; Mesna 400 mg/m^2 at 0^h, 4^h,

8[h]. After 3 weeks interval a new combination B is given: Cisplatin 90 mg/m^2; Etoposid 150 mg/m^2. These 2 combinations are repeated so that 4 cycles in total are administered within the first 3 postoperative months. PCI is not obligatory any more, but brain irradiation is given if it is indicated by symptoms.

The aims of our studies

The study participants agreed to the following tasks:
- Comparison of survival of groups of patients resected for SCLC at different pTNM stages and at different chemotherapy.
- Differences of clinical (cTNM) versus pathological (pTNM) staging after histological examination of the operation specimen and the impact of prognosis.
- Distribution of different histological subtypes of SCLC.
- Pattern of first local recurrence and distant metastases.
- Incidence of side effect caused by treatment and secondary malignancies.

The "local" pathologists agreed to send tumour samples and histo slides to 2 review pathologists to be additionally examined and to confirm the final classification.

Follow up forms

The evaluations are based on data given by the follow up forms which consist to:
- Registration, randomisation, diagnostic procedures for staging.
- Patients characteristics, age, sex, home physician.
- Laboratory data, performance stage.
- Surgery report, extent, localisation of primary tumour and lymphonodes.
- Chemotherapy administered, blood counts, side effects.
- Pathologist's report, tumour extension, lymphonodes labelled by the surgeon prove the final pTNMR classification.
- Report of death, tumour status preferably with autopsy report.

The follow-up forms must be filed at each treatment cycle and at every 6 weeks for the 1st and 2nd year, thereafter at every 3 months and after 30 months following the surgery once per year until death.

Statistics

Every patient has to be evaluated. All records are available for extramural review. The observed overall survival rates are calculated by the Kaplan-Meier method. Surgical and postoperative mortality is not excluded. Tests for p-values of biostatistical significance are used according to the generalised Wilcox method.[11]

Ethics and patients' consent

The approval of the ethical committee at the investigators hospital is sought according to their country's rules. The informed consent is gained from each patient prior to randomisation and is field in the hospital.

Consecutive, unselected, untreated patients enter the ISC-Study I/II if the minimum requirement for clinical staging as cTNM I or II is achieved. The clinical staging is based on physical examination, radiology such as chest film, CT scans of chest, brain, liver and bone and on invasive studies as mediastinoscopy and bone marrow examination. There are no contraindications against surgery.

Results

The following results are based on the preliminary evaluation of February 1994, after the average follow-up time of 70 months after the surgery as the beginning of treatment. 186 patients have been enrolled into the ISC-Studies I and II at the 23 cooperating departments of thoracic surgery and they are associated with the departments of medical oncology, radiology as well as pathology as it is listed in Table 1.

The numbers of patients are subdivided by the ISC-Study I or II, sex and pTNM stages (Table 2). The distribution by age and sex is as follows: 39 males and 12 females under 50 years old, further 99 males nad 21 females

between 51 and 69 years old and 16 males 70 years old and more.

The extent of surgery was 90 lobectomies, 63 pneumonectomies, 15 bilobectomies, 8 wedge or segmental resections, 7 extended pneumonectomies and 3 sleeve resections. Thirty-four % of tumours were an out-cell type, 57% an intermediate type and the remaining 9% were SCLC combined with adeno- or squamous-cell carcinomas. Pathological diagnoses were established predominantly by the »local« pathologist and then by 2 review pathologists.[12]

As the results of the 2 chemotherapeutic regimens didn't show any statistical significant difference, either in survival or in the incidence of side effects, both groups of patients are calculated together as one group. The focus for this evaluation is the different impact on the survival of patients with SCLC at different pTNM stages who were first operated and then got aggressive chemotherapy. Both chemotherapy regimens were well tolerated by the majority of patients (90%) whose leucopenia remained above 2000 leucocytes/mm^3. Only very few patients had leucopenia below 1000/mm^3 and all recovered spontaneously. In general, it was not necessary to extend the interval between chemotherapy cycles. No deaths occurred as a result of leucopenia. The observed overal survival rates of 184 patients at stages pTNM I–III until 60 months after surgery were fully calculated in relation to the different pTNM stages and are demonstrated in Figure 1 together with the numbers of patients at risk. Two other patients with pTNM stage IV, who had metastases, are not included in the calculation of survival rate in Figure 1.

The pTNM stages showed more advanced disease than pre-surgical cTNM in 50 patients and less advanced disease in 16 patients.

Most treatment failures occurred within the first two postoperative years. The slope of the survival curves flattened out to a plateau like shape 28–30 months after surgery (Figure 1). The period of the demonstrated time, from 30 to 60 months, has to be prolonged to be comparable to the time scale for first 30 postoperative months. From 184 patients 43 were still at

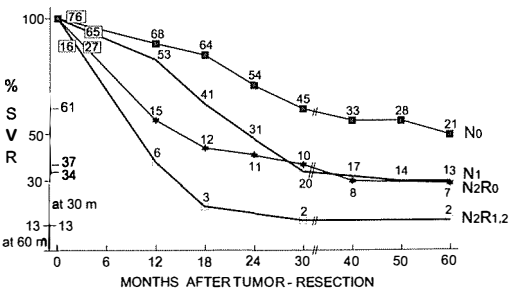

Figure 1. Actuarial survival and numbers of patients at risk after resection followed by chemotherapy and prophilactical cranial irradiation for patients with SCLC. ISC study I, II. Evaluation at February 1994.

risk in February 1994. In 108 patients the cause of death was directly related to the tumour's growth or later metastases; in 27 patients death was not caused by tumour; and in 6 patients the cause of death was unknown.

The localisation of the first relapse was locoregional in 38 patients, cerebral in 36 patients and other distant metastases occur in 44 patients. 64 patients lived longer than 30 months after surgery and there was no evidence of second malignancy, which could be caused by chemotherapy.

In ISC Studies V/VI 90 patients were included into 8 additional departments listed in Figure 1. Their survival seems quite similar as in ISC Studies I/II, but the observation time is not enough for the judgment at the critical 30ieth month after surgery.

In the ISC Study III 156 patients were enrolled to receive randomized preoperative neoadjuvant chemotherapy 1 or 2 as in the ISC Study I. Only 36 of them agreed to the adjuvant surgery after chemotherapy. The results are unfavourable in comparison to the ISC Study 1.[13] Therefore, we discontinued this preoperative neoadjuvant chemotherapy approach.

In the ISC Study IV 230 inoperable patients were treated for palliation; they were randomized by a different kind of chemotherapy. In general, chemotherapy was the same as in the ISC Study I, but regarding the condition of

Table 1. Participants of the Cooperative ISC. Studies I, II, III, V, VI, VII.

Country/City	Surgery	Medical Oncology	Radiology	Pathology
A Vienna	N. Pridun	M. Neumann, N. Vetter	G. Alth	E. Lintner
PL Gdansk	Z. Paplinski	H. Karnicka, J. Jassem	A. Jungowska, A. Sokol	K. Doerr
D Rohrbach	J. Vogt-Maykopf	P. Drings	M. Wannenmacher	K.-M. Müller
SLO Ljubljana	J. Orel, J. Erzen, B. Hrabar	M. Klevisar	M. Debevec	T. Rott
RC Shanghai	O. Wang, X. CHow	M. Liao, J. Zhao	M. Lin	Z. Lin
RC Beijing	G. Huang	Y. Sun	W. Yin	F. Liu
RC Shenyang	H. Li, d. Chen, L. Han			
D Bielefeld	M. Thermann	M. Körte	L. Arndt	U. Raute-Krensen
I Forli	A. Lattuneddu, D. Dell' Amore	A. Galassi, A. Campanini	G. Giorentini	F. Padovani
A Gaisbühel	G. Zimmermann	J. Rothmund, M. Amann	Oser	G. Breifellner
TR Istanbul	A. Sayin	B. Berkarda, S. Serdengecti	R. Ucel	G. Glirisken
Jp Kawasaki	H. Osada	M. Koike	M. Endoh	Kakimoto
A Vienna	E. Wolner, F. Eckersberger	W. Schlick	K. Kärcher	H. Holzner
RA B. Aires	A. Imposti	M. Bruno, N. Brocato	N. Ruggeri	
Jp Tokyo	E. Hata, R. Matsuoka			
PL Kraków	L. Kolodziejski	M. Pawlicki, M. Ziobro	S. Dyczek	a. Niezabitowski
RC Guangzhou	H. Zhou	Z. Guan	G. Zheng	
A Salzburg	O. Boeckl	H. Hausmaninger	D. Kogelnik	J. Thurner
A Vienna	E. Zwintz	G. Baumgartner, O. Kokron	G. Alth	J. Mühlbauer
A Linz	H. J. Böhmig	K. Aigner, J. Würtz	F. Mieß, J. Hammer	H. Regele
I Firenze	C. Crisci	N. Nozzoli, S. Nutini		N. Dini, N. Santucci
I Milano	I. Cataldo, A. Bedini, G. Ravasi		F. Milani	C. Patriarca
RA B. Aires	R. Grinspan, H. Hoyos	D. Levy	B. Dosoretz	a. Ferrari
I Cosenza		V. Zottola, S. Barbera		G,. Galippi
JP Tayama	Y. Kusajima	Y. Mizukami	M. Sugihara	N. Takayanagi
RA Buenos Aires	H. Della Torre	A. Pepe, L. A. Tabarews		
I Bologna	P. Sette		L. Cacciari	
D Donaustauf	F. v. Bültzinglöwn			

Byelar/Minsk	V. Zharkov, Y. Demidchik	V. Kurchin, P. Moiseev, N. Shishko	A. Furmanchuck	
CIS Moscow	M. Danydov, Al-Ansari,	V. Gorbunova, N. Smirnova N. Orel		
D Düren	R. Rios-Pooley	J. Karow		
Latv. Riga	H. Basko, R. Zaleskis	G. Purkalne, D. Lega, J. Berzins	A. Veinbergs	I. Rone
Lith. Vilnius	A. Jackevicius	V. Jakeleviciene P. Nzujokaitis	e. Aleknavicius	A. Felinskaite
CIS Kiev	E. Konovalov, Y. Kogoso	J. Smolanko, B. Radionov	V. Saphonov	e. Suslov
I Siena	g. Gotti, G. Biagi, P. Paladini	E. Tucci	L. Volterrani	V. Sforza
ISP Valencia	A. Canto	V. C. ALerola	v. Cervera	S. Navarro

ISC-Study Center: K. Karrer, N. Pridun, E. Ulsperger A. Schamanek Inst. for Cancer Research of the Univ. Vienna/A
M. Schemper, Institut für Medizinische Comprites – Wissenschaften Univ. Vienna/A.
T. Shields, Northwestern Univ. Chicago/USA, O. Selawry, Rileyville, Virginia/USA;
Reference-Pathologists: J. H. Holzner, Institute for Pathology of the University of Vienna/A
K.-M. Müller, Institute for Pathology of the Univ. of Bochum/D

Table 2. Distribution of Patients per ISC-Studies I, II, Sex and pTNM-stages.

Study	sex		I	II	IIIA				IIIB	IV
					T1,2		T3		T4	
					N2	N0	N1	N2	N1	N2	
ISC-I	f	10	7	2				1			
	m	58	31	15	4	2	1	5			
ISC-II	f	23	7	7	4		2		1	1	1
	m	95	28	32	23	1	4	4	1	1	1
TOTAL	f + m	186	73	56	31	3	7	10	2	2	2

patients, there were more reductions of a dose used.[13] Generally, the palliative effect was poor but similar after chemotherapy 1 and 2. Therefore, we also discontinued the ISC Study IV and recommended the individual chemotherapy according to the most up-to-date recommendations, for instance the recommendations of international Association for the Study of Lung Cancer (IASLC).[14]

Discussion

The hypothesis to consider SCLC as a systemic disease regardless the stage and to suggest that there is no place for surgery in SCLC, seems unjustified in the light of reports and our demonstrated results. The pTNM stage N_0M_0 in SCLC as well as in other histological subtypes of lung cancers and in other carcinomas is a reality. There were 38 patients with such a stage involved in the ISC Study I, and 36 patients in the ISC Study II, treated at 23 independent cooperating hospitals in 9 different countries. These patients are still alive and 47 of them are long term survivors of more than 5 years. These are reliable figures.

The importance of surgery seems convincingly substantiated by the relatively high level of the 5 year survival of 30% patients (of 27 patients) who were completely resected for SCLC and reached to stage $pTN_2R_0M_0$. With the development of more effective chemotherapy it becomes apparent that in patients treated with chemo- and radiotherapy a frequent site of failure was the tumour bed or regional lymph nodes. Thus, a more effective treatment of local control it appeared to be needed. The multimodality treatment starting with the resection for the cure of SCLC can be seen as another example of the concept that has led to major progress in curing malignant diseases during the last three decades. This concept of combined treatment from the time of diagnosis is of general importance, even though the number of suitable patients with SCLC may be relatively small in one hospital, as the result of limited activities in early diagnostic procedures. Surgery with attention to cure at very early stages is not enough because of the danger of clinically undetectable micrometastases. Postoperative chemotherapy appeared more effective than surgery alone.

Nevertheless, the initial complete surgical resection of the localised stage of SCLC, followed by intensive postoperative chemotherapy, is not the only viable option for patients with an early stage of SCLC, since some of the patients with incomplete surgical resection are still alive (Figure 1). However, the results of the initial complete surgical resection are much better, both if compared with non surgical treatments or the results of neoadjuvant preoperative chemotherapy.[13] The results obtained in patients with $pT_3N_0M_0$ SCLC appear to be satisfactory, even though only 3 such patients are under observation, but 2 of them are still alive 5 years after surgery.

Although the International Association for the Study of Lung Cancer (IASLC) published the consensus report about the positive role of surgery for the patients with cTNM stage I, II or IIIA,[15] the use of initial surgical complete resection followed by intensive postoperative

chemotherapy is still not in common use. Only a small number of reports have been published during the last 5 years.[16–19]

The indication of surgery for pTN2 has been extensively discussed for all lung tumours, since this group of patients is quite large and involves a great variety of prognoses. There are patients without detected macroscopically but histologically proven discrete tumour cell infiltration in mediastinal nodes. On another handthere are patients with real bulky N2 disease. The result presented in literature, as well as our own results, lead to the conclusion that the indication for surgery should be handled for patients with SCLC in the same way as for other histological subtypes of lung cancers. As long as the primary tumour and regional lymph nodes – also N2 – can be completely resected, such surgery with curative intent should be performed whenever possible. Extended surgical procedures to allow complete resection of the mediastinal lymph nodes should be followed by aggressive chemotherapy. This contention is supported by our observation of the 37% 30-month survival rate of the 27 patients whose SCLC stage pTN2 was completely resected. The inclusion of patients with operable N2 tumours should increase the number of evaluable patients for more future studies. The incidence of local recurrence at first relapse was 11/47 in our pTNO patients and 8/39 in pTN2. It indicates the low influence of the surgical procedures on local relapse rate.

Regarding the so called neoadjuvant preoperative chemotherapy, several critical aspects have to be considered, namely, if the primary tumour is localised at the very beginning of the treatment. That may present a problem, the case of fast growing tumours, which require preoperative chemotherapy. The time lost cannot be compensated through chemotherapy. Most of the reports show that the proportion of patients without any viable tumour cell after initial chemotherapy is small. The rate of still operable patients has also decreased. Patients with mixed tumours, including non-small cell elements, need surgery in any case. From the psychological point of view it seems more encouraging for the patients to undergo initial surgery, if the tumour is considered to be operable. The tumour heterogenity seems to be an important factor for treatment failures in patients with SCLC. Further biological studies might offer a better understanding of the fact that most of the patients with SCLC do relapse after initial effective treatment. For such investigations fresh tumour samples from surgical specimens are needed, which is another advantage of surgery as the first treatment modality.

Of 156 patients enrolled in our ISC Study III, only 82 showed a response after the preoperative chemotherapy. Secondly, a high proportion of responders have not received postchemotherapy surgery. It seems to be most important that there is a relatively low survival rate of the patients receiving surgery for pTN2M0 stages after preoperative chemotherapy. This seems quite similar to the results presented by Lad.[20] Therefore, we nolonger recommend preoperative neoadjuvant chemotherapy for SCLC and close the input for our ISC Study III.

We conclude that presented data imply that 30 months- and 5-year survival rate of patients with SCLC at pTNM stage I, II and pT3N0M0 becomes substantially improved by initial complete surgical resection and intensive postoperative chemotherapy. The results are superior to preoperative chemotherapy followed by adjuvant surgery. As long as pTN2M0R0 SCLC can be completely resected, surgery with an intent to cure should be performed as the first step of multimodality treatment. The indication for surgery for SCLC should be the same as for NSCLC. As surgery is not yet generally accepted as the crucial first step of multimodality treatment of SCLC, the intensification of cooperation and/or independent studies are necessary to confirm our promising results. Finally, our results should be convincing enough to stimulate future cooperation to get a substantial number of patients in each of the different prognostic subgroups, necessary for general recommendations. We strongly recommend full attention to be paid to diagnostic procedures, as these have been effective in Japan.[21] At

least, such efforts are indicated for high risk groups, which can be defined. With an increased therapeutic efficacy and with an increased number of longterm survivours, including cures, measures for early diagnosis became even more justified.

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Lasers in broncho-pulmonary cancer

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In a 10 year period laser photoradiation was used in 687 patients with lung cancer. Patients are grouped taking into account the type of laser employed and their treatment method. An overall majority of 628 received yttrium aluminium garnet (YAG) laser treatment in 3 sub-groups: 1a) 350 patients with inoperable broncho-pulmonary cancer and substantial intra-luminal obstruction received a total of 750 treatment sessions. 1b) 99 patients had operable coin lesions which were excised by YAG laser following standard limited thoracotomy. 1c) 179 patients had laser assisted lung resection. Group 2 consisted of 59 patients with inoperable extensive lung cancer who received bronchoscopic photodynamic therapy (PDT) having been presensitized 24–48 hours prior to radiation with 630 nm red light. All patients who underwent endoscopic treatment (group 1a and group 2) had symptom relief as a result of the bronchial desobliteration. There was no procedure related mortality. Patients undergoing YAG laser treatment had more immediate relief, whilst those receiving PDT had better long-term results with survival of over 36 months compared with 25 months for group 1a patients; 3 patients died in the combined groups 1b and 1c. There was no mortality in the 99 patients who had local laser excision of tumour. We conclude that lasers have considerable potential in broncho-pulmonary tumours allowing both palliation and economic lung resection. PDT has curative potential in some tumours.

Key words: lung neoplasms; laser surgery

Introduction

The acronym laser stands for Light Amplification by Stimulated Emission of Radiation. In simple terms this signifies change in the energy levels of an atom leading to photon (unit of light) emission and interaction with other excited atoms or molecules which go on to stimulate the emission of further photons leading to light amplification. Lasers are named after the active medium from which they derive their lasing action. This medium can be solid, as in the ruby laser, liquid, as in the dye laser, or gas as used in the CO2 laser. The overall biological effects of lasers are determined by light/tissue interaction which is governed by reflection, transmission, scattering and absorption. Of these it is the absorption of the light in tissue which is responsible for both the type and size of tissue injury and response. In practice tissue injury and response to laser radiation are translated as coagulation, vapourisation, burning and necrosis.

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Nevertheless whilst all lasers are "light" energy their lasing medium and the physical characteristics of their light as well as the delivery system of that light to the target tissue will determine the specific tissue response which reflects their therapeutic effect.

Of the many laser devices available two are currently in common use in broncho-pneumonology:

1. YAG laser

The Neodymium yttrium aluminium garnet (Nd YAG) laser emitting electro-magnetic radiation at 1064 nm is a laser with multiple potentials. YAG laser light can be delivered through optical fibres and is therefore suitable for tracheobronchial endoscopic use. Since the delivery fibres in the YAG can extend to some distance from the generator, its use in intra-operative situations is also a practical possibility.

2. Dye laser and photodynamic therapy (PDT)

A more recent development in medical laser technology has been the development of PDT. This is based on pre-sensitization of cancer tissue by a chemical, followed by its exposure, after an interval of 24–72 hours, to laser light of an appropriate wave length. The interaction between chemical and light in the presence of oxygen has a cytotoxic effect which leads to necrosis of the exposed tissue. The chemical most commonly used is a derivative of haematoporphyrin. This, administered intravenously, concentrates predominantly into cancer tissue, as compared with normal tissue, in 24 to 72 hours.

The laser equipment for PDT is a dye laser emitting red light of 630 nm delivered via an optical fibre with an end diffuser. Thus far PDT has been used almost entirely for endoscopic treatment of broncho-pulmonary cancer.

In this paper we present our experience in the use of lasers in broncho-pulmonary cancer, and will outline our current views on the place of lasers is such cancers.

Patients and methods

During a 10 year period up to December 1 1993 we have used lasers in the treatment of 687 patients with broncho-pulmonary cancer. Principally two types of lasers were employed in these patients, either endoscopically or at operation. Therefore patients are grouped firstly according to the type of laser and secondly based on their treatment method (Table 1).

All patients had routine work up which included clinical, radiological and endoscopic examination to assess operability, histology and preoperative staging, either before or following their referral to our centre.

Equipment and Method

The equipment for group 1 patients (YAG

Table 1. Lasers in broncho-pulmonary cancer, personal experience.

Type of Laser	Treatment Method	Sub-Group	Patient Nr	Treatment Nr
	All	1a, 1b, 1c	628	1028
	Endoscopic	1a	350	750
GROUP 1 YAG	Excision of Nodule	1b	99	99
	Laser Assisted Pulmonary Resection	1c	179	179
GROUP 2 PDT	Endoscopic		59	101
Total	All	All	687	1129

YAG = yttrium aluminium garnet (laser)
PDT = photodynamic therapy (laser)

laser) treatment consisted initially of a Fibrelase 100 (Pilkington) and later a Sharplan 3000. Both were Nd YAG (1064 nm) lasers capable of supplying up to 100 watts of power either for 1–25 seconds pulses or for continuous application and delivered through an optical fibre with a diameter of 0.6 mm. Patients in Group 1a had bronchoscopic YAG laser treatment under general anaesthesia using a rigid Moghissi-Jessop[1] bronchoscope. Repeated pulses of 30–60 watts for periods of 3–5 seconds were used, employing the laser in its non-contact mode, the aim being evaporation of the obstructing bronchial tumour. The treatment was repeated as necessary at intervals ranging from 6–12 weeks. Some patients in this group had adjuvent radiotherapy.

