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Chemotherapy as an Adjuvant to Surgery in Lung Cancer*

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Summary. *A preliminary evaluation of an adjuvant chemotherapy is presented. A highly dosed intermittent polychemotherapy consisting of 13 courses of three infusions separated by intervals of a week was administered over 3 years. Each infusion contained 12 mg/kg cyclophosphamide, 12 mg/kg 5-fluorouracil (5-FU), 0.5 mg/kg methotrexate and 0.1 mg/kg vinblastine. In all, 2,442 such infusions were given to 219 patients who had undergone radical surgery for bronchial carcinomas. This treatment was generally well tolerated; the leucopenia rate was within an acceptable range.*

A randomized control group consisting of 289 patients treated by radical surgery only was checked and examined at the same intervals as 229 patients who were allocated to the adjuvant chemotherapy group. Comparison of the survival rates of the subdivided treatment groups and control groups, calculated by the life-table method, shows differences in the prognosis, as well as in the effectiveness of the one chemotherapy used. These differences also existed with regard to tumor size (according to TNM stages), to the clinical symptoms (according to the Feinstein classification), and to the histological main tumor types. In the first years after onset of treatment in the groups of patients who had tumors of TNM stages I and II, a difference appears in the life-table curves favoring the chemotherapy-treated patients. In TNM stages III, IV, and C there seems to be an increase in survival rates.

One hypothesis is that the chemotherapy had a greater effect on the more rapidly growing tumors than seems to be the case in the slower-growing tumors. Squamous-cell and adenocarcinomas seem to be unfavorably influenced by this therapy, while a positive therapeutic effect seems observable in the carcinomas of the small-cell and of the other different histological types.

Of the more rapidly growing tumors (Feinstein 3 and 5, subdivided into squamous, adeno- and other cell type tumors) on the other hand, a therapeutic effectiveness of the chemotherapy in squamous-cell tumors too seems apparent.

The necessity of close cooperation with the family physicians is emphasized.

The observable differences of the treatment efficacy in patients with various biologically different tumor types, as seen in this preliminary evaluation, permit the formulation of working hypotheses which could lead to treatment optima for the various tumor types.

Taking into account the length of time necessary to conduct such a trial and to reach meaningful results, it is evident that with the increasing number of treatment possibilities such working hypotheses must be tested within the framework of larger international cooperative study groups.

Introduction

From the results of previous studies it has been concluded that adjuvant chemotherapy should be administered intermittently at the highest possible doses over a long period of time (Karrer and Denck, 1971).

As results of chemotherapy in patients with inoperable carcinomas of the bronchus indicate, a combination of cytostatics with different modes of action is superior to mono-drug therapy.

The application of a combination of cytostatic drugs after radical surgery seems to be the best treatment at present. This form of treatment, with long-term intermittent polychemotherapy seems to achieve a promising compromise between tumor inhibitory efficacy and undesirable effects such as immunosuppression.

In order to attain a maximal destruction of small tumor foci in the whole body the highest possible dose,

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limited according to the resulting side effects, should be administered.

Therefore, a randomized clinical trial was initiated to determine whether a high-dosed intermittent long-term polychemotherapy can increasing the survival rate and/or survival time of patients who have undergone radical surgery for bronchial carcinoma.

The trial was begun in autumn 1969 by the cooperative Viennese working group.

Material and Methods

The preoperative diagnostic procedures used to evaluate the anatomical size of the tumor are performed in the following sequence: X-ray, bronchoscopy, and mediastinoscopy including histology and angiography. Internal medical contraindications for surgery are decided on the basis of examinations such as ECG and lung function tests, and other tests if indicated. All the patients in this study are operated on in this hospital by one group of surgeons from one surgical school using the same methods of operation and criteria of indication for surgery. No other selection of patients was performed in the hospital and no patients in this study have been operated on outside this hospital. All slides made of the operation specimens have been evaluated by the same pathologist.

All patients are randomized after surgery. The stratification of the patients is performed thereafter according to the TNM classification based on histological examination of the operation specimens (Kreyberg et al., 1967), Feinstein classification (Feinstein, 1964), and histological main types. Thus four groups of patients are categorized: squamous-cell, adeno-, small-cell, and all other types of carcinomas, termed "diverse". No unknown histological type is included in this study.

