Radiol Oncol 1994; 28: 351-8.

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

Andreas Schamanek and Karl Karrer for the International Society of Chemotherapy (ISC)-Lung Cancer Study Group

Institute for Cancer Research of University of Vienna, Borschkegasse 8a, A-1090 Vienna, Austria

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

Correspondence to: Univ. Prof. Dr. med. Karl Karrer, Facharzt für Onkologie, Anton-Renk-Str. 2, 6330 Kufstein, Austria. Phone: +345372 63228.

UDC: 616.24-006.6-08

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

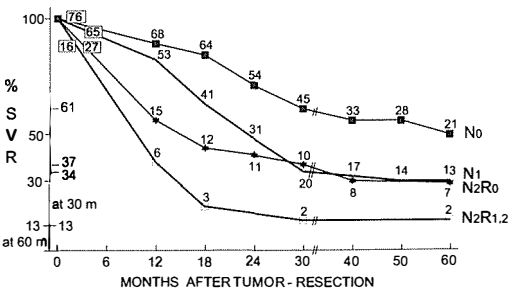

Figure 1. Actuarial survival and numbers of patients at risk after resection followed by chemotherapy and prophilactical cranial irradiation for patients with SCLC. ISC study I, II. Evaluation at February 1994.

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.

References

1. Karrer K. Adjuvant chemotherapy of postsurgical minimal residual bronchial carcinomas. *Recent results Cancer Res* 1979; **68**: 246–59.
2. Karrer K, Denck H, Pridun N and Ludwig Lung Cancer Stud. Group. Hämatologische Beobachtungen an Patienten nach intrapleuraler Applikation von Corynebacterium parvum zur Immunstimulation. *Acta med Austriaca* 1979; **6**: H5 209–12.
3. Karrer K, Denck H, Pridun N. Combination of early surgery for cure and polychemotherapy in small cell bronchial carcinoma. *Proc. of the 13th I.C.C.,* Vienna 1983 Tom 11: 228/52–60.
4. Shields T, Matthews M. Adjuvant therapy of small cell bronchial carcinoma. *Cancer Treat Rev* 1984; **11**: 331–3.
5. Karrer K, Shields TW, Denck H. The importance of surgical and multimodality treatment for small cell bronchial carcinoma. *J Thorc Cardiovasc Surg 1989;* **97**: 168–76.
6. Denk W, Karrer K. Modellversuch einer Rezidivprophylaxe des Karzinoms. *Wien Klin Wochenschr* 1955; **67**: 986.
7. Denk W, Karrer K. Combined surgery and chemotherapy in the treatment of malignant tumours. *Cancer* 1961; **14**: 1197–204.
8. Abrams J, Doyle LA, Aisner J. Staging, prognostic factors and special considerations in small cell lung cancer. *Sem Oncol* 1988; **3**: 261–77.
9. Theuer W, Selawry O, Karrer K. The impact of surgery on the multidisciplinary treatment of bronchogenic small cell carcinoma. *Med Oncol & Tumor Pharmacother* 1992; **9**(3): 119–37.
10. Pridun N et ISC-LCSG: Adjuvant chemotherapy after surgery with curative intent for SCLC. In: *Adjuvant Therapy of Cancer VII.* Salmon, Saunders Co, 1993.
11. Breslow N. A generalized Kruskal-Wallis test for comparing k-analysis subject to inequal patterns of censorship. *Biometrika* 1970; **57**: 579–94.
12. Theuer W, Holzner JH, Karrer K. The importance of staging and pathohistological subtyping in small celled lung cancer (SCLC). *J Cancer Res & Clin Oncol* 1992; Suppl to vol. 118, R 40.
13. Ulsperger E. Waldhör T for the ISC-LCSG. Adjuvant, Neoadjuvant and Palliative Chemotherapy in 550 Randomized Patients with Small Cell Lung Cancer. Sec Central Europ Conf Lung Cancer April 1994, Ljubljana, Slovenia.
14. Aisner J et al Role of chemotherapy in small cell lung cancer: A consensus report of the IASLC-workshop. *Canc Treatm Rep* 1983; **67**: 37–43.
15. Ginsberg RJ, Karrer K Surgery in small cell lung cancer: a consensus report. *Lung Cancer* 1989; **5**: 139.
16. Shepherd FA, Ginsberg RJ, Feld R, Evans WK, Johansen E. Surgical treatment for limited small cell lung cancer. *J Thorac Cardiovasc Surg* 1991; **101**: 385–93.
17. Salzer GM, Praeuer H, Mueller H, Huber H, Frommhold H. Langzeitergebnisse nach multimodaler Therapie des kleinzelligen Bronchialkarzinoms mit Einschluss der Chirurgie. Langenbecks Arch Chir Suppl Kongressbd 1991; 554–8.
18. Macchiarini P, Hardin M, Basolo F, Bruno J, Chella a, Angeletti CA Surgery plus adjuvant chemotherapy for T1-3N0M0 small-cell lung cancer. *Am J Clin Oncol* 1991; **14**(3): 218–24.
19. Davis St, Crino L, Tonato M et al. A Prospective Analysis of chemotherapy Following Surgical Resection of Clinical Stage I-II Small-cell Lung Cancer. *Am J Clin Oncol (CCT)* 1993; **16**(2): 93–5.
20. Lad T, Thomas P, Piantadosi S: Surgical resection of small cell lung cancer. *Lung Cancer 1991;* **7**: Suppl: 162.
21. Sobue T, Suzuki T, Naruke T et al: Efficacy of Lung Cancer Screening: Comparison of Results from a Case-Control Study and a Survival Analysis. *Jpn J Cancer Res* 1992; **83**: 424–30.