Patients in Group 1b had limited thoracotomy using conventional surgical methods to assess the tumour and its extent. Non-contact mode of YAG laser was then used to excise locally the tumour according to previously described methods.[2,3] In practice the healthy parenchyma around the tumour was evaporated and the tumour was shelled out. Only segmental and subsegmental broncho-vascular structures needed securing by surgical clips. Smaller bronchial branches and blood vessels could be sealed off by the laser itself. In those cases with superficial tumours no additional measures were required. In some cases it was necessary to suture the gap left through the local excision of deeper or larger tumours.

In Group 1c patients pulmonary resection was carried out principally using conventional methods. YAG laser was used in these cases to assist the separation of segments or lobes in order to reduce the broncho/pulmonary surface air leak and to acheive haemostasis. In some cases a small extension of the tumour to the neighbouring lobes/segments required wedge excision of this area which was undertaken using laser.

Group II patients received endoscopic PDT. They were first given intravenously 2 mg/Kg body weight Polyhaematoporphyrin or Photofrin II followed by exposure to laser light (Figure 1).

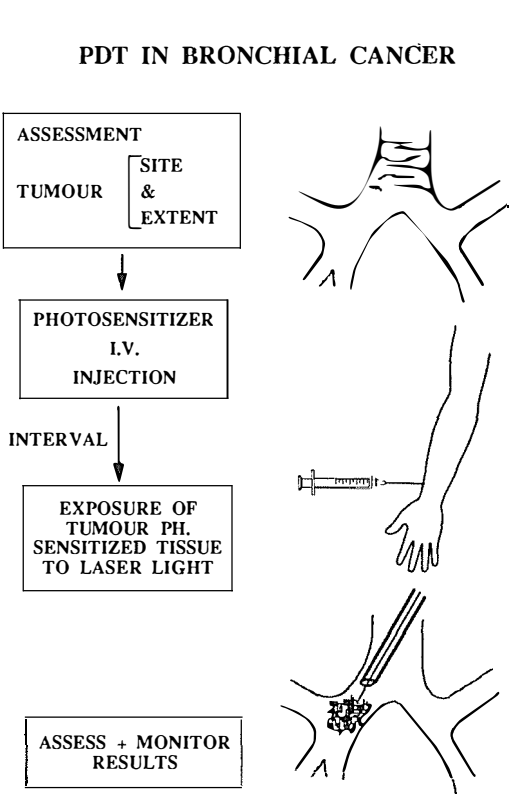

Figure 1. Schematic protocol of endoscopic photodynamic therapy (PDT).

Endoscopic PDT treatments were undertaken under general anaesthetia via both rigid and fibreoptic bronchoscopes, according to the previously described protocol.[4] Placement of the optical fibre with end diffuser was through the biopsy channel of the instrument. In all cases the treatment was interstitial; that is the diffuser was introduced into the bulk of the tumour.

Assessment of results

Endoscopic treatment (group 1 & 2) results were recorded as follows:

– Change in % of opening of bronchial diameter.

– Improvement/deterioration in WHO performance status, and pulmonary function (FVC and FEV1).

– Radiological changes. Patients were assessed 1 month post-treatment and then at 3 monthly intervals.

- Survival.
- Microscopic clearance (if any).

Results in Group 1b and 1c were assessed as follows.

- Hospital mortality.
- Complications (post-operative).
- Hospital stay.
- Survival.

Results

Group 1a

350 patients (275 male and 75 female) aged 43–85 (mean 73.5) received 750 treatments (2.2 treatments/patient). All had extensive unresectable lung cancer with substantial > 50% bronchial luminal obstruction (range 50–95%, mean 75%).

Table 2 presents the post-treatment data.

Table 2. Endoscopic YAG laser treatment for extensive inoperable broncho-pulmonary cancer (n = 350).

Results
No procedure related mortality
Improvement in bronchial opening (43% mean)*
Improvement in FVC: 0.1 litre*
Improvement in FEV1: 0.05 litre*
Symptom relief: Immediate – lasting 4–12 weeks
Survival 2–25 months

* 1 month post treatment

Group 1b

There were 99 patients in this group (62 male and 37 female) aged 33–80 years (mean 64.8). Eleven patients (11%) in this group had lymph node involvement on exploration. One patient died in hospital due to cardio-respiratory failure. Three patients had prolonged air leak necessitating prolonged tube drainage.

Hospital stay was 5–22 days (mean 9 days).

Pulmonary function carried out 4-6 months post-operatively showed a mean FVC and FEV1 deterioration compared with pre-operative figure of 11% and 4% respectively. Unexpectedly there was improvement post-operatively of FVC and FEV1 in 15% and 17% of patients respectively. Long-term results have been related to the histology and staging.

Group 1c

In this group there were 179 patients (120 male and 59 female) age 45–71 (mean 64.5). All had conservative lung surgery of lobectomy in which laser was used as a complementary measure to excise small subsidiary lesions separately or as a continuation of the main tumour. Twelve patients (7%) in this group had bilateral thoracotomy for a second tumour or metastases. The total mortality was 2 (1.1%). Long-term survival depended on the stage of the disease.

Group 2

There were 59 patients (47 male and 12 female) in this group, age 52–80 years (mean 75.5). All patients had inoperable Stage III tumour.

Table 3 shows the post-treatment data of these patients.

Table 3. Endoscopic PTD for broncho-pulmonary cancer (n = 59).

Results
No procedure related mortality
1 patient with mild skin photosensitivity reaction
Improvement in bronchial % opening 71% (mean)*
Improvement in FVC: 0.47 litres (mean)*
Improvement in FEV1: 0.35 litres (mean)*
Symptom relief: Lasting for 8–18 weeks
Survival: 2–36 months

* 1 month after treatment

Discussion

It is generally accepted that surgical resection of the tumour and its satellite lymph nodes, is the treatment of choice for all resectable non-small cell lung cancer. It is also an undisputable fact that only the minority of lung cancer sufferers qualify for receive such surgical treatment. Illustration of this fact may be furnished by referring to statistics provided by the Yorkshire Regional Cancer Organisation, an organisation which registers all cancer throughout the Yorkshire Region of the UK, with a population of 3.6 million. Some 2760 cases of lung cancer are diagnosed yearly, of which 9.6–11.8% receive surgical treatment.[5] When one considers that

many of the operated patients will have recurrence of their tumour, it becomes clear that at presentation a great many patients with lung cancer are receiving treatment which can be classified as palliative. It is against this backsteet was perceived. In fact, from the beginning of its introduction to the medical field, much of laser research has centred around evaluation of its benefit in cancer therapy generally and is directed towards palliation of patients with extensive tumour more specifically.

In broncho-pulmonary cancer lasers have been used predominantly for endoscopic treatment. Since the early 1980's thousands of patients have received bronchoscopic YAG laser treatment for palliation of their broncho-pulmonary cancer. This is well reflected in the number of surveys and review articles.[6-8] Our series of 350 patients (Group 1a) confirms the previous findings. In addition our experience suggests that in a selected group of patients laser treatment coupled with external beam radiotherapy, thus combining intra-luminal with external radiotherapy achieves palliation over a longer period.

Endoscopic PDT in our series of 59 patients had given still better symptom relief results and longer survival confirming our previous findings[9] that not only is PDT beneficial in extensive lung cancer with bronchial obstruction, but its benefits are more substantial and last for a longer duration thas those of YAG laser. Some authors[9, 10] believe that endoscopic PDT is indicated only in early endobronchial tumours. Our results and those of some other authors[11-15] demonstrate conclusively the value of PDT in early as well as extensive lesions when there is substantial obstruction of the bronchial lumen.

Intra-operative use of YAG laser in pulmonary surgery generally and lung cancer more specifically has received little attention. Nevertheless our previous studies[2, 3, 16] and the results of the present series clearly point out the advantages of the technique in which a nodular tumour is locally excised through a limited thoracotomy. In effect the use of laser allows patients with borderline pulmonary function to undergo lung resection for cancer because the technique is attended by preservation of pulmonary parenchyma which is essential to such patients. The low operative mortality[16] and insignificant post-operative complications are a reflection of this and alsoof the capability of YAG laser to seal off blood vessels and minute airways.[17] It is obvious that pre-operative assessment of pulmonary function and nodal status are particularly important in patients submitted to this type of surgery.

The association of laser with conventional surgery in Group 1c is another way of achieving conservative parenchyma saving surgery. It is to be emphasised that the use of laser either for local excision of "coin" lesions or in association with conventional surgery will not and should not compromise the oncological integrity of the lung cancer operation. To the contrary, it will add to the safety of the resectional surgery because of the destructive action of lasers on cancer tissue.

Conclusions

The use of lasers makes an important contribution to the treatment of lung cancer. Employed endoscopically they can disperse obstructive intraluminal lesions, thus improving ventilation. They can also reduce cough, frequency of haemoptysis and chest infection.

YAG laser and/or PDT used individually (and in some cases alternately) can achieve desobliteration of the airway.

In early tumours confined to the bronchial wall alone cure may be attained using endoscopic PDT.

At the present time intra-operative indications of laser in lung cancer is confined to YAG which is particularly useful in local excision of nodular tumours.

The potential intra-operative usage of PDT has yet to be defined.

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Long-term results of primary surgery for stage I small cell lung cancer

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Between January 1979, and December 1993, 17 patients (15 females and 2 males; mean age 57.9 ± 2.8 (SEM) yrs., median 55 yrs, (range 43–78) with stage I small-cell lung cancer underwent primary surgery followed by adjuvant polychemotherapy and prophylactic cranial irradiation. In no instance was preoperative histological diagnosis available. The extent of resection included a lobectomy in 9 patients, a pneumonectomy in 1, and a segmental resection in 7. Postoperative chemotherapy included three cycles of cyclophosphamide – 1000 mg/m², vincristine – 1.3 mg/m², doxorubicin or epidoxorubicin – 60 mg/m², administered every 21 days, followed by three additional cycles of cisplatin – 25 mg/m², and VP16–120 mg/m², administered in 3 consecutive days every 21–28 days. Prophylactic cranial irradiaton was given concurrently with the first cycle of chemotherapy and immediately after surgery. Actuarial 5-year survival was 47 % (Kaplan-Meier method). Median survival was 61 months. No statistically significant difference in terms of survival was detected between lobectomy and other procedures (p = 0.2, log-rank test).

Key words: lung neoplasms-surgery; carcinoma, oat cell, survival analysis

Introduction

Combined treatment modalities for stage I small-cell lung cancer are advocated in order to obtain long-term survival.[1] Surgery of the peripheral stage I small-cell carcinoma is warranted both for diagnostic and therapeutic purposes. Recently, the thoracoscopic approach has gained the favor of surgeons dealing with suspected lesions in the peripheral lung,[2] thus reducing postoperative morbidity.

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We report our experience concerning the management of stage I (T1NO/T2NO subsets) small-cell carcinoma over a 15-year period.

Material med methods

Between January 1979, and December 1993, 17 patients (15 males and 2 females; mean age 57.9 ± 2.8 (SEM) yrs., median 55 yrs., (range 43–78) with stage I small-cell lung cancer (SCLC) underwent primary surgery followed by adjuvant polychemotherapy and prophylactic cranial irradiation. In no instance was preoperative histological diagnosis available. In all patients, a peripheral nodule was visible on stan-

dard chest x-ray. The staging procedure for clinical stage I disease did not include a preoperative mediastinal exploration because of the lack of mediastinal node enlargement at CT evaluation.

A muscle-sparing limited thoracotomy was used in our early series.

Since 1992, video-assisted thoracoscopy was routinely used for resection of the nodule which was removed from the pleural cavity via an accessory thoracotomy (comparable in lenght to the previously used muscle-sparing limited thoracotomy). An effort to sample accessible nodal stations was routinely made. The extent of resection included a lobectomy in 9 patients, a pneumonectomy in 1, and a segmental resection in 7.

Intraoperative frozen section of the surgical specimen was obtained in all cases. Nine patients with stage I disease had a T1 and 8 had T2 subset.

Postoperative chemotherapy included three cycles of cyclophosphamide – 1000 mg/m^2, vincristine – 1.3 mg/m^2, doxorubicin or epidoxorubicin 60 mg/m^2, administered every 21 days, followed, more recently, by three additional cycles of cisplatin – 25 mg/m^2, and VP16 – 120 mg/m^2, administered in 3 consecutive days every 21–28 days. Prophylactic cranial irradiation (PCI) (30 Gy) was given concurrently with the first cycle of chemotherapy and immediately after surgery.

The survival rates were calculated according to the Kaplan-Meier method.[3]

Results

Histologic examination showed a pure small cell carcinoma in all cases.

There were no surgery-related deaths nor postoperative complications.

As of December 1993, 11 patients are alive and without evidence of disease. The longest survival has been 150 months.

Six patients died from disseminated disease with a longest survival of 48 months. In no instances was relapse of the disease in the primary site detected.

Actuarial 5-year survival was 47% (Kaplan-Meier method) (Figure 1). Mean and median survivals were 58 ± 10.4 (SEM) and 61 months, respectively. No statistically significant difference in terms of survival was detected between lobectomy and other procedures (p = 0.2, log-rank test) (Figure 2). Similarly, no significant difference in survival was seen between T1 and T2 subsets (Figure 3).

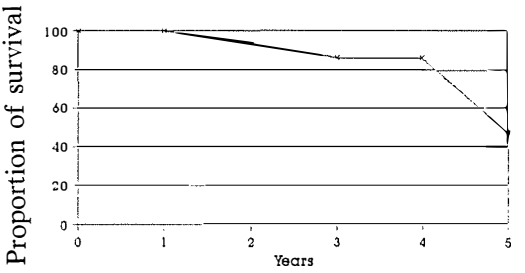

Figure 1. Overall survival of patients with stage I SCLC (Kaplan-Meier method).

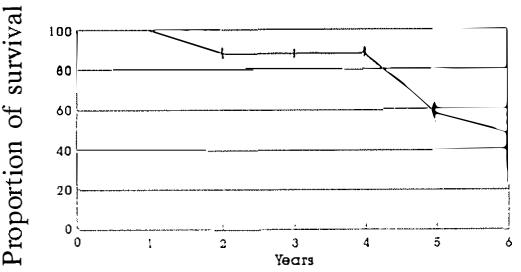

Figure 2. Survival of patients with stage I SCLC subjected to lobectomy.

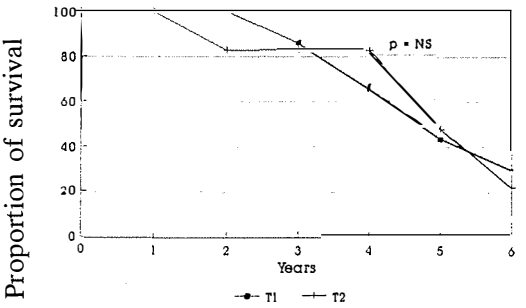

Figure 3. Survival of patients with stage I SCLC by stage (T1 vs T2).

No signs of PCI-related toxicity to central nervous system (CNS) were noted.

Discussion

Only 10% of patients with SCLC present with a peripheral nodule.[1] The 5-year survival of these patients is comparable to that of patients with other histotypes.[1] In our limited series, the 5-year survival of patients with stage I SCLC reached an actuarial survival of 47% which compares favorably with the 59.5% for T1NO and the 27.9% for T2NO reported in one study.[1] Similar results have been obtained in a multi-institutional study focused on initial surgery followed by chemotherapy (55% 4-year survival for stage I SCLC).[4]

The addition of chemotherapy, chest radiotherapy and prophylactic cranial irradiation in patients with limited disease has been advocated in order to obtain better local control and to avoid systemic recurrences.[1] Based on the observation of a very low incidence of brain metastases from stage I SCLC and the reported CNS toxicity, the routine resort to PCI is under debate.[4]

Furthermore, TXNO subsets are reported to have a 50% chance of systemic reccurences after surgery, and an identical 50% chance of local recurrence after chemotherapy.[1] In an effort to improve overall survival rates, we used this aggressive approach in our patients with stage I disease. Local control at the primary site was obtained and adjuvant treatments were well tolerated as no significant morbidity was reported.

Preoperative diagnosis of a peripheral nodule can be obtained through either needle biopsy or surgical resection. The latter is achieved via a thoracotomy or, more recently, via a thoracoscopic approach.[2] In our case, the significant false-negative rate of transthoracic needle biopsy has impaired the overall sensitivity of this procedure.[5]

Of greater importance is the possibility to draw distinction between SCLC and well-differentiated neuroendocrine tumors which are amenable to surgery alone.[1] To do so, an adequate specimen is needed in order to obtain a final pathologic analysis.[1] Accordingly, we believe that surgical resection only can provide an adequate tissue sample for this precise discrimination.

Before the thoracoscopic era, we favored a muscle-sparing limited thoracotomy for the diagnosis and resection of undefined peripheral nodules. Recently, the role of surgical staging procedures in the management of SCLC has been emphasized.[1] According to an observation made by the Toronto Lung Cancer Study Group,[6] nearly 48% of the patients with clinical stage I disease will be upstaged after histological examination of the surgical specimen. As a result, prethoracotomy mediastinal exploration is indicated,[4] for the evidence of N2 disease which is a contraindication to resection.[7] In this setting, video-assisted thoracoscopic techniques may be of value,[8] although, in our series, we have not observed a remarkable advantage of thoracoscopy over minithoracotomy as far as postoperative morbidity and hospital stay are concerned.

In conclusion, we emphasize the role of surgery as a part of a multimodality approach to stage I SCLC, yielding better local control of the primary and attendant satisfactory long-term survival rates.[6, 9]

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Surgery for lung cancer in the elderly

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Between January 1979 and December 1993, 162 patients aged more than 70 years underwent surgery for lung cancer. Thirty-eight patients (23%) were lost to follow-up. Overall median survival was 32 months. The overal five-year survival was 24% (Kaplan-Meier method). Age, histological type, stage and adjuvant treatments for stage IIIA were not significantly realted to survival. Female sex ($p = 0.03$), and extent of resection ($p = 0.02$) significantly correlated to survival. Lobectomies were associated with a better survival than pneumonectomies ($p = 0.03$), the latter showing a better outcome than lesser resections ($p = 0.03$). The extent of resection was the only variable indipendently influencing the overall survival ($p = 0.007$). Median disease-free survival was 24 months. Female sex ($p = 0.03$) was the only indipendent predictor of disease-free survival by multivariate analysis ($p = 0.02$).

Surgery for lung cancer in the elderly can be performed with acceptable long-term results in terms of overall and disease-free survival. The indications for pneumonectomy should be carefully weighed against potential postoperative risks. Even in the elderly patients, resections lesser than lobectomy, although functionally more acceptable, entail a greater risk for local recurrences.

Key words: lung neoplasms-surgery; aged; survival analysis

Introdnction

In the early 70's, it was perceived that lung cancer patients older than 70 years could not be suitable surgical candidates.[1]

The advances in anesthesia and the improvement in surgical technique enabled this population to benefit from the only effective treatment for lung cancer.[1] Conversely, surgical consideration for octogenarians is now under debate.[2]

We report our 15-year experience on the surgical treatment of lung cancer in patients older than 70 years.

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Material and methods

Between January 1979 and December 1993, 162 patients (146 males and 16 females) aged more than 70 years underwent surgery for lung cancer.

A clinically significant chronic obstructive

pulmonary disease was found in association with lung cancer in over 90% of our patients.

Preoperative workup included a careful evaluation of the performance status, an accurate assessment of pulmonary reserve through spirometric tests and the determination of maximum oxygen consumption. Cardiologic profile was documented by routine examination, ECG, and ultrasound, as indicated. Borderline function required ventilation/perfusion scans or 24-hour ECG monitoring. In no instance was preoperative coronary arteriography indicated.

Special attention was paid to preoperative physical therapy focused on postural drainage and diaphragmatic training.

Until recently mediastinoscopy was not included, among staging procedures for lung cancer. When an N2 disease was suspected, a muscle-sparing limited thoracotomy was used with mediastinal node sampling and frozen section.

CT evaluation of the brain was obtained routinely, whereas bone scans were done in the presence of symptoms suspicious for skleletal involvement.

For the sale of simplicity, the patients were grouped according to their age (group 1, including 110 pts. aged 70 to 73 years; group 2 including 36 pts. aged 74 to 76 years; group 3 including 16 pts. aged 77 yrs and older), gender (males = 146; females = 16), stage (I = 101 pts.; II = 11 pts.; IIIA = 50 pts.), histologic type (epidermoid = 97 pts.; adenocarcinoma = 47; other = 18 pts.), the extent of resection (lobectomy = 110 pts; pneumonectomy = 27 pts.; others = 24 pts.; unknown = 1), and the administration of adjuvant treatment for stage IIIA (yes = 20 pts.; no = 14 pts.).

The influence on survival and disease-free interval of these variables was evaluated by univariate (log-rank test or Mann-Whitney U test for two groups, and Kruskal-Wallis test for multiple groups) and multivariate analysis (Cox proportional hazard regression model), as appropriate.[3, 4]

Twenty-eight patients (17%) were lost to follow-up. These patients were evenly distributed among the three groups (stage I = 10; stage II = 1; stage IIIA = 17). Accordingly, we believe that this relatively high percentage of lost-to-follow-up patients has not affected the statistical analysis.

Results

Overall mean and median survivals were 22.7 ± 2.1 (SEM) and 32 months (range, 1–132), respectively. The overall five-year survival was 24% (Kaplan-Meier method) (Figure 1). The

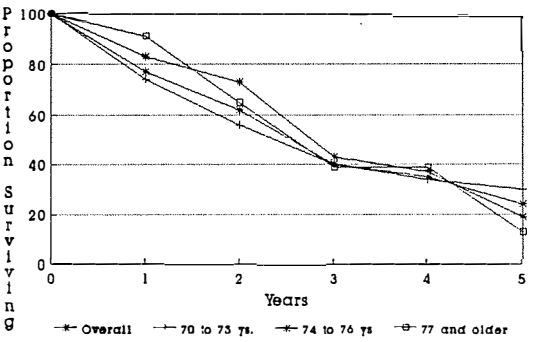

Figure 1. Survival by age groups.

5-year survival rates for patients aged 70–73, 74–76, and 77 years and older, were 30%, 19% and 13%, respectively.

Age (p = 0.16), histological type (p = 0.5) (Figure 2), and stage (p = 0.09) were not signi-

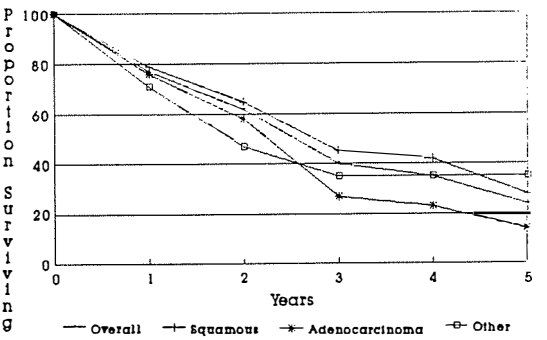

Figure 2. Survival by histology.

ficantly related to survival, although there is a trend towards better survival in patients with earlier stages of the disease.