Radical surgery is defined as the removal of the whole primary tumor together with the surrounding involved tissue. This is performed by lobectomy, bilobectomy or pneumonectomy, according to the localization and size of the primary tumor. The regional lymph nodes are also removed by this procedure. Additional lymph nodes are also removed if macroscopically involved. The operation specimen is examined by the same pathologist. The cutting board and the extent of the primary tumor as well as the labeled removed lymph nodes are evaluated. This provides the evidence for the subsequent postoperative TNM staging.

After histological examination of each operation specimen, two groups of patients are formed at random: one group receives adjuvant chemotherapy and the second group receives none and is used as a control group. No X-ray treatment was used at this stage. Both groups of patients received the same general medical care at equal intervals.

Chemotherapy was carried out as follows: 1–2 weeks after surgery the first intravenous infusion of 500 ml of 5% laevulose containing 12 mg/kg cyclophosphamide, 12 mg/kg 5-FU, 0.5 mg/kg methotrexate, and 0.1 mg/kg vinblastine was administered. This infusion was repeated a second and a third time at intervals of 7 days. The protocol requires the administration of 13 such series of three infusions within 3 years after surgery. The first series of three infusions is given within the usual time required for hospitalization for this type of operation. Subsequent infusions are given in the outpatient clinic. The hematogram is determined before chemotherapy is started. The minimum hematological level must be: 4,000,000 erythrocytes, 4,000 leucocytes, and 100,000 platelets per mm^3. During therapy a leucocyte count is required twice weekly. If the leucocyte and platelet counts fall below 4,000 and 100,000/mm^3 respectively, the intervals without treatment are prolonged.

The chemotherapy protocol was followed as closely as possible. No reduction schedule of chemotherapy was used. However, the interval of no treatment was prolonged as made necessary by low white blood counts. The exact number of chemotherapy infusions administered to the patients is given in Figures 1–5, in which each line represents one patient, giving the individual number of infusions and showing intervals and their lengths.

The chemotherapy is given in the outpatient clinic of the hospital, where the blood counts are also performed. Patients from outside Vienna are also treated (i.e., chemotherapy administration) and examined in the outpatient clinic mentioned above.

Monitoring examinations including X-rays, blood counts, body weight, etc. are performed every 6 weeks for the first 6 months, every 3 months for the next 18 months, and then every 6 months.

Close cooperation with the referring family physician is important. Therefore, the general practitioner is informed by an explanatory letter and asked to provide psychological support, advice, and care of the patients. The private physician is only requested to treat the general physical condition of the patient, but no cytostatic chemotherapy is administered by him. As indicated in Figures 1 through 5, many of these patients (predominantly from outside Vienna) are not willing to undergo regular chemotherapy. This is often because the patient does not understand his diagnosis and prognosis, which one is usually not told in Austria. Therefore treatment is unfortunately not administered to all patients, as would be required according to the protocol. Because they are convinced neither of the necessity for the long-term therapy nor of the rationale of the adjuvant chemotherapy, not only the patients themselves but also some of the private physicians involved do not cooperate in supporting the maintenance of the protocol schedule.

The preliminary evaluation of this study, at January 1, 1977, is based on 518 patients and is focused on the question of tolerance and survival. The parameter used for the evaluation of the chemotherapy administered is the survival time from the point of surgical tumor removal up to the patient's demise. Of the 518 patients, 289 received only surgical treatment (randomized controls) and 229 patients were treated both surgically and with chemotherapeutic agents. To define different prognostic groups of bronchogenic carcinomas and their reactions to the uniform therapy, detailed stratifications were used. This was accomplished by a definite description and classification of the tumor at the time of resection, using the TNM system (Arnal et al., 1967), the Feinstein categories (Feinstein, 1964), and histological maintypes (Kreyberg et al., 1967).

Calculation of the life-table survival curves is based on all randomized patients, including the postoperative mortality without exception even in the case of protocol violation or deviation. The establishment of criteria for defining whether or not treatment is adequate appears premature at the present stage of the investigation.

The extent of disease is classified as follows:

T_1 – Tumor 3 cm or less in its greatest dimension, surrounded by lung or visceral pleura and with no evidence of invasion proximal to a lobar bronchus. Tumor limited at the lung segment of origin.

T_2 – Tumor more than 3 cm in its greatest dimension and not extending beyond the lung.

T_3 – Tumor of any size with direct extension to adjacent structures such as the main bronchus, the chest wall, diaphragm, and mediastinum and its contents.

T_4 – Tumor extending far beyond the border of the lung, infiltrating the adjacent structures such as the pericard, chest wall, diaphragm, or mediastinum.

$N_a = N_0$ – No tumor infiltration into the regional lymph nodes.