Although no statistically significant difference was detected between stages I and II of the disease, stage I patients fared somewhat better than those with stage IIIA ($p = 0.03$). The estimated 3-year survival for stage I and IIIA patients was 48% and 36%, respectively. For T3 and N2 subsets, 3-year survival was 39% and 33%, respectively (NS). While T3 patients showed a 19% 5-year survival, no 5-year survival was established for N2 patients (Figure 3).

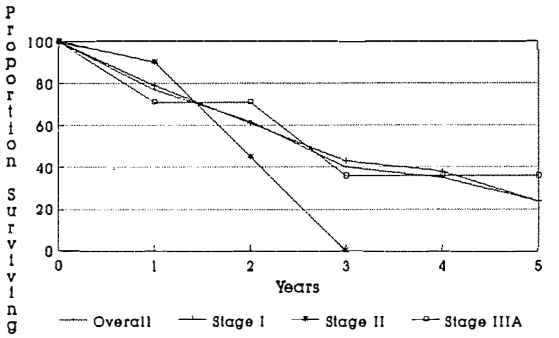

Figure 3. Overall survival and survival by stage in elderly patients undergoing surgery for lung cancer.

Adjuvant treatments for stage IIIA disease did not improve the survival ($p = 0.4$, log-rank test).

No patients with stage II lung cancer reached a 3-year survival.

Female sex ($p = 0.03$ log-rank test; $p = 0.009$ Mann-Whitney U test) (Figure 4), and the extent of resection ($p = 0.02$, Kruskal-Wallis) significantly influenced the survival.

Elderly patients subjected to lobectomies had a better survival than those with pneumonectomies ($p = 0.03$), the latter presenting with a better outcome than those with lesser resections ($p = 0.03$).

Operative mortality, defined as death occurring within 30 days from surgery, was 2.4% (4 patients). Two patients in the younger age group with stage IIIA epidermoid carcinoma died after lobectomy (1) and pneumonectomy (1). In addition, two patients in the middle age group with epidermoid (1) and adenocarcinoma (1) died in the postoperative period. They had undergone a lobectomy and a pneumonectomy for stage I and IIIA disease, respectively. Adult respiratory distress syndrome was the cause of death in all but one patient who died from post-pneumonectomy pulmonary embolism.

By multivariate analysis, the extent of resection was the only variable indipendently influencing survival ($p = 0.007$).

Overall mean and median disease-free survivals were 21.6 ± 2.1 (SEM) and 24 months, respectively.

Female sex ($p = 0.03$, log-rank test; $p = 0.08$, Mann Whitney U test), and lobectomy ($p = 0.02$), were significantly related to disease-free interval. The former was the only indipendent predictor of disease-free survival by multivariate analysis ($p = 0.02$).

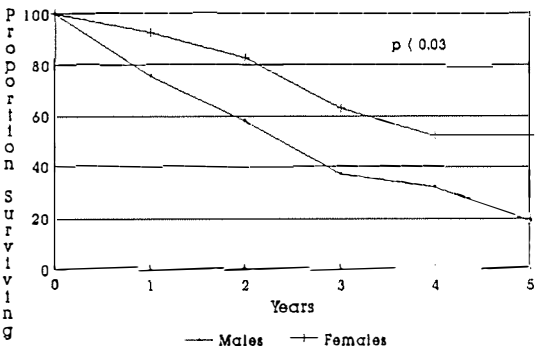

Figure 4. Survival by gender.

Discussion

The indications for resection of lung cancer in Japanese octogenarians have been expanded, based on the remarkable life expectancy in these patients (6.9 and 8.7 years for men and women, respectively).[1]

Osaki and coworkers have also observed a 5-year survival rate of 25.4% for resected patients aged 70–79 years.[1] Although the age groups in our study are different, we found a comparable overall 24% 5-year survival with a 26% 5-year survival if ages from 70 to 77 years were considered together. Our 13% 5-year

survival for patients older than 77 years is worse than the reported 32.2% 5-year survival for octogenarians.[1] Considering the high number of patients lost to follow-up that were included among the censored cases, we believe that our figure could be underestimated.

Our overall 2.4% operative mortality complies with the one reported by Yellin.[2] Significantly, no deaths occurred in the group of patients older than 77 years. Rigid functional selection criteria are crucial for obtaining low mortality rates since cardiorespiratory complications are reported to be a major prognostic factor of long-term survival.[1]

As noted by others,[1] elderly patients with IIIA disease have acceptable 3-year survivals. In this setting, no statistically significant difference was noted in our series ad to T3 vs. N2 subsets. However, after the 3-year limit, there is a worse prognostic trend for patients with N2 disease.

Surprisingly, there is no 3-year survival for stage II disease in our series. Although the number of stage II patients is too small to draw definitive conclusions, the lack of an adequate mediastinal staging might have played a role in underestimating N2 disease.

In our series, those patients undergoing lobectomy had a better survival than patients subjected to other surgical procedures. This finding is most probably attributable to the greater functional impairment caused by pneumonectomy, and to the overall likelihood of recurrence with lesser resections than with lobectomies.[5]

Surgery for lung cancer in the elderly can be performed with acceptable long-term results in terms of overall and disease-free survival.[1] The resort to pneumonectomy should be carefully weighed against potential postoperative risks.[2] Even in the elderly patient, resections lesser than lobectomy, although functionally more acceptable, are associated with greater risk of local recurrences.

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Carcinosarcoma of the lung

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Between January 1979, and December 1990, 1242 patients with primary lung cancers were observed in our Division. Among these, 3 (0.2% – 1 male and 2 females; mean age 53 yrs.; range 40–75 yrs.) had a postoperative diagnosis of carcinosarcoma of the lung. Stage I was found in 2 patients, and stage II disease (N1) in 1. The resection included lobectomy in 2 patients and wedge resection in 1. Postoperatively, the patients did not receive any adjuvant treatment. As of December 1993, only one patient (pT2NO) is alive and without evidence of disease at 36 months from surgery, with the other two patients showing short postoperative survivales (3 and 7 months).

Key words: lung neoplasms-surgery; carcinosarcoma

Introduction

Among rare primary tumors of the lung, carcinosarcoma occurs in about 1%.[1] Three patients recently observed and treated in our Division are the subject of the following report and the reason for our review of the literature.

Patients and methods

Between January 1979, and December 1990, 1242 patients with primary lung cancers were observed in our Division. Among these, 3 (0.2% – 1 male and 2 females; mean age 53 yrs.; range 40–75 yrs.) had a postoperative diagnosis of carcinosarcoma (fibrosarcomatous variant) of the lung.

Retrospective analysis of patients, records, revealed clinical stage I disease in 2 patients, and stage II disease (N1) in 1 patient.

In all cases, clinical diagnosis was made by conventional preoperative workup including chest and brain CT evaluation, and abdominal ultrasound. Endoscopic findings were unremarkable. Cytology was positive for undefined epithelial carcinoma in only one patient.

Based on CT findings preoperative mediastinal exploration was not indicated.

The resection included lobectomy in 2 patients and wedge resection in 1. In all patients, intraoperative frozen section yielded undefined carcinoma of the lung. Careful mediastinal nodal sampling was done. No significant morbidity was reported. Postoperatively, the patients did not receive any adjuvant treatment.

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Results

In all cases, postoperative histologic diagnosis revealed a spindle-cell fibrosarcomatous component (Figure 1). In one patient, the epithelial component was adenocarcinoma, whereas in the other two it was squamous cell carcinoma. A special kit for immunohistochemical studies was used to detect, among other antigens, keratin and vimentin in both the epithelial and sarcomatous components of the tumor.[1, 2]

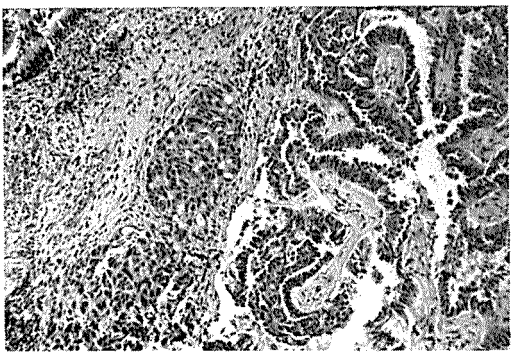

Figure 1. Histologic specimen with epithelial and sarcomatous components. Hematoxylin-eosin original magnification x 40.

As of December 1993, only one patient (pT2NO) is alive and without evidence of disease at 36 months from surgery, with the other two patients showing short postoperative survivals (3 and 7 months) due to disseminated metastatic disease.

Discussion

The carcinosarcoma is a rare primary tumor of the lung (about 1%).[1] It develops in the peripheral as well as in the central parenchyma.[3]

Despite the overall poor prognosis (with a median survival of one year),[3] there are some favorable indicators such as prevalent endobronchial growth,[1, 3] and the histological finding of a fibromatous sarcoma-like component.[1] The detection of a polypoid lesion inside the bronchus relates to early diagnosis due to bronchial obstruction symptoms.[1] In addition, extrabronchial tumors denote a higher degree of invasiveness towards the chest wall.[2] Preoperative diagnosis is rarely available also in the event of an endobronchial growth which at best yields an undefined epithelial tumor.[2, 4]

Crucial to the distinction among different histological subsets is the immunohistochemical analysis of a large surgical specimen.[1]

Accordingly, the role of transparietal fine needle biopsy in the diagnostic work-up seems to be limited. In addition, histological differential diagnosis is to be made between carcinosarcoma and spindle-cell variant of squamous cell carcinoma.[3] This distinction can be important in a prognostic perspective.[3]

Histogenesis is controversial,[1] although the predominant view support the origin of the tumor from a omnipotent stem cell of the lung tissue.[5]

Complete surgical removal of the pathologic material is mandatory when both diagnosis and an attempt at cure are to be made. Nodal involvement, detected in up to 25% of the patients,[1] does not seem to worsen the overall prognosis.[6] The impact of adjuvant treatment on survival is unremarkable.[1, 3]

In one series of patients subjected to surgery plus chemo/radiotherapy, the longest survivor was alive at 22 months from surgery.[1]

In conclusion, despite a dismal prognostic outlook, surgery for carcinosarcoma of the lung is warranted in order to provide diagnosis and tentative cure. Adjuvant treatment is of no additional benefit in improving overall survival.

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The role of radiotherapy in lung cancer treatment. Report from Slovenia

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Background. *In order to evaluate the role of radiotherapy in lung cancer treatment in Slovenia, 276 pts treated in 1988 at the Institute of Oncology in Ljubljana were investigated.*
Patients and methods. *There were 253 males and 23 females, aged 31–83 yrs (median 59); 6 pts had clinical St.I, 19 St.II, 78 St.IIIa, 65 St.IIIb and 108 pts had St.IV lung cancer. Distant metastatic sites were as follows: generalised in 29 pts, bone in 32, brain in 21, liver in 9 and other organs in 14 pts. Of 267 histologically confirmed lung cancers, 126 were squamous, 62 small-cell, 44 large-cell, 23 adenocarcinomas, and 12 others (mixed, unspecified). Performance status (Karnofsky) was assessed as > 70 in 199, 50–70 in 57 and < 50 in 20 pts. Primary therapy was: RT in 189, RT + ChT in 44, OP + postop. RT in 20, OP + ChT in 2, ChT in 14, and solely symptomatic in 7 pts. In 253 pts treated by RT, tumor dose was > 5.000 cGy (= radical) in 88, palliative in 156, and only initial in 9 pts. RT as the only method of treatment was applied loco-regionally (& supraclaviculary) in 135, to local + distant metastases in 8, only metastases in 43, whereas in 3 pts first to distant metastases and later on to the lung.*
Results. *By the end of 1993, 7/276 (2.5 %) pts were still alive. One-year survival of all treated pts was 25 %, and two-year 9 %. Of 75 pts irradiated loco-regionally with radical doses, 49 % survived one year, 17 % two years, and 3 % 5 years. There was a significant difference in the survival according to tumour dose ($p<0.001$) and performance status ($p<0.001$), but none with reference to clinical stage I–IIIb ($p<0.1$) and histology ($p<0.1$). Treatment response was assessed after loco-regional radiation in 79 %, and after radiation of metastases in 70 % of cases.*
Conclusions. *Radiotherapy has proved beneficial for the majority of our patients in terms of life quality and short term survival.*

Key words: lung neoplasms-radiotherapy, lung cancer, radiotherapy; survival analysis; indications, life quality

Introduction

Radiotherapy is the most common specific method of lung cancer therapy. Unfortunately, not so much owing to its success, but rather due to the lack of more suitable treatment methods. Radiotherapy could be performed in cases of inoperable non-small and small-cell cancer with or without, chemotherapy. The aim of radiotherapy is to diminish the disease-related problems caused by a lung tumour and/or its regional and

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distant metastases, and to prolong the duration of survival, sometimes also to care. Another important reason is that such specific treatment maintains the patient's hope that not everything has been lost yet, since the patient is not trated only symptomatically.

In the selection of patients, we had to consider the actual possibilities for radiation: the capacities of radiation machines and hospitalization possibilities for in-patients.

This paper is aimed to present a review of one-year turnover of patients admitted to the Institute of Oncology Ljubljana in 1988: the types of patients managed, the primary treatment approaches used and the results obtained.

Patients and method

In 1988, 795 new cases of lung cancer were registered by the Cancer Registry of Slovenia. The incidence per 100,000 population was 68.4 for males and 12.7 for females.

Thoracic surgery was performed at the Department for Thoracic Surgery, Univ. Medical Centre Ljubljana, and at the Thoracic Surgery of the General Hospital of the second greatest Slovenian town, Maribor.

All radiotherapy is concentrated at the Institute of Oncology Ljubljana. The radiation facilities comprise 2 linear accelerators, 2 cobalt unites, 1 conventional x-ray machine ant 2 superficial x-ray machines.

Chemotherapy was performed at the Institute of Oncology Ljubljana, and at the Institute for Respiratory Diseases Golnik.

There were 369 new patients with lung cancer treated at the Institute of Oncology Ljubljana in 1988, but only 276 of them were evaluable. This represents 35 % of the registered and 75 % of those treated in the year under study. There were 253 males and only 23 females, aged 31–83 years, median 59 years; 220 of these patients were in the age of 50–70 years.

Od 267 histologically confirmed lung cancers, 126 were squamous, 62 small-cell, 44 large-cell, 23 adenocarcinomas and 12 others (mixed, unspecified), whereas 9 were microscopically not confirmed.

Clinical stage was established on the basis of clinical examination, chest x-ray, bronchoscopy and abdominal ultrasonography. Other procedures such as chest CT, bone scan and other x-ray examinations were performed only in the case of suspicious symptoms or doubtful operability. Six patients had stage I, 19 stage II, 78 stage IIIa, 65 stage IIIb and 108 stage IV lung cancer. Distant metastatic sites were as follows: generalized in 29 patients, bone in 32, brain in 21, liver in 9 and other organs in 14 patients.

Performance status (Karnofsky) was assessed as >70 in 199, 50–70 in 57 and <50 in 20 patients.

Reliable data on the duration of symptoms were available for 224 patients: <3 months in 146, 3–6 months in 37, 6–12 months in 23 and >12 months in 18 patients.

The leading symptoms at the beginning of treatment were due to primary tumour in 161, regional metastases in 12, both in 11, and distant metastases in 72; 7 patients presented with general symptoms while 13 were asymptomatic.

Most patients, 222 (80 %), were referred to the Institute after previous team consultation, 43 (16 %) patients on the basis of phone agreement and 11 (4 %) without previous agreement.

The primary treatment was as follows in Table 1.

Table 1. The primary treatment of lung cancer patients.

Treatment method	No. of pts.	Percent
radiotherapy	189	68 %
radiotherapy + chemotherapy	44	16 %
surgery + radiotherapy	20	7 %
surgery + chemotherapy	2	1 %
chemotherapy	14	5 %
symptomatic only	7	3 %
Total	276	100 %

Radiotherapy was applied in 253/276 (92 %) patients. Of these, 88 patients received a "radical" tumour dose, i.e. equivalent dose > 5.000 cGy in 5 weeks, whereas 156 had a lower palliative dose. In 9 patients radiation was started and finished before an expected pallia-

tive tumour dose could be achieved. In 7 patients radiation was planed but was cancelled before even started because of complications. Daily doses were 250-400 cGy, radical radiation was delivered according to split-course regimen.

Results

By the end of 1993, 7 of 276 (2.5%) treated patients were still alive. One-year survival was 25% and two-year 9% (Figure 1). The value

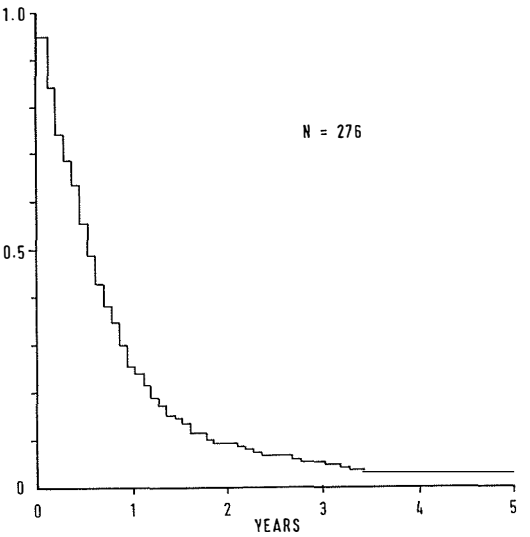

Figure 1. Patients with lung cancer treated in 1988 at The Institute of Oncology of Ljubljana.

of radiation could be estimated in patients treated by radiation alone, without chemotherapy or previous surgery, either of primary lung tumour and regional metastases or distant metastases. Radiotherapy as the only method of treatment was applied loco-regionally in 135, to lung and distant metastases in 8, only metastases in 43, whereas in 3 patients was radiotherapy applied first to metastases and later on the lung.

The survival of radically loco-regionally irradiated patients is significantly better ($p < 0.001$) than that of palliatively irradited ones (Figure 2). After radical irradiation one- and two-year

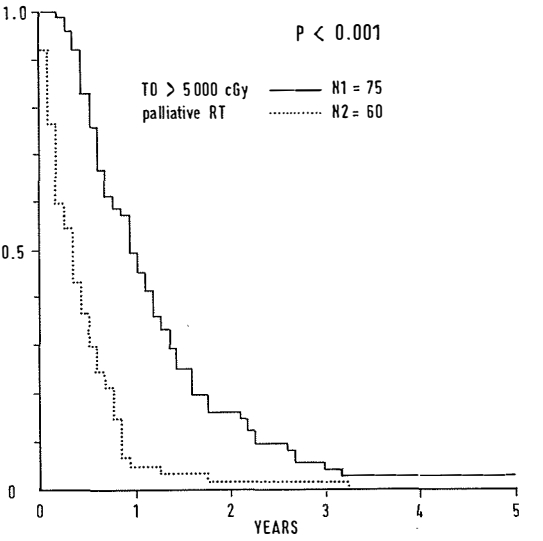

Figure 2. Survival after loco-regional radiation therapy by tumour dose.

survival was 49% and 17% respectively, but five-year survival was only 3%. In palliatively irradiated patients one-year survival hardly reached 19%; all the patients died in 3.5 years.

Survival by performance status was significantly different ($p < 0.001$) (Figure 3). Survival in

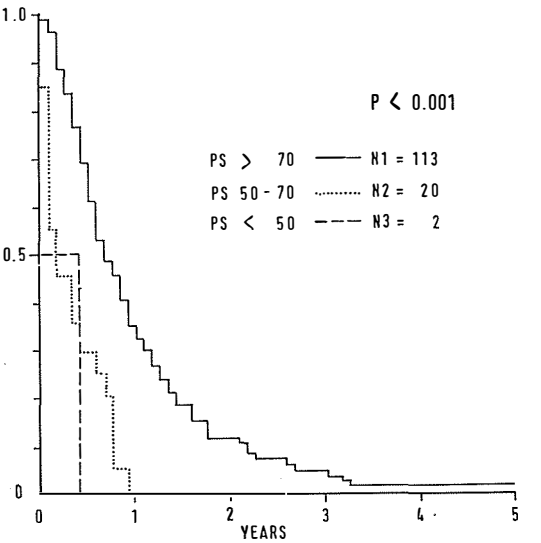

Figure 3. Survival after loco-regional radiation therapy by performance status.

stage I–IIIb was not statistically different ($p < 0.1$), but there was difference in stage IV ($p < 0.001$) (Figure 4). Histology of nonsmall cell

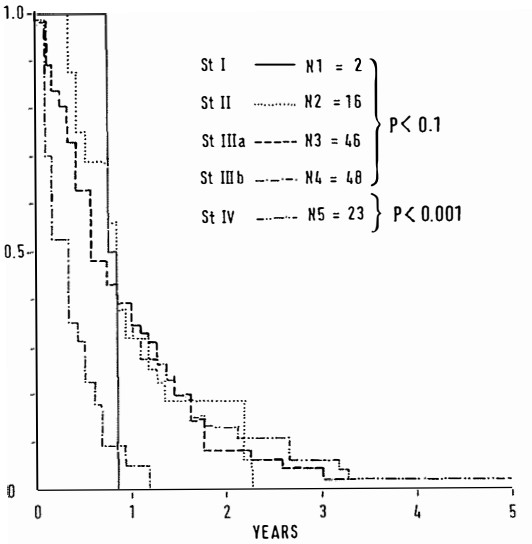

Figure 4. Survival after loco-regional radiation therapy by stage.

cancer irradiated loco-regionally has not influenced survival ($p < 0.1$).

Survival of 28 patients with small-cell carcinoma treated by chemotherapy and loco-regional radiotherapy is evident from Figure 5. There

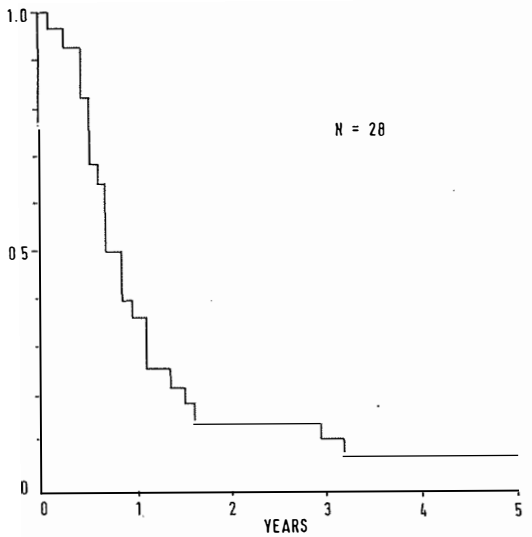

Figure 5. Survival after chemotherapy and loco-regional radiation therapy.

are also patients treated by chemotherapy before admission to the Institute for radiotherapy and therefore their survival is not a reliable indicator of such treatment. It refers only to the survival after admission to our Institute. Similar situation is associated with the survival of patients irradiated after surgery (Figure 6):

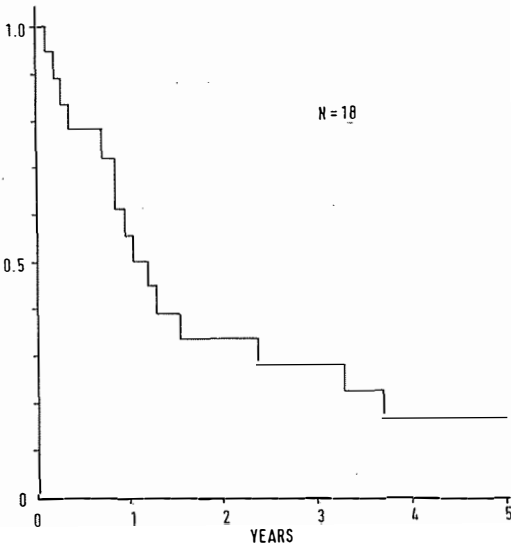

Figure 6. Survival after surgery and postoperative loco-regional radiation therapy.

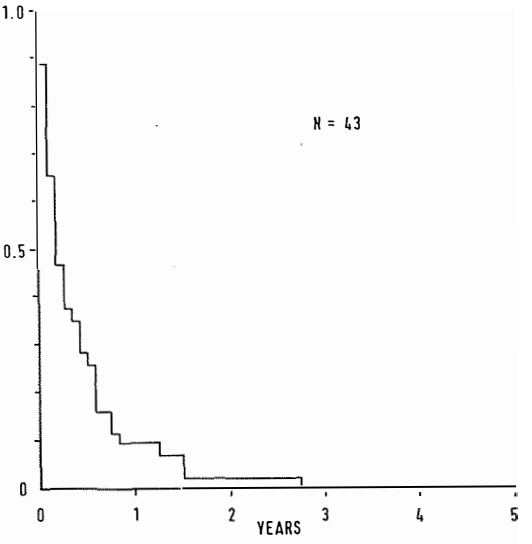

Figure 7. Survival after radiation therapy for metastases.

besides the patients irradiated postoperatively, the group also comprises those with bronchial or mediastinal recurrence.

The survival after radiation of metastases was considerably shorter: Only 9% of patients survived one year, and all of them died within 3 years from the beginning of therapy (Figure 7).

Effectiveness of radiation could be estimated not only by survival but also by objective and subjective response reflected in the presence or absence of patient's disease-related problems. Adequate data were available for 211 of 253 patients (Table 2).

Table 2. Effectiveness of radiation of lung cancer patients.

Radiation results	No. of pts	Percent
obj. + subj. response	107	51%
subj. response	31	15%
obj. response	15	7%
st. idem	43	20%
progression	15	7%
Total	211	100%

Radiation response was estimated in 153 of 211 (73%) patients; In 112 of 135 loco-regionally irradiated patients the results were as follows in Table 3.

Table 3. Results of loco-regionally irradiated patients with lung cancer.

Radiation results	No. of pts	Percent
obj. + subj. response	58	52%
subj. response	18	16%
obj. response	12	11%
st. idem	20	18%
progression	4	3%
Total	112	100%

Radiation response was obtained in 88 of 112 (79%) patients.

In patients irradiated of distant metastases, the results were available for 27 of 43 patients (Table 4).

Table 4. Patients irradiated for distant metastases.

Radiation results	No. of pts	Percent
obj. + subj. response	13	48%
subj. response	6	22%
obj. response	0	0%
st. idem	6	22%
progression	2	8%
Total	27	100%

Radiation response was obtained in 19 of 27 (70%) patients.

The duration of response in patients irradiated loco-regionally wad reliably assessed in 67 patients only (Table 5).

Table 5. The duration of response in patients irradiated loco-regionally.

Duration of response	No. of pts.
< 2 mos	10
2–6 mos	18
6–12 mos	19
> 12 mos	20

Discussion

The patients treated at the Institute of Oncology were mostly in progressed stage of disease, aged from 50 to 70 years, with good performance status, and a few-month history of chest symptoms. Among those treated only by radiation there were no operable cases. Four fifths of patients were discussed at team consultation with thoracic surgeon who suggested additional examinations such as CT, mediastinoscopy, parasternal mediastinotomy, thoracoscopy or exploratory thoracotomy.

The report includes routines cases and therefore examinations performed before treatment were extremely rational and in agreement with the principles of lung cancer management accepted in last year.[1] Probably, the actual tumour stages were higher than stated in the report because of the unavailability of CT and radionuclide examinations.

The patients were referred to the Institute soon upon the completion of diagnostic proce-

dures so that the therapy could be started without delay. Radiotherapy was a primary treatment in 92 % of patients. Despite the planned radiation treatment, 7 patients received only symptomatic therapy because of rapidly deteriorating condition. In 9 patients radiation was started, but the intended palliative dose could not be achieved. In order to diminish the number of fractions and to shorten hospitalization time, the daily doses used most frequently were 250, 300 and 400 cGy. Split-course regimen is very suitable for lung tumours in order to alleviate esophagitis; on the onset of this symptom, a 3–4 week break is made. Sometimes after the break new disease symptoms may appear which render further radiation unreasonable.

Equivalent tumour dose > 5.000 cGy/5 weeks calculated by Kirk and coworkers[2] is considered as radical. However, this dose was not found to be curative. Generally, it is very difficult to speak about curative radiotherapy with such a low five-year survival rate. This depends on the selection of patients rather that on the kind of radiotherapy and support therapy. Most articles report results by Smart and Hilton in 1966:[3] in 40 selected irradiated patients with lung cancer five-year survival was achieved in 22.5 %. The 32 % five-year survival was reported by Zhang and co-workers 1989[4] in 44 patients with operable non-small cell lung cancer who have refused surgery. In most unselected patients the survival was essentially lower and did not exceed 5 %.

Better survival of radically irradiated patients and patients with higher performance status has confirmed our criteria for the selection of treatment method: unrestricted use of high-dose radiation therapy in patients with lower performance status and/or progressed tumour does neither improve the survival nor alleviates the symptoms. Therefore, patients in worse general condition were irradiated with palliative doses and the resulting survival rates were lower.

The survival of patients with small cell cancer after combined chemotherapy and radiation of lung tumour and regionall lymph nodes was reported to be somewhat better than that obtained by chemotherapy alone, but above all, there were less loco-regional recurrences.[5] Repeated bronchoscopy after complete regression evident on x-ray often confirms a tumour of bronchial mucosa. Therefore, we consider irradiation of chest in limited stage small cell lung cancer despite possible loco-regional regression after chemotherapy indicated for safety reasons.

We did not perform routines prophylactic cranial irradiation. The exception were some patients included in the study in whom prophylactic cranial irradiaton was ordered in protocol.

The preoperative radiotherapy was not performed. The postoperative radiation therapy was performed in the cases of nonradical surgery, metastases in mediastinal lymph nodes and recurrence. Five-year survival of those patients was 17 %.

Conclusion

Radiotherapy as a primary treatment modality for lung cancer was performed in 92 % of our patients.

Suitable for radiation were patients with inoperable or nonradical operated lung cancer, mostly with progressed disease and good performance status, with symptoms of primary tumour, regional and/or distant metastases.

Treatment response was obtained after loco-regional radiation in 79 % and after radiation of metastases in 70 % of patients. We believe that the improved quality of life may result in better short term survival.

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Experience in preoperative radiotherapy for non small cell lung cancer (NSCLC)

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Four hundred and thirty lung cancer patients were drawn into randomized study of the induced hyperglycemia (IH) as a radiosensitizer for preoperative large fraction irradiation; 217 patients underwent IH carried out on the 1-st, 3-rd, and 5-th days or radiotherapy by the i.v. infusion of 40 % glucose; 213 patients were enrolled in the control group. There were the following criteria for the patients' enrolment into the protocol: males, age younger 66 year, cT1-3NO-2MO, histologically proved NSCLC, no contraindications for surgery and IH. The preoperative irradiation was carried out by a total dose of 20 Gy, delivered in five 4-Gy fractions per week; using 20 MeV equipment. Surgery was carried out three days after radiotherapy. Patients with pN1-pN2 received additionally postoperative radiotherapy: 30–36 Gy, 2 Gy per fraction. In stage IIIA, patients' survival was significantly higher for IH compared with the control group: the median survival was 2.0 ± 0.3 years in the study group vs 1.1 ± 0.23 in the control group ($P < 0.05$). The duration of survival differed significantly for the second year of follow up (50.0 ± 6.0 vs 32.3 ± 4.6 %, $P < 0.05$). For the fifth year the survival rates were: 29.2 ± 5.2 for the study group vs 17.2 ± 4.2 % in the control group; in N2 patients: 23.9 ± 4.3 vs 10.3 ± 3.4 % ($P < 0.05$).

Key words: non-small cell lung carcinoma; preoperative radiotherapy therapy

Introduction

Preoperative standard radiotherapy (40–60 Gy) for operable lung cancer shows no clear evidence of improvement in the survival. Even for marginally resectable cases as superior sulcus cancers, the problem remains open.[1] According to L.H. Einhorn[2] there were three phase III non randomized studies that revealed no difference in long-term results. These researches were aiming at gross eradication of the primary tumor, considering the well-known fact that responders have longer survival than other patients. The program usually takes from 4 to 6 weeks, and further resection is attempted 3 to 5 weeks after radiotherapy. The whole period before surgery usually takes 2 or 3 months, and this interim tumor can produce metastases.

Another way is to use large-fraction irradiation to impact the conditions of ablastics at the time of surgery. This treatment is shorter and takes 4 or 5 days. From the data presented by co-operating centres in Eastern Europe it is evident that such a program improves survival

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in comparison with surgery alone. [3] But despite the use of thoracic irradiation, the local recurrence was an appreciable site of treatment failure. This concurs with the fact that curability of tumors depends on strongly marked devitalization of clonogenic tumour cells. The problem is to overcome the tumour hypoxia that may cause a recurrence of cancer after complete control. Obviously it is impossible to escalate the dose of irradiation without running a risk of complications.

The present paper reports the results of using preoperative large fraction radiotherapy with or without radiosensitization by induced hyperglycemia (IH) in operable lung cancer patients.

Material and methods

Four hundred and thirty NSCLC patients were enrolled in the randomised study (From December 1983 till December 1988) of IH as a radiosensitizer for preoperative radiotherapy. The research was aimed at determing whether radiosensitising can increase tumour alteration and improve the long term survival.

Patient's selection

The criteria for patients' enrolment in to the protocol were as follows:

1) males; 2) age under 66 years; 3) cT1-3NO-2MO; 4) histologically proved NSCLC; 5) no contraindications for surgery and IH (low cardio-pulmonary reserve, diabetes mellitus).

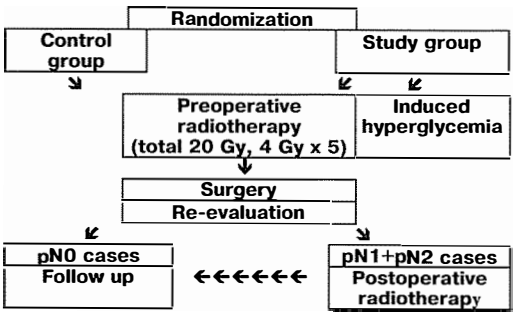

Figure 1. Schedule for protocol study.

Randomization

All the enrolled patients were randomized into two groups depending on the method of preoperative treatment (Figure 1). The comparison of the baseline features of both groups revealed no statistic ally significant differences (Table 1).

Table 1. Patient's data.

Variables	Study group	Control group
Mean age:	56 ± 0.45	55 ± 0.42
30–39 age group	4 (1.9 %)	3 (1.4 %)
40–49 age group	30 (14.1 %)	36 (16.6 %)
50–59 age group	121 (56.8 %)	129 (59.4 %)
60–69 age group	58 (27.2 %)	49 (22.6 %)
Stage I	52 (24.5 %)	71 (32.7 %)
Stage II	46 (21.7 %)	50 (23.0 %)
Stage IIIA	82 (38.7 %)	69 (31.8 %)
Stage IIIB	23 (10.4 %)	24 (11.1 %)
Stage IV	10 (4.7 %)	3 (1.4 %)
Squamous	197 (92.4 %)	207 (95.4 %)
Adenocarcinoma	11 (5.2 %)	6 (2.8 %)
Large cell	4 (1.9 %)	3 (1.4 %)
Carcinosarcoma	1 (0.5 %)	1 (0.4 %)
Lob-bilobectomies	73 (34.3 %)	68 (31.3 %)
Pneumonectomies	89 (41.8 %)	112 (51.6 %)
Explorations	51 (23.9 %)	37 (17.1 %)
Type of cancer:		
Central	166 (77.9 %)	178 (82.0 %)
Peripheral	47 (22.1 %)	39 (18.0 %)
Total cases	213 (100 %)	217 (100 %)

Preoperative radiotherapy

The preoperative course of irradiation was carried out by a total dose of 20 Gy delivered in five 4-Gy fractions per week. A 20 MeV equipment was used. The two oposing radiation fields included the primary tumor, the hilar zone and the mediastinum.

Surgery

Surgery was carried out three days after the last course of radiotherapy. The extent of resection was influenced by the tumour size and its location. A large proportion of explorations was due to the fact that thoracotomy was considered the final procedure of patient's staging.

Postoperative radiotherapy

The patients with pN1-pN2 disease additionally received postoperative radiotherapy by a total dose of 30–36 Gy, 2 Gy per fraction. There was a 3-4 week interval between preoperative and postoperative courses for postoperative care and cardiovascular – respiratory recovery.

Induced hyperglycemia procedure

217 patients underwent IH that was carried out on the first, third and fifth days of radiotherapy by the i.v. infusion (v. subclavia) of 40% glucose and maintaining the level of glycemia in the range of 22 to 33 mmol/l for 3 hours. The interval between IH and irradiation was 45-90 minutes. This interval was tested in preliminary experimental studies published in the former USSR.[4]

Staging

The patients were staged according to X-ray, bronchoscopic procedure. bone scans, ultrasonography of the abdomen and CT scans of the chest. The tumor staging was determined by UICC rules.[5]

Results

Operative mortality and morbidity

There were 8 (3.8%) hospital deaths in the control group and 14 (6.4%) in the study group. The mortality rate did not differ significantly. The causes of death in the control group were as follows: 4 pneumonia, 2 cardio-pulmonary insufficiency, 1 bronchial fistula, 1 thromboembolism. In the study group there were 4 pneumonias, 5 thromboembolisms, 1 cardiopulmonary insufficiency, 1 insult, 3 bronchial fistulas. Although thromboembolism was more frequent in the study group, as regards morbidity, there was no significant difference.

Survival

Survival was calculated by the Kaplan-Meir method considering operative mortality.[6] All the patients were followed up for at least five years or until death.

It turned out that a five-year survival was not significantly higher in the study group (38.7%) vs. the control group (32.2%). There was no difference in the assessment of survival rates for stage I, stage II and stage IIIB. Only in the patients with resectable stage IIIA, the survival differed significantly for the second year of follow up (50.0 ± 6.0 vs 32.3 ± 4.6%, $P < 0.05$). For the fifth year, the survival rates were 29.2 ± 5.2 for the study group vs. 17.2 ± 4.2% in the control group ($T = 1.8$, statistic tendency, Figure 2).

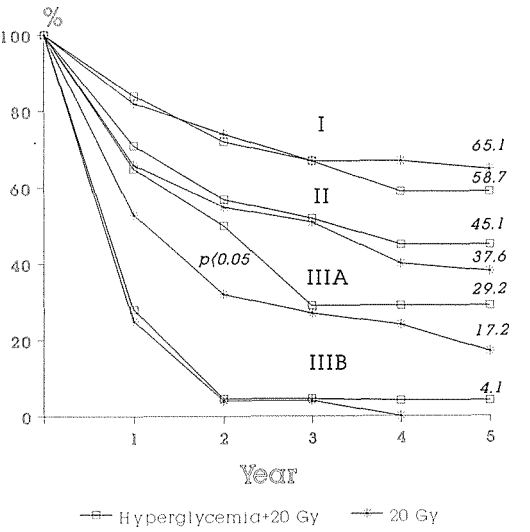

Figure 2. Survival curves by stage.

The median survival for stage IIIA was 2.0 ± 0.3 years in the study group vs. 1.1 ± 0.23 in the control group ($P < 0.05$).

The survival rates significantly differed for N2 patients (Figure 3): 29.9 ± 4.3 vs 16.8 ± 3.5% for the fourth year and 29.9 ± 4.3 vs. 10.3 ± 3.4% for the fifth year for both groups respectively.

Discussion

The survival in lung cancer patients depends on the tumor extent, its histology and therapeutic strategy. The method of choice for NSCLC

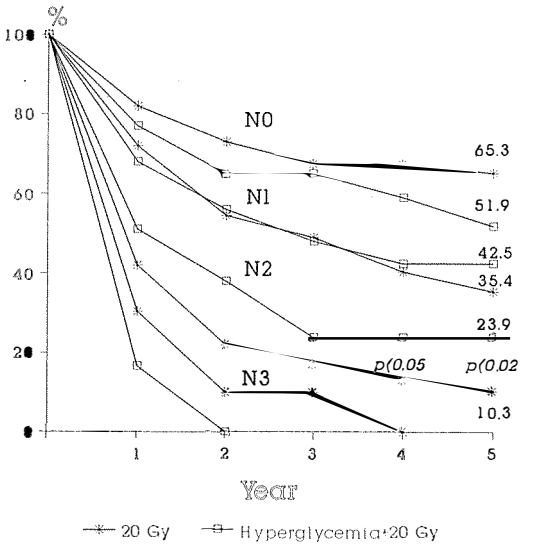

Figure 3. Survival for N0 – N3.

treatment is surgical removal of the tumour and regional lymph nodes. There is a general agreement that stages I and II must be managed surgically whenever possible. Unfortunately, life duration after surgery in operable stage IIIA remains very low.[1]

There have been many attempts to develop an effective therapy for advanced lung cancer. Recent studies indicate that the use of adjuvant or neoadjuvant therapy is beneficial but indications for these approaches are still not conclusive.[2]

The present study is an attempt to use a high dose of radiotherapy (about 60 Gy) by the split-course delivery before surgery (20 Gy total, 4 Gy per fraction) and 3–4 weeks after the procedure (30–36 Gy, 2 Gy per fraction). IH was undertaken to determine the feasibility and efficacy of such an approach to achieve a better survival.

IH is known as a part of von Ardenne multistep anticancer therapy tested and widely used in the Cancer Research Institute of Belarus.[4] As predicted from preliminary data, hyperglycemia has two advantages over chemical radiosensitizers: it causes an interphase death of tumour cells in vivo; glucose is a natural substance that does not complicate human metabolism.

According to the data obtained, a five year survival in stage I and stage II patients did not differ significantly. The distinction was evident only in stage IIIA patients, especially in N2 cases. As long as N2 tumors can be removed, IH could be a constituent part of the anticancer treatment for advanced lung cancer.

Conclusion

IH + preoperative large-fraction radiotherapy (20 Gy total, 4 Gy per fraction) + postoperative mediastinal irradiation (30–36 Gy, 2 Gy per fraction) improves the survival rates as regards preoperative radiotherapy alone in stage IIIA operable lung cancer patients.

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The role of chemotherapy in non-small cell lung cancer

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While surgery is the treatment of choice for non-small cell lung cancer (NSCLC) patients with tumor confined solely within the lung (stage I and II), controversy exists with regard to the optimal treatment of more advanced disease (stage IIIa, IIIb and IV). The effectiveness of chemotherapy for NSCLC has been limited by the existence of few active cytostatic agents, the most active being ifosfamide, vindesine, vinblastine, mitomycin C, and cisplatin, all with average response rates of around 20%. Usually only partial responses are seen, and the duration of the responses is short. Identification of new drugs with significant activity against NSCLC is therefore needed, and a total of 26 new investigative drugs have been evaluated since 1985. The most promising agents seem to be campthotecin-11, gemcitabine, vinorelbine, taxol, taxotere, fotemustine, and zeniplatin, which all have shown cumulative response rates above 20% among previously untreated patients. Combination chemotherapy regimens, usually including cisplatin together with one or more of the other active single agents, have generally improved response rates, including a small percentage of complete responses. The activity is, however, unsatisfactory as combination chemotherapy regimens in randomized studies usually reveals response rates of 25--40%. In order to evaluate whether chemotherapy offer any survival advantage in non-resectable NSCLC, several studies of chemotherapy versus best supportive care has been published during the last 7 years. All studies showed a survival advantage for patients receiving chemotherapy, and the overall median survival was increased by 25% to 80% compared to patients receiving solely supportive car. Even though there are concerns about the modest absolute increase in survival and the toxicity of therapy, these results allows for a cautious optimism with regard to chemotherapy in patients with non-resectable NSCLC.

Key words: lung neoplasms; carcinoma; non-small-cell lung – drug therapy; treatment outcome

Introduction

Lung cancer is the most common cancer type in men, and its incidence in females is rapidly increasing, making lung cancer one of the leading causes of deaths in all industrialized countries. Non-small cell lung cancer (NSCLC) constitutes three quarters of all lung cancer cases and the cure rate and survival in patients with NSCLC have not changed during the last decades. The treatment of choice is surgery in earlier stages of NSCLC (i.e. stages I, II, and some cases of IIIa). However, only 20% of patients with NSCLC are

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resectable at the time of diagnosis, which renders other treatment possibilities necessary.

On an experimental basis, chemotherapy has been used in NSCLC in a large number of studies during the last decades. Chemotherapy has been used both in a neo-adjuvant setting before surgery, in an adjuvant setting after surgery and has also been used for more advanced (non-resectable) disease. In patients with advanced NSCLC, cytostatic agents have been employed both as monochemotherapy and in combination chemotherapy. Additionally, the impact of chemotherapy has been evaluated against best supportive care, i.e. patients without specific antineoplastic treatment. These aspects of chemotherapy in NSCLC will be discussed in the following, while the combined use of chemotherapy and radiotherapy will not be included.

Material and methods

An update on the current status of chemotherapy in NSCLC is given with the emphasis on randomized trials. The studies will be discussed according to whether the chemotherapy has been used in an adjuvant setting, neo-adjuvant setting or is given for advanced disease. In advanced disease, the effects of single agents, of combination chemotherapy, and chemotherapy evaluated against best supportive care will be discussed.

Results

Adjuvant chemotherapy

Distant recurrence after surgery is common in patients with NSCLC, indicating a need for systemic therapy. Several randomized trials of adjuvant chemotherapy given after complete surgical resection of the malignant disease have been reported[1-9] (Table 1). Most of the early studies have used single agent chemotherapy, often including agents which are today not considered to be among the most active in NSCLC. None of these studies have demonstrated a survival benefit of patients receiving chemotherapy.[1-5]

Four studies have evaluated combination chemotherapy as adjuvant treatment using a regimen of cyclophosphamide, doxorubicin and cisplatin (CAP), either alone[6-9] or in combination with radiotherapy.[7] None of these studies have observed a significantly improved overall survival, but two of the studies, reported by Holmes and Gail[6] and by Niiranen et al.,[8] have shown a significant increase in time to recurrence for patients receiving adjuvant chemotherapy with CAP. No similar increase was observed in studies by Lad et al.[7] and by Feld et al.[9] using the same treatment regimen. In the study by Feld et al.[9] solely patients with complete by resected stage I NSCLC were included while in three other studies[6-8] patients with stage II and stage III were included as well, which might probably influence the results.

The median survival and five year survival rates in the four studies using combination chemotherapy CAP[6-9] have generally been longer for the groups of patients receiving adjuvant chemotherapy compared to the groups of patients without it. However, the difference was not statistically significant (Table 1).

In the study by Niiranen et al.[8] the five year and ten year survival rates were about 67% and 61%, respectively, in the chemotherapy group, compared with 56% and 48%, respectively in the control group ($p = 0.05$). Most relapses were distant (65%). These results suggest that NSCLC patients who have undergone complete resection may benefit from adjuvant chemotherapy. However, it is anticipated that the beneficial effect would be the largest in patients with stage II or stage IIIa.

Feld et al.[9] reported that only 53% of the eligible patients received all four planned courses of CAP, and only 57% of such patients received all four cycles on time. Thus, a likely explanation for the lack of efficacy may be poor compliance. Further trials of adjuvant chemotherapy are warranted, especially with the use of cisplatin containing combination chemotherapy and with use of modern antiemetic treatment in order to improve patient compliance.

Neo-adjuvant chemotherapy

During the past years, neo-adjuvant treatment has been intensively studied in locally advanced

Table 1. Randomized trials of adjuvant chemotherapy for completely resected NSCLC.

Therapy		No. of pts			Median survival (mths)		Disease-free survival	
Control	Chemotherapy	Control	Chemotherapy	Stage	Control	Chemotherapy	P-value	P-value	Authors
Surgery	Surgery mechloretamine	604	588	I-III	NA	NA	NS		Slack, 1970[1]
Surgery	Surgery/CTX	94	95	I-III	25	16	< 0.1		Brunner et al, 1973[2]
Surgery	Surgery/CTX	143	132	I-III	21	16	NS		Shields et al, 1977[3]
	Surgery/CTX/MTX		142	I-III		20	NS		
Surgery	Surgery/CCNU/HU	433	432	I-III	45	35	NA		Shields et al, 1982[4]
Surgery	Surgery/busulfan	249	243	I-III	23*	23*	NA		Girling et al, 1985[5]
	Surgery/CTX		234			23*	NA		
Surgery/BCG	Surgery/CAP	68	62	II, III	16	23	.078	< 0.05	Holmes and Gail, 1986[6]
Surgery/RT	Surgery/RT/CAP	86	78	I-III**	13	20	NS	0.01	Led et al, 1988[7]
Surgery	Surgery/CAP	56	54	I-IIIa	66	not reached	0.05	0. 01	Niiranen et al, 1992[8]
Surgery	Surgery/CAP	133	136	I	76	83	NS	NS	Feld et al, 1993[9]

NA – not available; NS – not significant; CTX – cyclophosphamide; MTX – methotrexate; CCNU – lomustine; HU – hydroxyurea; BCG – Bacille Calmette-Guérin; CAP – cyclophosphamide + doxorubicin + cisplatin; RT – radiotherapy.
* Estimated from data
** Included also patients with either microscopic residual disease or extensive lymph node involvement at the time of resection.

NSCLC with the concept of administering chemotherapy prior to surgical resection in an attempt to sterilize micrometastases, minimize local seeding of cancer resulting from surgical manipulation, conserve normal lung tissue by allowing less extensive resection, or permit the resection of previously unresectable disease. A large number of studies have evaluated this concept in phase II trials.

Shepherd[10] summarized the results of 15 phase II pilot trials of induction chemotherapy (5 studies with chemotherapy alone; 4 studies with chemotherapy and radiotherapy; and 6 studies with chemotherapy and concurrent radiotherapy). Ten studies comprised exclusively stage IIIa patients, while 5 trials included both stage IIIa and IIIb patients. The studies employed a variety of chemotherapy and radiotherapy induction regimens, and overall responses were observed in more than 50% of patients, although the complete clinical remission rate was less than 15%, and the pathological complete response rate was usually less than 10%.[10] After induction therapy, approximately 70% of the patients were eligible for thoracotomy, and complete resection was possible in 16% of the patients.[10] Two- and three-year survival ranged from 25% to 30%.[10] From the review of these 15 studies it is clear that induction therapy followed by surgical resection is feasible, and even though toxicity is encountered, in most studies this does not appear to be unacceptable. However, randomised trials are needed in order to document a beneficial effect on survival.

Unfortunately, only few prior randomised studies have adressed the benefit of preoperative chemotherapy, with the first three studies being without a beneficial effect for patients receiving chemotherapy.[11-13] Among the patients in these trials, the three year survival rate ranged from 25-40% for those treated with chemotherapy + surgery and from 15-40% for those treated with surgery alone. Thus, these prior studies do not point out a survival advantage by neo-adjuvant treatment.[11–13]

However, a recent study by Rosell et al.[14] reported a beneficial impact on survival by the use of a combination chemotherapy regimen con-

sisting of mitomycin C, ifosfamide and cisplatin every 3 weeks for three courses before surgery. All patients had stage IIIa NSCLC, 30 patients were randomized to chemotherapy + surgery and 30 patients to surgery alone. Both groups of patients received mediastinal radiotherapy 1.8 Gy to 2.0 Gy for 5 days per week until a cumulative dose of 50 Gy. Median survival was 26 months for patients receiving neo-adjuvant chemotherapy compared to 8 months in patients without it ($p<0.001$), and the median duration of disease-free survival was 20 months compared to 5 months, respectively ($p<0.001$).[14] This study has been somewhat critizied because of a low number of patients randomised, as well as because of a short follow-up period and multiple interim analyses.[15]

Recently, another group of investigators from M. D. Anderson Cancer Center have also published a report on beneficial effect in patients receiving neoadjuvant chemotherapy.[16] Twenty eight patients were randomized to receive 3 courses of cyclophosphamide, etoposide and cisplatin before surgery, followed by 3 more courses after surgery for responding patients, while 32 patients were randomized to surgery alone. All patients had potentially resectable clinical stage III a disease. The estimated median survivals were 64 months and 11 months respectively ($p<0.008$). Even though these results by Rosell et al.[14] and by Roth et al.[16] are encouraging, neo-adjuvant therapy should still be considered experimental, and should at this point be used solely in controlled investigational protocols.

Chemotherapy for advanced disease

Single agents

A number of single agents are shown to be of moderat activity in advanced NSCLC (Table 2). A cumulative response rate of more than 15% has been encountered for vinblastine,[17] ifosfamide, [18] cisplatin,[19] vindesine,[20] and mitomycin-C[21] (Table 2). The majority of responses are only partial while complete remissions are rare and occur in less than 5% of patients treated.[22]

Recently, the literature on new cytostatic drugs in the treatment of patients with NSCLC reported in the literature since 1985 has been reviewed together with new methods for administration of established drugs.[23] With respect to new methods for drug administration two well known cytostatic drugs, ifosfamide and etoposide, have recently been evaluated in trials using oral administration instead of the usual intravenous route. A cumulative response rate for oral etoposide of 17% was shown in 4 studies including the total number of 104 patients.[24-27] Also oral administration of ifosfamide yields a cumulative response rate of 18% when the dose intensity is 7g or more during a 4 week period.[28]

Among the new drugs tested, the most active are outlined in Table 3. Among the most promisings seem to be campthothecin-11 (CPT-11), gemcitabine, vinorelbine, taxol, fotemustine and zeniplatin which have all shown response rates above 20% among previously untreated patients.[23] Taxotere has shown a promising cumulative response rate of 32% among a total of 92 patients included in 3 studies.[29-31] The semi-synthetic campthothecin analogue topotecan, which like CPT-11 also is a topoisomerase I inhibitor, has been evaluated in two studies including 19 patients.[32-33] Patients were treated with 0.5 mg/m^2 daily for 5 days and the cumulative response rate was 26%.[32,33] Also, the antimetabolites 10-EDAM and trimetrexate and the platinum analogues carboplatin and (glycolate-0.0) diammine-platinum II are of interest with cumulative re-

Table 2. Established single agents in NSCLC.

Agent with	No. of pts	Cumulative response rate (%)	Authors
>15% activity			
Vinblastine	22	27	Schulman et al, 1982[17]
Ifosfamide	420	26	Drings P, 1987[18]
Cisplatin	568	21	Bunn PA, 1989[19]
Vindesine	295	18	Sørensen et al, 1993[20]
Mitomycin	115	18	Kris MG, 1989[21]

Table 3. Effectiveness of the most active new drugs in patients with previously untreated non-small cell lung cancer.

Cumulative Response rate	Treatment (overall response rate)
> 20 %	Taxotere (32 %, 3 studies, 92 patients)
	Campthothecin-11 (32 %, 1 study, 72 patients)
	Gemcitabine (26 %, 2 studies, 87 patients)
	Topotecan (26 %, 2 studies, 19 patients)
	Vinorelbine (23 %, 4 studies, 381 patients)
	Taxol (22 %, 2 studies, 49 patients)
	Fotemustine (21 %, 1 study, 29 patients)
	Zeniplatin (21 %, 1 study, 28 patients)
≥ 15 %	10-EDAM (19 %, 2 studies, 64 patients)
	(Glycolate-0,0) diammine-platinum (II) (17 %, 1 study, 38 patients)
	Carboplatin (16 %, 3 studies, 171 patients)
	Trimetrexate (16 %, 4 studies, 141 patients)

Table 4. Response rate in NSCLC according to no. of cytostatic agents (Metaanalysis of 100 studies, 6,247 pts).

No. of cytostatic agents	No. of pts	Response rate %
1	914	6
2	1,643	26
3	2,185	28
4	1,070	28
5	226	50
6	180	24
2–6	5,304	28

Modified from Donnadieu et al., Lung Cancer 1991.[34] Single agents (27 studies including 914 patients) vs. combination chemotherapy, (73 studies including 5,404 patients) $p < 0.001$.

sponse rate above 15% in previously untreated patients.[22]

Combination chemotherapy

It is generally accepted that combination chemotherapy is more active than single agent treatment in patients with NSCLC. The response rate in patients with NSCLC according to the number of cytostatic agents employed was examined by Donnadieu et al.[34] The authors performed a meta-analysis of 100 studies including a total of 6,247 patients with NSCLC receiving chemotherapy. Among these patients, 23% had limited disease and 77% disseminated disease. An overall 25% objective response rate was obtained with a 3% complete response rate. Overall response rate, partial response rate and complete response rate were all significantly better in patients with limited disease being 34%, 27% and 5%, respectively, compared with 22%, 19% and 3%, respectively in patients with extensive disease ($p = < 0.001$).[34]

The response rate in NSCLC according to the number of cytostatic agents observed in the meta-analysis by Donnadieu et al.[34] is shown in Table 4. Twenty-seven studies used single agent chemotherapy with an overall response rate of 6% among a total of 914 patients while 73 studies used combination chemotherapy with two to six cytostatic agents with a 28% cumulative response rate among the 5,304 patients included ($p = < 0.001$).[34] These results point towards a better effect of combination chemotherapy than of the single agent treatments evaluated.

A large number of combination chemotherapy regimens has been evaluated in NSCLC. The most frequently used regimens among the 100 studies included in the meta-analysis by Donnadieu et al. are shown in Table 5, yielding response rates from 22% to 41%.[34] A review by Soyez and Kleisbauer[35] have suggested that the most active combinations consist of cisplatinum together with either a vinca alkaloid or etoposide with or without mitomycin-C. The cumulative response rate in 14 trials with a total of 565 patients employing combinations of cisplatin plus vindesine were 37%, while the combination of cisplatin and etoposide was evaluated in 32 studies including 1,534 patients with a response raate of 27%. A combination of cisplatin, vindesine and mitomycin-C was evaluated in 8 trials including 485 patients, giving a cumulative response rate of 41%, and a combination of cisplatin, vinblastine and mitomycin-C was evaluated in 5 trials including 301 patients with an overall response rate of 37%.[35]

Table 5. Objective response rate with the most frequently used chemotherapy regimens in NSCLC.

Regimen	Number of studies	Cumulative results	
		n	% resp.
VBL + MMC + CDDP	6	406	41
VDS + CDDP + VP16	3	104	37
VDS + MMC	3	172	34
VDS + CDDP	8	357	30
MTX + ADR + CTX + CCNU (MACC)	5	282	29
CTX + ADR + CDDP (CAP)	12	722	25
VP16 + CDDP	13	775	24
CTX + ADR + MTX + PCZ (CAMP)	5	409	22

Modified from Donnadieu et al., Lung Cancer 1991.[34]
CDDP = cisplatin; VP16 = etoposide; ADR = adriamycin; CTX = cyclophosphamide; VDS = vindesine; VBL = vinblastine; MTX = methotrexate; PCZ = procarbazine; MMV = mitomycine.

Randomised studies comparing a combination of cisplatin plus vindesine to a combination of cisplatin plus etoposide has recently been reviewed by Sørensen and Hansen.[20] These combination chemotherapies were equally active in randomised studies, both with respect to response rates and survival.[20] In the same review, the effect of the addition of 1 to 2 other drugs to these combinations has not yielded an increase in the survival,[20] and the addition of 1 or more cytostatic agents to a two-drug regimen consisting of either cisplatin plus etoposide or cisplatin with a vinca alkaloid has not demonstrated uniformly increased response rates.[20,34,35]

No combination chemotherapy has at this point been shown to be clearly more active than other commonly used combination chemotherapy regimens. Thus, a standard chemotherapy for advanced NSCLC has not been established at this point.

Chemotherapy compared to supportive care in advanced NSCLC

Several studies have compared the effect of combination chemotherapy with best supportive care in randomized trials.[36-43] All studies showed a trend towards longer survival for patients receiving chemotherapy compared to patients without (Table 6), and this trend was statistically significant in four studies.[37,40,41,44]

Souquet et al.[45] published a meta-analysis of 7 studies of combination chemotherapy versus the best supportive care.[35-41] Endpoints in the meta analysis were the number of deaths at 3-,

Table 6. Combination chemotherapy (CT) vs. best supportive care (BSC) in NSCLC.

Regimen	No. of pts		Median survival (wks)		P-value	Authors (reference no.)
	CT	BSC	CT	BSC		
CCMEP	62	61	8.5	5.0	0.15	Cellerino, 1988[36]
MACC	20	19	30.5	8.5	0.005	Cormier, 1982[37]
VP	32	31	19.9	14.4	0.09	Ganz, 1989[38]
EP	44	43	21.6	16.0	0.5	Kaasa, 1989[39]
VP	22	21	27.6	9.7	0.03	Quoix, 1991[40]
VP	44		32.6		0.01	
or		53		17.0		Rapp, 1988[41]
CAP	43		24.7		0.05	
VP	105	96	27.0	17.0	0.075	Woods, 1990[42]
MACC		175	32.0	20.0	0.01	Buccheri, 1990[43]
CMP	52	50	36.4	17.1	< 0.0001	Cartei, 1993[44]

CCMEP – cyclophosphamide + CCNU + methotrexate + etoposide + cisplatin; MACC – methotrexate + adriamycin + CCNU + cyclophosphamide; VP – vindesine or vinblastine + cisplatin; EP – etoposide + cisplatin; CAP – cyclophosphamide + adriamycin + cisplatin; CMP – cyclophosphamide + mitomycin C + cisplatin.

6-, 9-, 12-, and 18 months. The analysis showed a statistically significant reduction in mortality at 3 months ($p = <0.001$) and 6 months ($p = <0.00001$).[45] Even though the odds ratio for mortality also was lower at 9-, 12-, and 18 months, this trend was not statistically significant, as p values were $p = 0.02$, $p = 0.03$, and $p = 0.15$, respectively.[45] These results can also be expressed as the risk reduction for patients receiving chemotherapy as compared to best supportive care, which was found to be 0.65 at 3 months, 0.73 at 6 months, 0.86 at 9 months, 0.91 at 12 months, and 0.96 at 18 months, respectively.[45] Although small, this increase in survival suggests that combination chemotherapy has a role for patients with non resectable non-small cell lung cancer, though the effect seems to be most pronounced with respect to increase in short term survival.

Discussion

The recent results of adjuvant combination chemotherapy are somewhat encouraging and suggest that patients with apparently completely resected NSCLC may benefit with respect to disease free survival, but at the cost of toxicity. A significant impact on overall survival has as yet not been documented. It is also apparent that some of the widely used regimens employing either etoposide and cisplatin or a vinca alcaloid and cisplatin have not been evaluated in an adjuvant setting. The effect of such regimens should be evaluated together with a careful description of known prognostic factors in order to identify the patient groups which are most prone to benefit from the treatment.

With respect to neo-adjuvant chemotherapy, it has repeatedly been shown that such treatment is feasible. Additionally, the two most recent studies,[14,16] have also reported a beneficial impact on overall survival. However, there is still limited data from randomized studies, and at this point induction chemotherapy followed by surgical intervention for locally advanced non-small cell lung cancer must still be viewed as experimental.

A number of new cytostatic agents have been evaluated within the last few years in NSCLC patients with advanced disease, and several of these agents have repeatedly yielded response rates above 20%. Several of these drugs are real innovations, (with quite novel structure), and these agents hold promise of improvement in the therapy of NSCLC. In the planning of new trials, the evaluation of such agents should have a high priority.

A large number of combination chemotherapy regimens have been evaluated in patients with advanced NSCLC without any of these regimens being documented as clearly superior. Thus, a standard treatment has as yet not been established.

The impact of combination chemotherapy on the survival of patients with advanced NSCLC has repeatedly been shown to be beneficial with respect to the quantity of life when evaluated in randomized studies against best supportive care. This suggests that the clinical course of NSCLC can be improved by chemotherapy, but at the expense of toxicity. Accordingly, the quality of life in patients receiving chemotherapy must be balanced against the possible gain in the quantity of life. Decisions as to whether chemotherapy for NSCLC should be used in clinical practice, and whether economic resources should be allocated to such issues, are not simply not tecnical questions that could be answered by clinicians or health economists. Individual patients and their relatives must be involved in the decision-making process to address adequately the preferences for the potential benefits, harms and costs associated with chemotherapy. To ensure such decision makings are based on a firm ground we sorely need information on the quality of life with respect to different treatment options.

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Cisplatin/etoposide combined with interferon-gamma in non-small cell lung cancer

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In order to assess the clinical efficacy of interferon-gamma (IFN-gamma) in non-small cell lung cancer (NSCLC), IFN-gamma was added to three cycles of chemotherapy (cisplatin, etoposide) and applied as maintenance therapy in patients with advanced NSCLC. So far, 32 patients have been admitted to this trial. Twenty-nine patients were evaluable with regard to response. Complete remissions, partial remissions and minor responses were observed in 0%, 7% and 28% of the patients, respectively. Stable disease was seen in 1 (3%) patient and progressive disease in 18 (62%) patients. In the case of progressive disease, the treatment was discontinued. The duration of median survival was 7 months and the 1-year survival rate was 40%. Only few patients did receive IFN-gamma maintenance therapy. Further follow-up of the patients is required in order to determine the influence of this combined treatment on long-term survival.

Key words: carcinoma, lung cancer, non-small cell lung cancer-drug therapy; interferon type II; chemotherapy, cisplatin, etoposide

Introduction

A recent meta-analysis has indicated that combination chemotherapy for unresectable non-small cell lung cancer (NSCLC) results in prolonged survival of the patients.[1] However, in order to further improve the clinical outcome of this disease, new cytotoxic drugs and/or biological agents are required.

Previously, interferon-gamma (IFN-gamma) was found to inhibit tumour growth by its antiproliferative properties and by activating effector cells.[2] In addition, synergistic or additive effects of interferons on the activity of cisplatin have been reported.[3] Thus we initiated a clinical trial on chemotherapy combined with IFN-gamma in patients with advanced NSCLC in order to assess whether the addition of IFN-gamma improves the clinical outcome in patients with NSCLC. Here we report on this ongoing trial.

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Patients and methods

From January 1992 to December 1993, 32 patients (6 females, 26 males, median age 59

years) with unresectable NSCLC were admitted to this study. The inclusion criteria were histologically confirmed diagnosis of NSCLC, good performance status, no prior chemotherapy, adequate renal as well as bone marrow function, and written informed consent. The tumour was staged as described.[4]

Chemotherapy consisted of cisplatin (25 mg/m2 per day intravenously on days 8, 10 and 12) and etoposide (100 mg/m2 per day intravenously on days 8, 10 and 12). IFN-gamma (Bender + Co GmbH, Vienna, Austria) was given subcutaneously (100 µg per day on days 1, 3, 5, 8, 15, 17 and 19). In case of fever associated with IFN-gamma application, paracetamol was added. These combined treatment cycles were repeated every 3 weeks. After three cycles, the patients proceeded to maintenance therapy with IFN-gamma (100 µg subcutaneously three-times per week). Any progression of the disease resulted in discontinuation of treatment.

Survival analysis

The duration of overall survival of the patients was estimated according to Kaplan-Meier.[5] The analysis was based on the patients' status as of the end of March 1994.

Results

The patients' characteristics are summarized in Table 1. Fifty-three percent of the patients presented with stage IV disease. Except in patients with progressive disease, response was evaluated after 3 treatment cycles. So far, 29 patients were evaluable for response (Table 2).

Table 1: Patients' characteristics.

No.	32
Age	
median	59
range	41–70
Sex	
female/male	6/26
Histologic type	
adenocarcinoma	17 (53 %)
squamous carcinoma	11 (34 %)
large cell carcinoma	4 (13 %)
Stage	
IIIA	4 (13 %)
IIIB	11 (34 %)
IV	17 (53 %)
Prior treatment	
explorative thoracotomy	4 (13 %)
radiation	1 (3 %)
chemotherapy	0 (0 %)

Table 2: Response to treatment (after 3 cycles) in 29 evaluable patients.

Response	No. (%) of patients
complete remission	0 (0 %)
partial remission	2 (7 %)
minor response	8 (28 %)
stable disease	1 (3 %)
progressive disease	18 (62 %)

The overall response was poor with complete and partial remissions in 0 (0 %) and 2 (7 %) patients, respectively. Minor responses and stable disease were seen in 8 (28 %) and 1 (3 %) patients, respectively. During treatment, 18 (62 %) patients presented with progression. The most frequent treatment-related side effects were leukopenia (mostly WHO grade 1 or 2), nausea and vomiting, flu-like symptoms and fever (data not shown).

Only five patients have received IFN-gamma maintenance therapy. The reasons for unfeasibility of maintenance therapy included progressive disease, side effects of IFN-gamma and patients' refusal of further treatment.

According to Kaplan-Meier analysis, the median duration of overall survival was 7 months and the 1-year survival rate was 40 % (Figure 1).

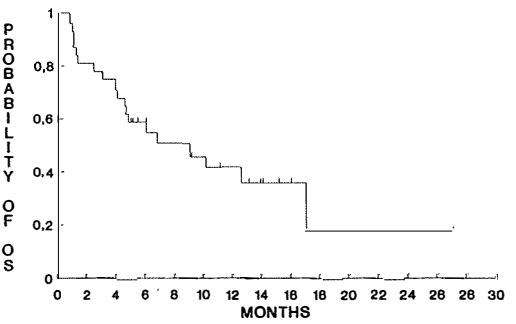

Figure 1: Survival of patients. The overall survival of patients was calculated according to Kaplan-Meier.[5] OS = overall survival.

Discussion

Although the response rate seen in our study was low as compared to other studies, the duration of overall survival of our patients was similar to the one reported in another recent study.[6] The low response rate seen in our study might be due to the rather low dose of cisplatin (75 mg/m2 per cycle) and due to the fact that the majority of patients had stage IV disease which is less responsive to chemotherapy. Thus the initial analysis of our study suggests that the addition of IFN-gamma to chemotherapy does not improve clinical outcome in patients with advanced NSCLC. This is consistent with a recent randomized trial in which the addition of IFN-gamma or IFN-alpha plus IFN-gamma to chemotherapy did not influence the response rate or survival of the patients.[6]

Whether higher doses of IFN-gamma might be efficacious, remains unclear. In a recent study,[6] however, higher doses of IFN-gamma did not improve clinical outcome as compared to chemotherapy alone.

The present study was also planned to test the clinical efficacy of maintenance therapy with IFN-gamma, because the effects of interferons might be more pronounced in patients with low or even clinically undetectable tumour burden. Because only few patients proceeded to maintenance therapy, no conclusions with regard to the efficacy of IFN-gamma during maintenance therapy can be drawn from our study. For this purpose, large study populations are required.

Acknowledgement

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Endobronchial chemotherapy in combined treatment for non-small cell lung cancer

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From 1990–1993, 73 patients with non-small cell lung cancer (NSCLC) underwent combined treatment using endobronchial bleomycin (BL) instillations. These patients were divided into three groups as follows: 21 patients of Group 1 underwent preoperative endobronchial chemotherapy (EBCH) with BL, and radical surgery; 40 patients of Group 2 had EBCH and conventional split-course radiotherapy (RT); 12 patients of Group 3 underwent EBCH and dynamic fractional radiotherapy (DFRT). In Group (21 patients) Bleomycin was injected using a fiber-bronchoscope 2-3 times before radical surgery. A cumulative dose of BL was 60–120 mg. Thirteen lobectomies and 8 pulmonectomies were performed. After surgery, tumors and lymph node (l/n) specimens were morphologically evaluated in order to determine tumor and response to BL injections. In Group 2, 40 patients with locally advanced NSCLC were treated by BL injections and conventional radiotherapy. Cumulative does of BL was 120–150 mg. We instilled BL endobronchially 15 mg twice a week. The first course of radiotherapy (RT) was 40 Gy. During the treatment, tumor volume was followed by X-ray, CT-scanning and fiberbronchoscopy (producing endophotoimages). If the first course of treatment resulted in partial tumor response (> 50 % tumor mass reduction), RT and EBCH were continued up to 70 Gy and 200–210 mg of BL. In cases when tumor response was < 50 %, or there was no regression (< 30 %), only RT up to 60–70 Gy was delivered in daily fractions of 1.8–2.0 Gy. Group 3 (12 patients) received RT in 4-2-2-2-4 Gy weekly regimens with BL applied on Days 1 and 5. So the daily dose of 4 Gy was combined with a 15 mg injection of BL; the cumulative dose of BL was the same as in Group 2. Not all of our patients tolerated this treatment. In Group 2, partial tumor response was achieved in 32 cases, 3 patients had partial tumor regression, and in 5 patients the treatment proved ineffective. In Groups 3, rapid tumor response was achived in 8 cases, 2 patients had no response, while in another two patients the treatment had to be discontinued because of complications (one of them died). During EBCH, the following complications were noted: fever in 16 patients, leukopenia in 2, and death due to bleeding after rapid tumor necrosis in one patient.

Key words: carcinoma, non-small cell lung; combined modality therapy

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Introduction

The treatment for lung cancer is one of the most difficult problems in oncology. Only 10–

15% of all patients with lung cancer can be treated surgically.[1] It means that the majority of patients with lung cancer must be treated by other methods such as radiotherapy and chemotherapy. There are some reports on endobronchial chemotherapy of patients with lung cancer. At the 4th Congress of Bronchologists Seiguchi N[2] reported on bronchial chemotherapy for non-small lung cancer. The author claims having injected bleomycin and immunomodulator OK-132 through a bronchoscope. The patients also received irradiation. The results of this treatment were good: tumor response was achieved in 23/53 cases. No severe treatment-related complications were observed. Henry P, and Pierson Jr[3] injected mitomycin C endobronchially to patients with carcinoid. Thirty-four patients underwent surgical treatment; tumor response was achieved in 75%. Other authors[4] tried to treat their patients with laser, but the treatment entailed severe complications such as tumor hemorrhage. Therefore, less aggresive methods of treatment were suggested. Photochemotherapy was used in patients with central lung cancer.[5] This treatment modality was used in patients with advanced lung cancer. Tumor response was ahcieved in 20 cases. In recent years, there has been a tendency to use photodynamic therapy for central lung cancer.[5] Initial endobronchial injection of bleomycin into the tumor was followed by laser irradiation. According to the authors, the results of treatment were good. The majority of authors have published their immediate treatment results, whereas on information is available on the follow-up results of such treatment. Based on these reports, the indications and contraindications for bronchial chemotherapy remain doubtful. Hopefully, our investigations will help to provide some explanation as to the usefulness of endobronchial chemotherapy.

Material and methods

Patients

From 1990–1993, 73 patients with NSCLC were treated by a combination of endobronchial chemotherapy (EBCH), BL surgery, conventional radiotherapy (RT) and high-fractional radiotherapy (HFRT). The patients were divided into three groups as follows: Group 1 consisted of 21 patients treated by EBCH and surgery, Group 2 of 40 patients treated by EBCH and RT, and Group 3 of 12 patients treated by EBCH and HFRT. The age of patients ranged between 34–72 yrs, mean 55 yrs. There were 5 females among them. The distribution of patients by pTNM stage was as follows: Group 1 : 15 patients – pT2N1M0, 5 patients – pT3N0-1M0, and 1 patient – pT3N2M0. In 18 cases the tumor was endobronchial and in 3 cases peripheral. In 8 cases we performed pulmonectomy, in 11 lobectomy, and in 2 bilobectomy. Three patients had adenocarcinoma and others epidermoid cancers.

The distribution of patients in Groups 2 and 3 is evident from Figure 1. The majority of

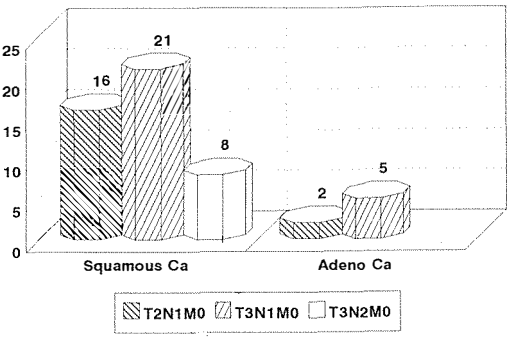

Figure 1. Distribution of patients in groups 2 and 3 according to morphology and TNM.

patients (26) had T3N0-1M0, 18 patients were treated in T2N0-1M0 stage, and 8 patients had T3N2MO stage of the disease. According to clinical type the patients were distributed as follows: 45 patients had central tumors and 7 peripheral. In 45 cases the pulmonary tumor was epidermoid carcinoma, in 7 adenocarcinoma.

Group 4-controls: 70 patients underwent only surgical treatment; of these 45 were with T2N1M0, 12 with T1N1M0, 10 with T3N1M0 and 3 with T3N2MO. Ten patients had periphe-

ral and 60 endobronchial tumors. Sixty-two patients had epidermoid carcinoma and 8 adenocarcinoma.

Group 5-controls: 46 patients received 5-FU 0.5 g i.v. half an hour before conventional radiotherapy twice weekly, up to the tolerable dose (5–6 g of drug). Twenty-seven patients had T3N1MX, 5–T3N2M0, and 14 patients T2N1M0 stage. There were 7 peripheral adenocarcinomas and 39 central epidermoid tumors.

Endobronchial chemotherapy

Bronchoscopy was performed under local anesthesia. Tumor surface was washed with sodium chloride solution. Bleomycin was injected with a special needle into the tumor area 3–5 mm in depth in 3–4 points. It is necessary to be careful during the injection of bleomycin; it must not be injected into normal tissues. Bioptic samples from tumors were taken during bronchoscopy. The procedure was completed if there were no signs of hemorrhage. We used a modified COX mathematic model for chemotherapy. Bleomycin injection dosage program was calculated to each patient.[6,7] We injected bleomycin using a BFB2 "Olympus" bronchoscope twice a week before radiotherapy. Cumulative dose of bleomycin ranged between 90–125–150 mg. Fractionation of radiation dosage was 1.8–2 Gy per week by conventional radiotherapy and 4-2-2-2-4 Gy per week by dynamic hyperfractionated radiotherapy. Radiotherapy was applied in the split-course mode. Tumor response was followed by endobronchoscopy and X-ray. Biopsies were taken before and after the study to evaluate the tumor mass difference.

Results

In Group 1, BL 15 mg was injected 2–3 times through a bronchoscope before surgery. Postoperative complications were similar in both groups, i.e. in patients treated with BL (Group 1) and in controls (Group 4). Bronchus stump leakage was observed only after right pulmonectomies (3 and 4 respectively in both groups). Morpohological investigations of the tumor and lymph node specimens show a decreasing mitotic activity of tumor cells (18 cases), and considerable degenerative changes in the tumor after 3–5 endobronchial injections of BL. These changes are equivalent to grade IVa by Ohboshi-Shimosato criteria. Hypertrophy of lymph follicles and strong interstitial reaction were detected in the resected lymph node specimens. The main effect of BL was coagulative necrois with a slight interstitial and submucosal reaction (16 cases). Partial tumour regression was noticed in 17 cases.

In Group 2 (40 patients) partial tumor response (tumor mass reduced by more than 50%) was achieved in 32 cases; 3 patients had partial tumor regression (less than 50%), while 5 patients failed to respond to therapy (less than 30%). In Group 2 (EBCH + RT) better results were achieved when the tumor was situated endobronchially. Tumor was sensitive after 5–7 injections of BL. In other cases, to reach a partial tumor response (more than 50%) we had to use 60–70 Gy of RT and 120–200 mg of BL.

The results of our 3-year follow-up show that the median survival rates of treated patients in Group 1 and cntrols by stage were as follows: T2N1M0 – 30 and 31 mos, T2N1M0 – 26 and 27 mos, and T3N2M0 – 24 and 26 mos. The median survival in Group 2, and Group 3 in treated patients vs. controls, was as follows: T2N1M0 – 24 mos vs. 19 mos, T3N1M0 21 mos vs. 13 mos, and T3N2M0 – 15 mos vs. 12.5 mos. These data show no significant difference in survival.

Discussiou

The use of local chemotherapy for superficially situated malignant tumors such as melanoma and breast cancer has been reported effective. Along with the development of endoscopic surgery (laser, intraluminal radiotherapy) we have been trying to use local chemotherapy in the form of transbronchial intratumoral instillation in lung cancer patients. This method is comparable with other endobronchial treatment approaches such as laser applications, intraluminal

brachytherapy, intratumoral ethanol injections, nebulisation etc. By combining BL injections and radiotherapy, we try to reduce tumor volume and thus sensitize tumor cells to RT. There are a lot of other substances known to have the same effect. Using BL, we do not only sensitize tumor cells to RT but also achieve chemotherapeutical effect, knowing that epidermoid carcinomas are sensitive to bleomycin. Palliation effect is achieved through tumor mass reduction. Patients fell better after the disapperance of atelectasis. In our cases, histopathological and endoscopical findings confirmed great effectiveness of this method, whitch also proved its clinical value by reducing such as obstructive pneumonia. Buton L. Speiser[8] used after-load brachytherapy for local control of endobronchial caracinoma. In three groups of patients treated with different dosages, curative doses resulted in 87% obstucting improvement and palliative doses in 84%, where the group of patients with recurrence showed 70% improvement. The author also reported the following treatment-related complications: fatal bleedings in 7%, bronchial stenosis and radiation bronchitis in 11%, pneumothorax, cardiac arrhythmia and infection. Nevertheless, the method proved to be an effective palliation treatment for lung cancer; 24% of his patients were treated by laser destruction. Cox and Byhar reported about hyperfractionated radiation and pulmonary toxicity, which was high and depended on the fields of HFRT.

EBCH can be used as adjuvant therapy. Group 2 (40 patients) underwent EBCH and conventional RT, while Group 3 (12 patients) received DFRT. The comparison of treatment results in both groups has shown that more rapid tumor regression was achieved in Group 3. In Group 2, better tumor response was obtained when the tumor was situated endobronchially, and when it was smooth, without signs of hemorrhage and superficial necrosis. In the cases with T3N2M0 and T3N1M0 stages, when the tumor was solid (cartilaginoid), endobronchial regression was dubious and more difficult to achieve. The patients in Group 3 showed rapid tumor necrosis, but one of them died due to fatal pulmonary bleedding. In comparison with their controls (Group 5), the patients in Group 2 presented with more rapid tumor regression. However, the follow-up results in Groups 2 and 5 show no significant difference in the survival of patients in both groups. The presented method is very simple, and the fact that it does not require any additional equipment is certainly and advantage, considering our economic situation. The method is not well known and can be associated with various problems, but nevertheless, our results show that it is comparable with other endobronchial methods for tumor volume reduction in operable patients. Low rate of severe complications renders this treatment approach suitable for outpatient use. It should be combined with other methods of lung cancer treatment. In our opinion, endobronchial chemotherapy can be used only as adjuvant therapy. There are two conditions for such treatment: 1) the tumor must be situated in the bronchus, and 2) there should be no evidence of hemorrhage in the tumor. The drug which is injected into the tumor area can affect it. There is a danger of rapid tumor necrosis.

Conclusions

1) endobronchial intratumoral chemotherapy with bleomycin is technically easy to perform, and should be used in combination with other methods of treatment in patients with non-small-cell lung cancer.

2) Endobronchial chemotherapy and radiotherapy should be used in patients with locally advanced tumors of the lung without distant metastases. The occurrence of treatment-related complications is low.

3) This method of treatment has proved ineffective in patients with locally advanced peribronchial tumors.

4) Immediate results were better in the group of patients who received endobronchial chemotherapy (bleomycin) and dynamic hyperfractionated radiotherapy.

5) The comparison of three-year follow-up

results showed no significant difference in the survival of treated patients and those in the control groups.

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Brain metastases from lung cancer

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Our analysis included 150 patients who were treated by whole-brain irradiation between 1983 and 1993. All of them received 10 × 3 Gy over 2 weeks. In 12 cases surgical resection of brain metastases preceded radiotherapy. 49 patients had primary small-cell lung cancer (SCLC), and 81 non-small cell lung cancer (NSCLC). The others had mixed tumors. The evaluation of their CT-scans showed a significantly different average number of brain metastases (SCLC 4 met., NSCLC 2 met.) and a smaller surrounding edema in the case of SCLC. Diameter of metastases and total cerebral tumor volume were distributed equally. The interval between primary tumor and development of brain metastases, presence of extracerebral metastases and Karnofsky performance status were also distributed equally, but SCLC patients were significantly younger. The local remission rate was dependent on histology as well as on the diameter of metastases. In 44% of all cases a complete or partial remission was found (SCLC 60%, adeno-ca 39%, squamous-cell-ca 21%, $p = 0.007$). However, after multivariate analysis, histology was not found to be a prognostic factor for survival. Surgical treatment also had no influence on the survival. Patients'age, Karnofsky-performance status, extracerebral metastases and the diameter of brain metastases were the only prognostic factors. Mean survival was 123 days (median 69 days). The survival of patients with extracerebral metastases and a Karnofsky-performance status < 70 was very poor. Therefore, they should be treated only in the case of disabling symptoms, when application of corticosteroids has failed. For the majority of patients radiotherapy with 10 × 3 Gy seems to be appropriate.

Key words: lung neoplasms, lung cancer; brain neoplasms-secondary, brain metastases; radiotherapy

Introduction

Due to the generally high incidence of the disease and the high frequency of spread, lung cancer is the predominant primary tumor of patients presenting with brain metastases (Egawa,[1] Order,[2] Turalba).[3]

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Various autopsy series demonstrated that 17 – 50% of all lung cancer patients developed brain metastases (Davis,[4] Doyle,[5] Newman[6]), dependent on the histological tumor type. This retrospective analysis of 150 irradiated cases is targeted to investigate the differences in pattern of spread and treatment results between brain metastases from small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) and their influence on patients' prognosis.

Material and methods

The data of 150 consecutive patients with brain metastases from histologically proven lung cancer, treated between 1983 and 1993, have been analysed retrospectively.

Patients' characteristics

Fourty-nine patients (33%) had SCLC, 34 patients (23%) squamous-cell lung cancer (SQCLC), 34 (23%) suffered from adenocarcinoma of the lung and 33 (22%) from other and mixed tumor types. 87% of all patients had signs of increased intracranial pressure and/or other symptoms due to brain metastases; 13% were asymptomatic.

Table 1 and Table 2 show all other pretreatment characteristics.

Table 1. Patients' characteristics.

Parameter	All patients
median age (years)	60
median interval (days)*	87
multiple brain metastases	61.5%
average number of brain met.	2.6
median diameter of brain met. (cm)	2.2
median total cerebral tumor volume (cm^3)	8.7
extracerebral metastases	49.7%
median Karnofsky-index	7
male : female ratio	9:1

Table 2. Patients' characteristics.

	SCLC	adeno-ca	SQCLC	P-value
median age (years)	57	60	62	0.01
average number of brain met.	3.9	2.3	2.0	0.02
surrounding edema				
≤ 1 cm (%)	67	24	32	< 0.001
1–3 cm	27	56	50	
> 3 cm	6	19	18	

* (between primary diagnosis and development of brain metastases)
SCLC = small-cell lung cancer,
SQCLC = squamous-cell lung cancer

Methods

Brain metastases were diagnosed by CT. In each case radionuclide bone scan abdominal ultrasound, chest x-ray and CT were performed for tumor staging. The primary tumor was confirmed histologically by biopsy (mediastinoscopy or bronchoscopy). Twelve patients received radiotherapy after surgical resection of a solitary brain metastasis. All of them had preoperative MRI. In 31 cases chemotherapy was administered during the course of the disease, but always before detection of brain metastases and never with curative intent. All patients received radiotherapy 5 days a week. Either Co-60-gamma-rays or photons of a linac were used. In all cases a whole-brain-irradiation of 10 × 3 Gy over 2 weeks was given. The dose specifications refer to a reference point in the middle of the brain. The target volume was enclosed by the 80%-isodose. Ninety-eight % of all patients received dexamethasone throughout the course of radiotherapy.

The daily dose was < 10 mg in 15%, 10 – 20 mg in 46% and > 20 mg in 29%, depending on the symptoms and the clinical course. In 8.5% the exact dose was unknown.

On the last day of radiotherapy, further CT-scans of the brain and clinical examinations were performed, and later on repeated at 3-month intervals. Survival time was calculated from the beginning of radiotherapy. Survival curves were obtained using the Kaplan-Meier-method. Local remission was evaluated according to the UICC criteria. All patients who failed to complete their planned treatment course were also included in the analysis.

Results

All different pretreatment characteristics of SCLC and NSCLC patients are presented in Tables 1 and 2. Twenty-three patients (15%) failed to complete their planned radiotherapy course due to progressive deterioration of their general condition. Karnofsky performance status before therapy was the only parameter

which correlated with incomplete therapy ($p < 0.001$).

In 129 cases, CT-scans were performed by the end of therapy. All 12 operated patients (9%) had their metastases completely removed and were without recurrence. The results of other cases were as follows: complete remission in 17 cases (13%), partial remission in 40 cases (31%), no change in 50 cases (39%), progression in 3 cases (2%); in 7 cases the course of multiple metastases was different (5%).

The remission rate was 60% for SCLC, 39.3% for adeno-ca and 21.4% for SQCLC, $p = 0.007$.

The estimated probabilities and the 95%-confidence intervals of complete and partial remission were 56% (43–69%) for SCLC, 41% (32–50%) for adeno-ca and 34% (24–45%) for SQCLC. The remission rate was dependent on histology as well as on the diameter of metastases (> 2.5 cm versus ≤ 2.5 cm) (Cox proportional hazards model).

A symptomatic relief was obtained in 48% of all cases. Additionally, 13% of patients were asymptomatic before irradiation and remained in this state. Clinical improvement was dependent on local remission of brain metastases. An improvement was noted in 76% after complete remission, in 60% after partial remission and in only 47% of cases without remission.

The mean Karnofsky performance status of the whole group of patients remained stable with a slight tendency towards improvement. (Figure 1).

Mean survival of all patients was 123 days (median 69 days).

The survival after surgery was 141 days (95%-range: 93–155) and after radiotherapy alone 122 days (95%-range: 88–156). (Figure 2). This difference was not statistically significant, although the operated patients were significantly younger and had less extracerebral metastases. The histological type of lung cancer was also not prognostically relevant for survival (Figure 3).

When a complete remission (CR) was obtained, survival was significantly longer as compared to partial remission (PR) and no change

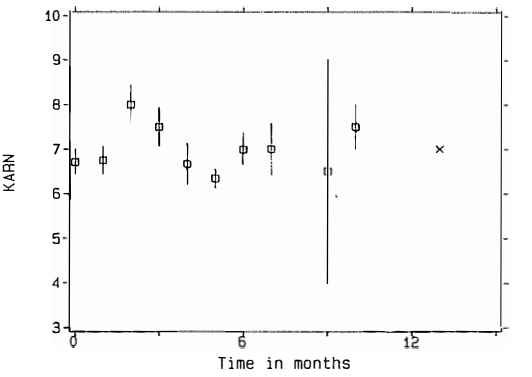

Figure 1. Mean Karnofsky-performance status (karn) and standard deviation before and after radiotherapy (n = 150).

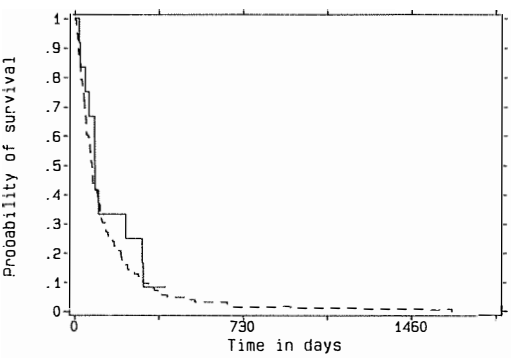

Figure 2. Survival after surgery and radiotherapy (——) or radiotherapy alone (– – –). ($p > 0.05$).

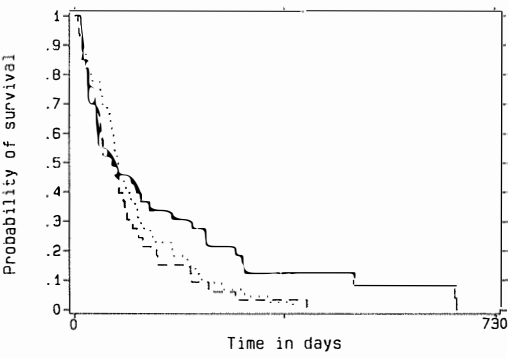

Figure 3. Survival by histology. Groups: —— Adenocarcinoma, – – – Squamous cell carcinoma, ... SCLC ($p > 0.05$).

(NC). The mean values were 294 days (CR), 142 days (PR) and 103 days (NC), $p = 0.003$

(CR vs NC), 0.04 (CR vs PR), > 0.05 (PR vs NC).

In multivariate analysis (Cox proportional hazards model) Karnofsky performance status ($p < 0.0001$), extracerebral metastases ($p = 0.02$), diameter of brain metastases ($p = 0.04$) and patients' age ($p = 0.05$) were prognostic factors for survival.

If only the most important prognostic factors were taken into account, the following probabilities to survive at least 150 days were calculated:

1. Karnofsky – PS ≥ 70, no extracerebral met. 32% (22–45%)
2. Karnofsky – PS ≥ 70, extracerebral met. 28% (19–39%)
3. Karnofsky – PS < 70, no extracerebral met. 17% (8–35%)
4. Karnofsky – PS < 70, extracerebral met. 3% (0–29%).

Discussion

Compared to the reports from literature, our treatment results concerning local remission, clinical improvement and survival are largely similar to others published so far (Newman,[6] Robin,[7] Chatani,[8] Mandell,[9] Trillet[10]). Better results have been obtained either by other patients' selection or exclusion of cases with incomplete treatment from the analysis.

Görich[11] also reported a higher average number of brain metastases in cases with SCLC. But in our own study all differences between small-cell and non-small-cell lung cancer also in local results had no impact on the survival. We found a markedly longer survival for patients with adenocarcinoma and small-cell carcinoma compared to those with squamous-cell carcinoma, which was also shown by Flentje.[12]

The better local responsiveness of metastases from small-cell cancer is probably due to their radiosensitivity, because the diameter of brain metastases, which also was a prognostic factor for local remission, did not differ from that of non-small-cell metastases.

Radiotherapy results in a moderate prolongation of the survival of patients with brain metastases (Posner,[13] Lang[14]). Indeed, their survival is mostly limited by the extent of extracerebral disease. Certain prognostic factors are helpful in estimating the patients' survival and planning adequate treatment. Performance status and the presence of extracerebral metastases are known since the publication of prospective RTOG-trials (Borgelt).[15, 16] Diameter of brain metastases has seldom been investigated so far. The study of Swift[17] could not confirm its relevance as prognostic parameter. Therefore, diameter of metastases and patients' age, which was also controversially discussed in the literature, have not been taken into account in (the following recommendation regarding) patient's selection. Our analysis showed that patients with extracerebral metastases and a Karnofsky-performance status < 70 have a very poor prognosis. For those a clear prolongation of survival by whole-brain irradiation is unlikely. Therefore, they should be treated only in the case of disabling symptoms, when application of corticosteroids has failed to produce a satisfactory improvement.

Patients with favourable prognostic factors may profit from a more aggressive treatment (surgery or radiotherapy with local boost). In this series, the survival of patients who underwent surgical resection for their metastases was not prolonged. But the number of these patients was rather small and our trial was not prospective. Other authors (Mandell,[9] Smalley,[18] Hendrickson[19]) reported significant advantages of combining surgery and radiotherapy, and a prospective randomized trial by Patchell[20] confirmed the superiority of the combined treatment.

After all, radiotherapy with 10 × 3 Gy in 2 weeks seems to be appropriate for the majority of patients. Hypofractionated regimens as reported by Chatani,[8] Borgelt,[16] Haie-Meder[21] and Trovo[22] yielded similar results, but entailing a higher risk of late radiation sequelae in potential long-time survivors due to a higher dose per fraction.

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Pulmonary metastases from osteosarcoma

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Between January 1979, and December 1990, 16 young patients (9 males and 7 females, at an average age of 19 ys., range, 10–25) were observed for the detection of pulmonary metastases from osteosarcoma. The average disease-free interval from the treatment of the primary bone tumor was 14 months (range, 1–36). In all otherwise asymptomatic patients the pulmonary metastases (one metastasis in 9 patients, and more than one in 7) were detected during routine radiological follow-up (nine in the left lung and seven in the right lung).

Six patients presenting with local relapses of primary tumor (4), disseminated metastatic disease (1), and poor functional reserve (1), were excluded from surgery.

Ten patients (62.5 %) underwent 12 operations. The type of surgery was pneumonectomy in 2 patients (in 1 of them for reccurent disease, i.e., completion pneumonectomy), lobectomy in 6 (in 1 one of them for recurrent disease following a wedge resection), and, wedge resection in 4 patients. Perioperative mortality was 0 %. The observed five-year survival in the operated and in the non-operated patients was 35 % and 0 %, respectively.

Key words: Lung neoplasms – secondary; osteosarcoma; surgery

Introduction

Among patients who develop metastatic disease arising from osteosarcoma, 70 % or more have metastases in the lung.[1,2]

Patients who die from metastatic spread of osteogenic sarcoma to the lungs often have no other metastatic sites[3] and present with resectable pulmonary metastases.[4]

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Several authors[4,5] suggest that excision of these pulmonary lesions might prolong the survival or provide worthwhile palliation.

This study is a retrospective review of our experience with surgical intervention for pulmonary metastases from osteogenic sarcoma.

Materials and methods

Between January 1979, and December 1990, 16 patients (9 males and 7 females, at an average age of 19 ys., range, 10–25) were observed for the detection of non synchronous pulmonary metastases from osteosarcoma. The average disease-free interval following the treatment of

the primary bone tumor was 14 months (range, 1–36). Primary sites were the tibia in 7 patients and the femur in 9. The surgical treatment for the primary tumor was amputation in 15 patients, and excision in one. All patients received chemotherapy at the time of surgery. In all otherwise asymptomatic patients the pulmonary metastases (one metastasis in 9 patients, and more than one in 7) were detected during routine radiological follow-up (nine in the left lung and seven in the right lung). Preoperatively, the assessment of adequate pulmonary function was made by conventional spirometry and the determination of maximum oxygen consumption.

Special attention was paid to those patients presenting with recurrent pulmonary metastases, who had already undergone surgical procedures. Functional eligibility to the anticipated extent of resection was warranted prior to surgery. Bone scans were routinely obtained in order to rule out other foci of metastatic disease. Pulmonary involvement was studied with standard radiographs and CT evaluation of the chest.

The criteria for exclusion from surgery were lack of local control of the primary tumor (4 patients), presence of other sites of metastatic disease (1), and, poor pulmonary function (1). Ten patients (62.5 %) underwent 12 operations. The type of surgery was pneumonectomy in 2 patients in one of them for recurrent disease, i.e., completion pneumonectomy, lobectomy in 6 in one of them for recurrent disease following a wedge resection, and, wedge resection in 4 patients. The usual surgical procedure was posterolateral thoracotomy. The influence of gender, location and number of metastases and treatment of primary and metastatic disease on desease-free interval (DFI) and overall survival have been analyzed. The survival rates were calculated according to the Kaplan-Meier method;[6] the results were compared by univariate analysis (Mann-Whitney U test).[7]

Results

The patients' characteristics and outcomes are summarized in Table 1. Of the 10 patients with complete resection, 5 are alive, with survivals ranging from 7 to 102 months (median, 35 months); all patients are without evidence of disease. Two of the patients had undergone a second thoracotomy within 12 and 14 months from the first thoracotomy. There were no

Table 1. Characteristics and outcomes of 16 patients with pulmonary metastases from osteogenic sarcoma.

Patient no.	Sex	Age (yr)	Site of primary	DFI (mo)	Lung lesions	Surgical therapy	Recurrence after-therapy	Survival (mo)	Outcome
1	M	16	tibia	12	single	wedge	negative	102	ned
2	M	19	femur	9	single	wedge	positive	19	dead
3	M	19	tibia	24	multiple	lobectomy	negative	18	dead
4	F	23	femur	20	single	wedge	negative	36	ned
5	M	16	tibia	12	multiple	lobectomy	negative	12	dead
6	F	10	femur	23	single	lobectomy	negative	32	ned
7	F	16	tibia	30	single	lobectomy	negative	26	ned
8	M	25	tibia	1	multiple	pneumonectomy	positive	30	dead
9	M	20	femur	8	single	wedge	negative	7	dead
10	F	19	femur	36	single	lobectomy	negative	64	ned
11	M	18	femur	12	multiple	none	–	6	dead
12	M	20	femur	2	single	none	–	8	dead
13	M	24	tibia	10	multiple	none	–	12	dead
14	F	19	femur	12	multiple	none	–	3	dead
15	F	20	tibia	10	single	none	–	6	dead
16	F	19	femur	3	multiple	none	–	2	dead

DFI: disease-free interval; NED: alive with no evidence of disease.

surgery-related deaths. Four patients died of metastatic disease and one of an unrelated cause 7 months after the second operation.

Of the 6 patients who were not subjected to surgery, all died within 2 to 10 months (median, 6 months) from diagnosis.

The survival data are shown in Figure 1.

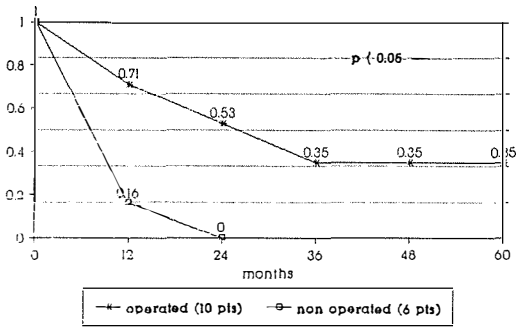

Figure 1. Survival in patients with lung metastases from osteogenic sarcoma.

The observed five-year survivals in the operated and in the non-operated patients were 35 % and 0 %, respectively.

The survival of patients with pulmonary metastases from osteogenic sarcoma related to the operability of the lesions and the feasibility of a complete resection ($p < 0.05$). The disease-free interval from the time of diagnosis of the primary tumor to the detection of pulmonary metastases as well as the number of pulmonary metastases yielded no statistically significant influence on the survival. However, there was a betler prognostic trend noted in patients with a long DFI (more than 12 months) and with single lung metastases. The location of pulmonary nodules showed minor correlation with survival. There was no significant difference in survival between patients who received chemotherapy after primary treatment and those who did not.

Discussion

In patients with osteosarcoma, the commonest site of metastatic spread is the lung. Before the widespread use of chemotherapy, the incidence of pulmonary metastases was at least 80 %.[1,2] The intensification of chemotherapy regimens has seen a drop to 30 % to 40 % in the incidence of pulmonary metastatic disease.[8,9] Although combination chemotherapy produces significant responses in many patients with metastatic osteogenic sarcoma, few patients with metastatic disease achieve long-term survival with chemotherapy alone.[10]

If the hypothesis that the lung is the first step in the metastatic cascade[11] is true, the possibility of surgical treatment of pulmonary metastases from osteosarcoma is to be considered. In fact, a surgical approach enabling total removal of a resectable tumor has been advocated as potentially curative with a reported 5-year survival rate of 20 % to 50 %.[4,5,12–14]

Our results seem to be consistent with the reports that favor surgery in metastatic osteosarcoma patients. The outcome appears closely related to the operability of the lesion (Figure 1). Among the patients who underwent thoracotomy and complete removal of metastases, five are alive with no evidence of disease. Six patients, judged to be inoperable, died from metastatic dissemination (median survival 8 months).

Thoracotomy or median sternotomy are standard surgical approaches for pulmonary metastasectomy.[15] The introduction of thoracoscopy has increased interest in using this approach for the resection of metastatic tumors.[16] There is concern that this method, which permits excellent exposure of the lung surfaces but does not permit lung palpation, may not allow the surgeon to identify and remove all metastatic lesions.[17]

The mortality rate associated with surgery for pulmonary metastatic disease is less than 1 %;[18] in our series, there were no surgery-related deaths.

The criteria for exclusion from surgery were as follows: 1. lack of local control of the primary; 2. presence of other sites of metastatic disease; 3. poor pulmonary function.[4,18] Therefore, proper selection of patients for pulmonary resection is important. The use of CT scan probably plays a decisive role in the follow-up

of patients' with osteosarcoma,[18] allowing earlier detection of metastatic disease and improving the overall survival rates.[14]

Limited pulmonary resections for secondary tumors are recommended when the metastases are adjacent to the pleural surfaces.[19] The possibility of multiple and sequential resections[20,21] and the failure of pneumonectomy to control metastatic disease show that wedge or lobar resections play an important role in the struggle for total disease control.[4]

The number of lung metastases, tumor doubling-time, time before recurrence and treatment of primary and metastatic disease have been shown to be prognostic indicators by some authors.[1,13,14,22]

Regarding the number of resected lesions, the existence of 5 or fewer lesions was associated with a more favorable outcome.[1] Flye[12] and Belli[13] found no adverse influence on the post-thoracotomy survival. In our series, no patients had more than 4 nodules and the survival showed no difference in relation to whether the pulmonary metastases were single or multiple.

However, there was a better survival in patients with a solitary metastasis. A frequently analyzed factor is the interval between the detection of primary osteosarcoma and the appearance of pulmonary metastases. Several authors have reported that the duration of this interval bears no relation to survival.[12–14] In our series, a better prognostic trend was found in patients with a DFI of more than 12 months.

The tumor doubling time defined more clearly the indications for resection of pulmonary metastases.[22] In fact, the prognosis appears to be better in patients with a doubling time of more than 40 days. Few authors have evaluated this discriminant, due to understantable ethical reasons.[4,20] Belli[13] and Carter[14] found a better prognosis in female patients with metastases confined to one lobe of the lung.

The role of chemotherapy in the management of lung metastases from osteogenic sarcoma is very controversial. Belli and coll. [13] believe that chemotherapy may prevent the development of micrometastases. Unfortunately, the response of patients with metastatic disease who have received prior aggressive adjuvant chemotherapy is poor.[13]

The excision of pulmonary metastases may result in a prolonged survival or even cure.[4,20] If the basic criteria can be fullfilled, surgical resection is recommended.[4,18]

In summary, with improved surgical technique and perioperative care, surgeons have become more aggressive and liberal in the indications for resection of pulmonary metastases.[23] An aggressive surgical policy towards metastatic osteosarcoma confined to the lung has resulted in rewarding disease-free survival and remarkable palliative benefit for appropriately selected patients.[4] Since the most significant factors in determining the aggressiveness of the disease (tumour doubling-time, disease free interval, number of pulmonary lesions) do not influence post thoracotomy long-term survival, the criteria for selecting surgical patients must be carefully weighed.[14] In fact, of all patients with metastatic osteogenic sarcoma, only a few will be suitable surgical candidates.[23] We must, therefore, be cautious in applying local treatment for a systemic disease.

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Tobacco policy recommendations of the International Association for the Study of Lung Cancer (IASLC): A 10 point program

Preamble

The IASLC is an international organization whose goal is to decrease the worldwide lung cancer epidemic through research, education and prevention methods. The IASLC members are surgeons, medical oncologists, radiotherapists, pulmonologists, radiologists, pathologists, epidemiologists, basic research scientists and allied health professionals from 56 countries across six continents. The association sponsors a number of meeting and workshops and publishes the journal Lung Cancer to promote the exchange of ideas for reducing lung cancer mortality. Our association is well aware that 85 percent of all lung cancer cases are caused by active cigatette smoking and that 3 percent of all non-smoking lung cancer deaths are the result of exposure to environmental tobacco smoke. Furthermore, the regular use of pipes and cigars also increases the risk of lung cancer. Despite the facct that the association between tobacco smoke and lung cancer has been scientifically known for well over 30 years, lung canccer deaths continue to rise throughout the world. In developed countries the incidence of lung cancer for 1990 was 530.00. In developing nations the incidence of lung cancer cases was 430.000 in 1990 with an estimated 600.000 in 1995 and 10 million by the year 2025. Tobacco use is also associated with other deadly cancers including cancers of the oral cavity, larynx, esophagus, pancreas, bladder, kidney and stomach in both men and women and cervical cancer in women. In addition, smoking is a major cause of coronary heart disease and is the leading cause of chronic obstructive lung disease.

Introduction

The following policy recommendations were developed by the IASLC in June 1994 in the hope that their worldwide implementation would help eradicate tobacco-induced diseases, including lung and other cancers, on a global basis. The IASLC firmly believes that health organizations and its individual members have a special responsibility to help society and governmental organizations adopt and implement tobacco programs and policies to decrease tobacco use worldwide. While the IASLC does not advocate an outright ban on tobacco products it does not oppose such actions. This policy statement outlines a reasonable and realistic publish health approach to significantly reduce smoking and tobacco use world-wide and the creation of a smoke-free world.

Tobacco policy recommendations

1. Taxes

The IASLC confirms that a substantial and sustained tax increase on all tobacco products is the single, most effective public health strategy currently available for reducing smoking and tobacco use among both adults and children and to improve the health of a nation. The Association recommends that governments consider using some proportion of such taxes to help fund smoking education and prevention programs, to help tobacco farmers convert to other crops, and provide basic health care services for its citizens.

2. Tobacco Advertising and Promotion

The advertising, packaging and promotion of tobacco clearly increases consumption and entices children to experiment with tobacco by fostering the positive image that tobacco use increases the users social prominence, sex appeal and maturity. The IASLC recommends that all forms of advertising and promotion should, at a minimum, be severely restricted, and preferably banned. Such measures should apply to all forms of advertising and promotion including tobacco company sponsorship of sporting evens where the product or company logos are displayed and promotion of tobacco products coupon offers and free distribution of all products. The IASLC also recommends a requirement for plain packaging and package-based health information for all tobacco products.

3. Education and Counter-advertising

Information about the health risks of tobacco use are the cornerstone for most successful public health efforts in reducing smoking and tobacco use. The IASLC recommends that all nations develop comprehensive tobacco prevention and educational programs and that a special effort should be made to reach individuals at high risk such as children, ethnic minorities, individuals with less education, and pregnant women. Programs should be developed for schools, communities, the mass media and other channels as appropriate to reach both smokers and potential smokers within the context of the individual country's customs and culture.

4. Children's Access to Tobacco

In most countries throughout the world, regular tobacco use often begins while the individual is stil an adolescent. The IASLC recommends that the sale of tobacco products should be prohibited until at least age 18 and that laws regulating the sale of cigarettes and other tobacco products to underage individuals should be strongly enforced. In addition, the Association recommends that sales througth self-service displays and sales of tobacco through vending machines should be banned completely.

5. International Tobacco Trade

Some industrialized governments have aggressively assisted the multi-national tobacco companies in promoting the sale of tobacco, especially cigarettes, in other countries; often these efforts are directed at developing countries and countries in the 3rd world who are still burdened with basic health problems such as nutritional deficiencies and infectious diesases. The IASLC recommends that all developed nations should refrain from promoting tobacco for export; no country should be pressured to weaken their laws and regulations on tobacco advertising and promotion, sales or distribution, and tobacco excise taxes.

6. Exposure to Environmental Tobacco Smoke

Scientific evidence has counclusively established that involuntary exposure to environmental tobacco smoke (ETS) is a cause of lung cancer in adults as well as a major cause of respiratory symptoms and diseases (bronchitis, pneumonia and asthma) in children. The IASLC recommends that worldwide efforts be adopted that eliminate nonsmoker exposure to ETS. At a minimum smoking should not be permitted in health care facilities; workplaces; schools; airplanes, buses, trains and other forms of public transportation; restaurants, and all indoor public facilities.

7. Nicotine Addiction

All tobacco products contain nicotine and it is nicotine that is directly responsible for the addiction associated with tobacco use. The IASLC recommends that nicotine levels in cigarettes and other tobacco products be reduced over time to non-addicting levels.

8. Tobacco Growing and Forming

Many countries actively support the growing of tobacco including offering subsidies to farmers which guarantee a base price for their

tobacco. The IASLC is sympathetic to those farmers whose income comes substantially from the sale of tobacco and recommends that governments provide economic assistance to farmers in pursuit of other occupations or to help grow crops other than tobacco. The Association strongly believes that the easiest means of accomplishing this is through new excise taxes on cigarettes and dedicating some portion of the tax to assist tobacco farmers.

9. Health Professional's Responsibility

Health professionals can play a significant role in reducing smoking in their communities. The IASLC recommends that all health professionals should receive proper training to counsel their smoking patients to quit and to take an active role in support of tobacco control initiatives within their own communities.

10. Lung Cancer Diagnosis and Treatment

Even if smoking were completely eliminated today, lung cancer would continue to be a significant problem for decades. The IASLC strongly supports the continuation of basic and applied research programs for the better diagnosis and treatment of lung cancer as a means of increasing survival and thereby reducing the overall lung cancer mortality rate.

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Prof. Dr. Božena Ravnihar: Her 80th anniversary

It is the people whose work has brought outstanding results, that are usually remembered when they celebrate their jubilees, remembered for their exceptional drive and distinguished abilities. Professor Ravnihar dedicated her professional, creative and intelectual potential to The Institute of Oncology in Ljubljana and to the development and growth of the Slovenian oncology. As such she is honoured and will be remembered by her students and colleagues.

In 1946, she joined The Institute of Oncology as its Head of Laboratory Department, after having graduated at Belgrade Medical Faculty in 1940, worked as an intern for a year, and having spent more thant three years as an active member of the Partisan Medical Forces.

At the time of her arrival, the Institute consisted of Surgery and Gynaecological Departments and a small Radiotherapy Department. Her task was to set up the histological and clinical laboratories, and to specialize in oncology at the same time. The work in the newly established histology laboratory started in 1946. Professor Ravnihar was not only its Head; she also worked as a pathologist which enabled her to gain knowledge of histopathology of tumours.

She was able to enlarge her self-taught knowledge by studying at foreign institutions like Radiumhemmet in Stockholm, Radiumstationem in Kopenhagen, Institut du Radium Foundation Currie in Paris and later, at the Department of Radiotherapy at the Zurich Hospital. In 1953 she became an Assistant Professor of Radiotherapy and Oncology, having also obtained the specialization in these fields and gained some experience in nuclear medicine at home and abroad.

In 1958/59 she won a scholarship to study in the USA where she visited the leading institutions and obtained some knowledge of the organized forms of cancer prevention.

After that, her work at the Institute was extremely multifarious: she was the Head of the Laboratory Department, the Head of the Radiotherapy Department, the Head of the Cancer Registry of Slovenia, the Head of the Epidemiology Studies, and the Assistant Director of the Institute of Oncology. Under her leadership and with full support of the Director of the Institute of Oncology, prof. dr. Leo Šavnik, the Institute grew and developed into a modern clinical, educational and research centre.

Numerous new departments in different fields of treatment and research were established and encouraged to develop under her directorship from 1964 to 1982. They were, for example, the Clinical Department, the Radiotherapy Department, complete with all the latest equipment, and the Laboratories into which all the modern examination techniques had been introduced.

Especially important from the patients' point of view were the following services: psycho-oncology, physiotherapy and social medicine, and the policy of adopting the modern concept of multidisciplinarity and team work in treating the various forms of cancer.

Professor Ravnihar recognized the great value of research for the development of oncology. In the early sixties already, she was the one who gave initiative for the research work, although the staff potential and the working conditions were still quite modest. She put a special emphasis on systematic planning of the research, her scheme of research planning in medicine had been widely used by all research institutions in Slovenia for many years. She established a research foundation at the Institute of Oncology and determined its grant-awarding principles. The research work, carried out at the Institute was at her instigation made a part of bigger research programmes on the state and international level. As a result, the Institute of Oncology was given a university status and quite an impressive number of academic distinctions were awarded to her colleagues at the time of her directorship of the Institute (20 PhD's, 10 MSc's, 2 academic specializations, and 17 of her colleagues were made university theachers). Many of them remember Professor Ravnihar as their thesis supervisor; the commitment and dedication to work was certainly one of the unforgettable and everlasting features which were passed on from her to younger generations. The results of their common endeavour are quite impressive: more than a hundred professional publications home and abroad per year, international awards won by numerous scientists working at the Institute, awards given by The Boris Kidrič foundation, and many other scientific distinctions.

Professor Ravnihar was especially interested in developing research documentation infrastructure: the membership of the Institute Library and the Indok Centre of the international Cancernet, is only one of the results of her endeavours in this field. In 1964, she and her fellow workers established the radiology and oncology journal *Radiologia Iugoslavica,* which had been published for 25 years, and is now published under the title *Radiology and Oncology*. Professor Ravnihar was its first Editor-in-Chief.

One of her most important achievements was the establishing of Cancer Registry as early as 1949. After that, every case of cancer had to be registered under Slovenian law, which made the Registry a reliable and valuable source of information. Cancer Registry of Slovenia was one of the first of its kind in Europe and the means of connecting The Institute of Oncology and Slovenian medical research with the rest of the world. Professor Ravnihar's work in this field was internationally recognized: she had been the Head of the European and Middle East Branch of The International Association of Cancer Registries for three years.

She was also active in the development of medical studies on all levels. In 1947, the Chair for Oncology and Radiotherapy at the Medical. Faculty of Ljubljana was founded, also at her instigation. After that, she was actively engaged in preparing the curricula of the medical and stomatological courses at the Medical Faculty. On the post-graduate level, Professor Ravnihar had made it possible for radiotherapy and oncology to become an independent field of specialization, and introduced the study of its basic principles into the majority of post-graduate medical courses. Her contributions to educating general public at home and abroad were considerable, too. She was the member of the UICC from 1960 to 1962.

Besides being a distinguished academic and scientist, Professor Ravnihar was also a great administrator. Under her directorship the Institute of Oncology was considerably enlarged,

renovated and modernized. But one of her greatest wishes, namely the erection of a new building, which could house all the various departments and wards of the Institute, has not been realized yet.

Since she was also involved in preparing its building plans, may her next anniversary bring about the commencement of the building of the new Institute!

And may she be as active as she has been all her life – and remain the guiding spirit for all her numerous students and colleagues, who wish her many happy returns of this day!

Prof. Marija Us-Krašovec, M.D., Ph.D.

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Notices

Notices submitted for publication should contain a mailing address, phone and/or fax number of a contact person or department.

Radiology

The 9th European Congress of Radiology – ECR'95 will take place in Vienna, Austria, *March 5–10, 1995.*

Contact Prof. A. Baert, ECR-Office, Neutorgasse 9/2a, 1010 Vienna, Austria; or call -43 1 533 4064; Fax: + 43 1 533 40649.

Imaging in Oncology

The 19th LH Gray conference »Quantitative Imaging in Oncology will be offered in Newcastle-upon-Tyne, UK, *April 3–7, 1995.*

Contact Dr. K. Faulkner, Regional Medical Physics Department, Newcastle General Hospital, Westgate Road, Newcastle-upon-Tyne NE4 6BE, UK; or call + 4491 273 881. Fax: + 4491 226 0970.

Breast cancer

The 4th Maritemer workshop of Austrian Society for Senologie with the international attandance will take place in Taormina, Sicilia, Italy, *April 29–May 6, 1995.*

Contact Mrs Elisabeth Stradal, Wachringer Guertal 18–20 (im Neuen AKH), A-1090 Wien, Austria; or call + 43222402 406 113; Fax: + 43222 402 406 120.

Brachytherapy

The Annual Brachytherapy Meeting GEC- ESTRO will be offered in York, United Kingdom, *May 10–12, 1995.*

Contact the ESTRO Secretariat, Radiotherapy Department, University Hospital St. Rafael, Capucijnenvoer 35, B-3000 Leuven, Belgium; or call + 32 16 33 64 13; Fax: + 32 16 33 64 28.

Radiotherapy

The 5th International Meeting on Progress in Radio-Oncology ICRO/OcGRO 5 will take place in Salzburg, Austria, *May 10–14, 1995.*

Contact Univ.–Prof. Dr. H. D. Kogelnik, Institute of Radiotherapy and Radio-Oncology, Landeskrankenanstalten Salzburg, Muellner, Hauptstr. 48, A-5020 Salzburg, Austria; or call + 43 662 44 82 39 00; Fax: + 43 662 4482 887.

History of medicine

The »1995 Annual Meeting« of the American Association for the History of Medicine will take place in Pittsburgh, USA *May 11–14, 1995.*

Contact Dr. Jonathon Erlen, 123 Northview Dr., Pittsburgh, PA 15209, USA; or call + 1 412 648 8927.

Cancer and quality of life

The conference organized by Organization of European Cancer Institutes (OECI), the Institute of Oncology in Ljubljana and National Cancer Institute of Genova will take place in Bled, Slovenia, *May 12–14, 1995.*

Contact Dr. M. Zwitter, Institute of Oncology, 61105 Ljubljana, Slovenia; or call + 38661 1314 225; Fax: + 386 61 1314 180.

Pediatric Radiology

The 32th congress of the European Society of Pediatric Radiology will be offered in Utrecht, The Netherlands, *May 15–230, 1995.*

Contact Prof. Dr. M. Meradij, Sophia Kinderziekenhuis, Dr. Molewaterplein 60, 3015 GJ Rotterdam, The Netherlands; or call + 31 10 463 6166; Fax: + 31 10 466 6865.

Lung Cancer

The 3rd Central European Lung Cancer Conference will take place in Prague, Czech Republic, *May 28–31, 1995.*

Contact the Conference Secretariat, 3rd Central European Lung Cancer Conference, Czech Medical Association J. E. Purkyne, P.O. Box 88, Sokolska 31,

120 26 Prague 2, Czech Republic; or call + 422 296 889 / + 422 297 271 / + 422 249 151 95; Fax: + 422 294 610 / + 422 242 168 36.

Radiology

The Roentgen Centenary Congress will be held in Birmingham, United Kingdom, *June 12–16, 1995.*

Contact Mrs. V. Whitehead, British Institute of Radiology, 36 Portland Place, London W1N 4AT, United Kingdom; or call + 4471 436 7807; Fax: + 4471 255 3209.

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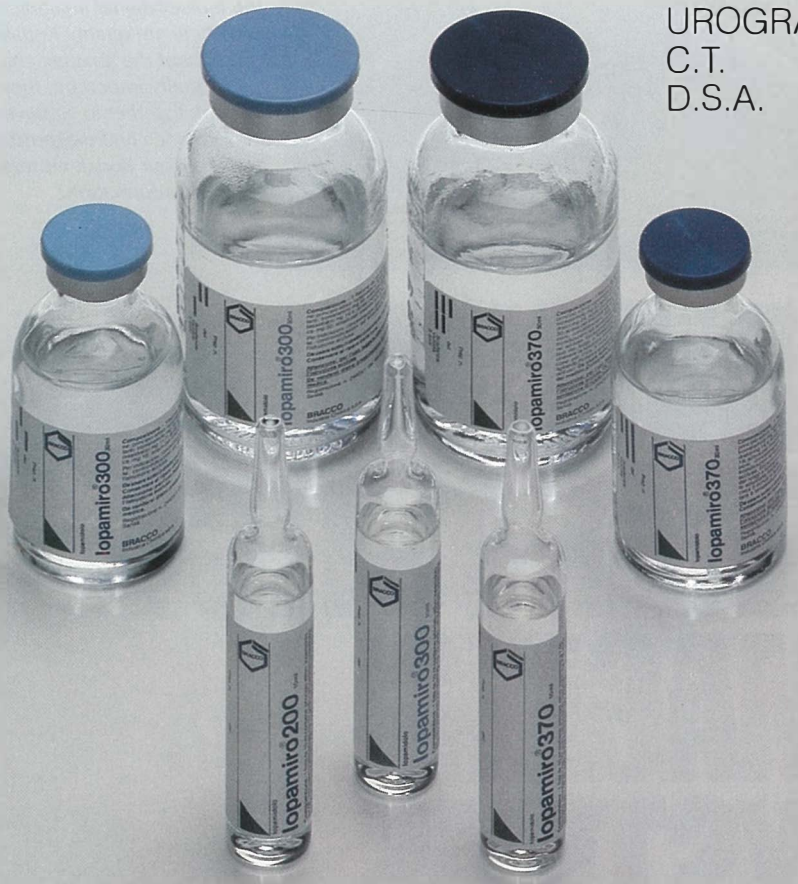

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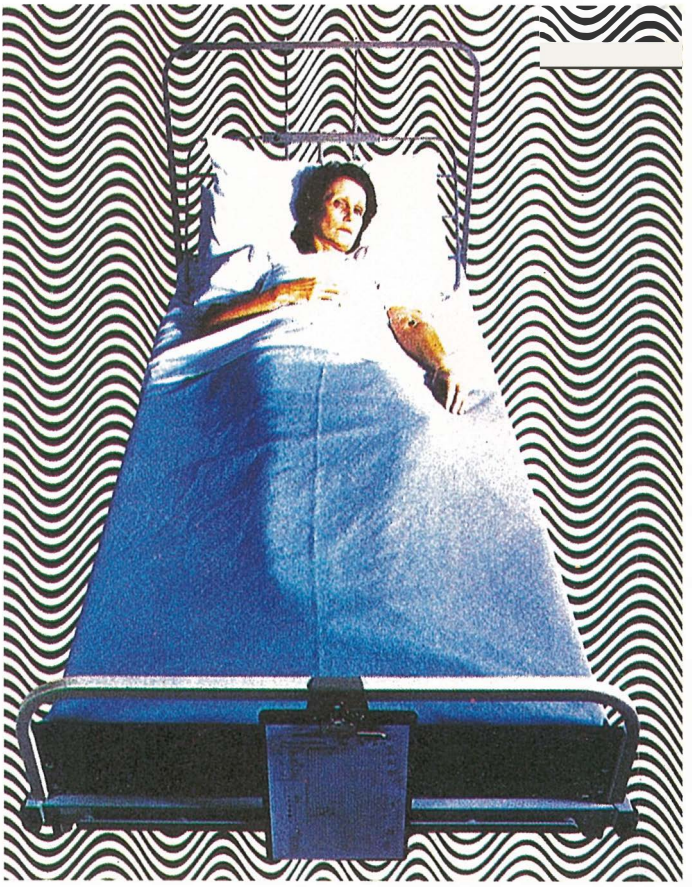

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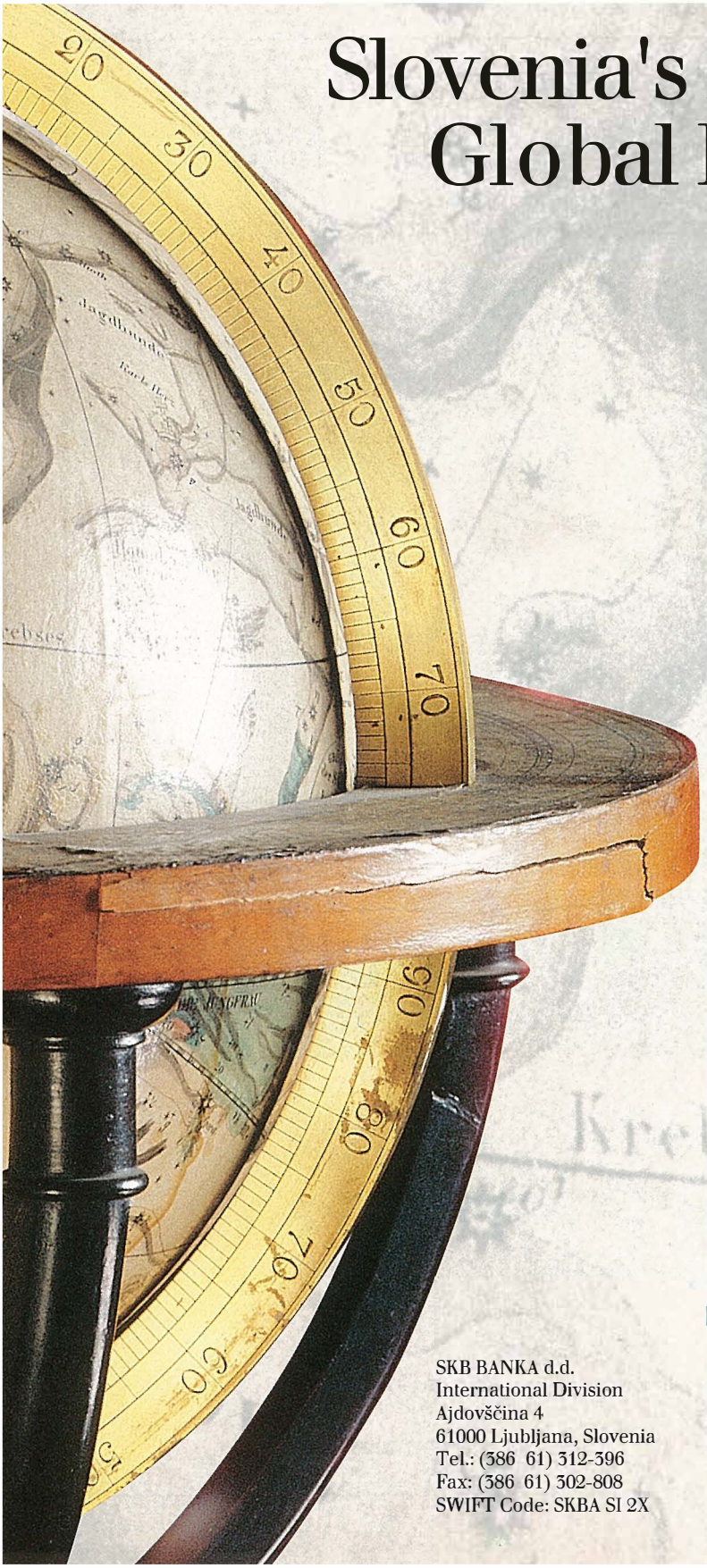

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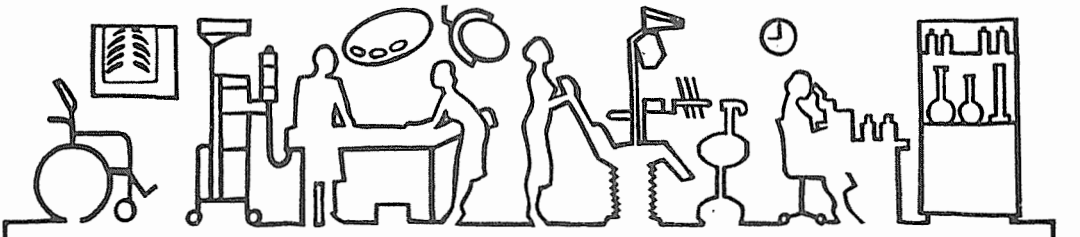

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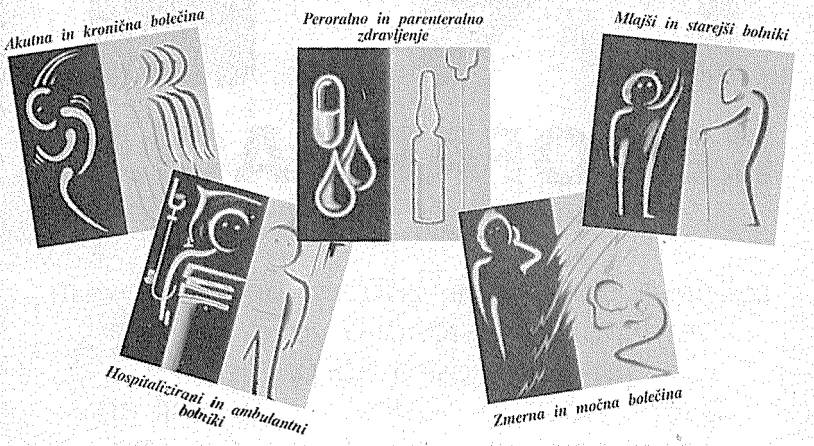

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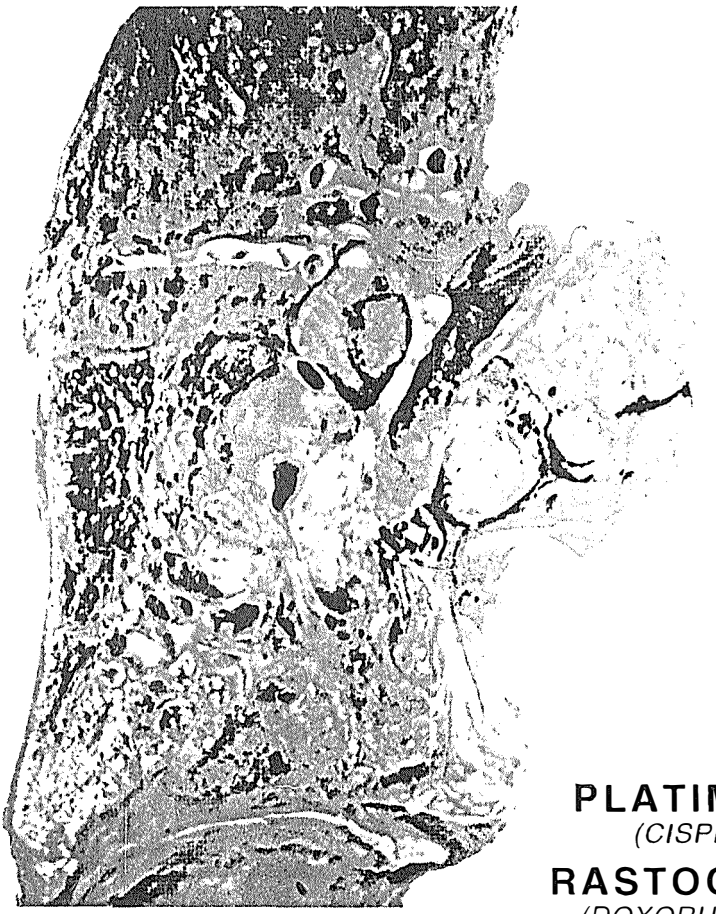

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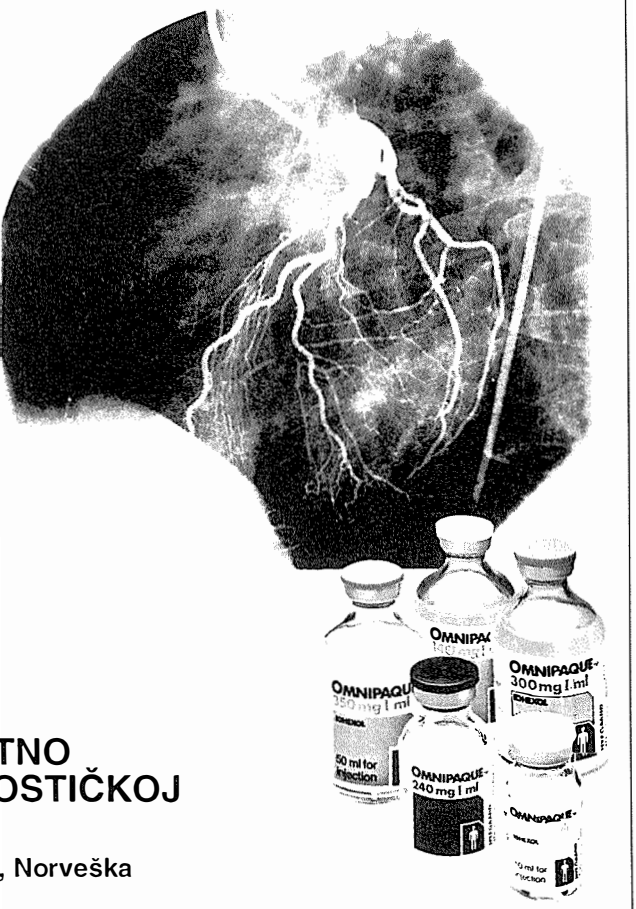

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