$N_b = N_1$ – Tumor cell infiltration into the regional bronchopulmonal lymph nodes.
$N_c = N_2$ – Tumor cell infiltration into the tracheobronchial (mediastinal) lymph nodes.
M_0 – No evidence of distant metastases.
$M_1 = M_+$ – Distant metastases present including scalene, cervical or contralateral hilar lymph nodes and metastases to brain, bone, or other organs.

The following TNM staging is used:

Stage I	Stage II	Stage III	Stage IV
$T_1N_aM_0$	$T_1N_bM_0$	$T_1N_cM_0$	$T_3N_cM_0$
$T_2N_aM_0$	$T_2N_bM_0$	$T_2N_cM_0$	$T_4N_{a,b,c}M_0$
		$T_3N_{a,b}M_0$	$T_xN_xM_1$

A	B	C
$T_1N_aM_0$	$T_1N_bM_0$	$T_{1,2,3}N_cM_0$
$T_2N_aM_0$	$T_2N_bM_0$	$T_4N_{a,b,c}M_0$
$T_3N_aM_0$	$T_3N_bM_0$	$T_xN_xM_1$

Feinstein categories are classified according to the definitions published. In short:
Group 1 – Diagnosis at random, no symptoms before.
Group 2 – Pulmonal symptoms for more than 6 months.
Group 3 – Pulmonal symptoms for less than 6 months.
Group 4 – Same as group 2 plus extrapulmonary symptoms.
Group 5 – Same as group 3 plus extrapulmonary symptoms.

Results

Tables 1 and 2 show the number of patients grouped according to TNM stages, Feinstein categories, and three main carcinoma cell types (squamous-cell, adeno-, oat-cell and all others, i.e., "diverse" tumor types). "Diverse" histology means all other histological types than

Table 1. Number of bronchial carcinoma patients treated with radical surgery and adjuvant chemotherapy

Feinstein category	TNM stages																Total
	I				II				III				IV				
	S	A	O	D	S	A	O	D	S	A	O	D	S	A	O	D	
1	11	3	1	4	3	6	–	–	4	–	1	3	–	3	–	1	40
2	6	3	1	1	5	1	–	2	5	–	2	–	2	–	1	1	30
3	24	6	1	5	13	8	3	1	9	4	1	–	12	5	6	2	100
4	1	–	–	–	1	–	–	–	2	1	–	1	2	1	–	–	9
5	9	2	1	2	6	2	1	1	6	1	1	–	8	2	1	–	43
U	1	1	–	–	1	–	–	–	1	–	1	–	1	–	–	1	7
Total	52	15	4	12	29	17	4	4	27	6	6	4	25	11	8	5	
Grand total	83 (36%)				54 (24%)				43 (19%)				49 (21%)				229 (100%)

S = Squamous-cell carcinoma; A = Adeno carcinoma; O = Oat-cell carcinoma; D = Diverse carcinomas
U = Feinstein category unknown

Table 2. Number of bronchial carcinoma patients treated with radical surgery only and used as randomized controls

Feinstein category	TNM stages																Total
	I				II				III				IV				
	S	A	O	D	S	A	O	D	S	A	O	D	S	A	O	D	
1	25	16	2	8	4	6	1	–	1	2	–	3	4	2	1	1	76
2	13	4	1	1	3	3	2	–	4	–	–	1	3	–	–	–	35
3	30	9	–	8	11	2	4	2	15	6	1	2	10	1	1	5	107
4	3	3	–	–	2	1	–	–	2	–	–	–	1	–	–	–	12
5	14	5	–	2	4	2	2	–	11	1	–	–	2	1	–	4	48
7	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–	–	1
U	1	2	–	2	–	1	–	–	2	1	1	–	–	–	–	–	10
Total	86	39	3	21	24	15	9	2	35	10	2	6	20	5	2	10	
Grand total	149 (52%)				50 (17%)				53 (18%)				37 (13%)				289 (100%)

S = Squamous-cell carcinoma; A = Adeno carcinoma; O = Oat-cell carcinoma; D = Diverse carcinomas
U = Feinstein category unknown

the three main cell types already mentioned, and no "unknown" histological type is included in this group. In accordance with the Viennese School of Surgery the oat-cell carcinomas are also included for surgery.

A rather large number of patients are classified in TNM stages I and II; this might possibly be explained by the preselection of patients in private practice, which is essentially beyond our control. Most of these cases have been diagnosed as squamous-cell or adenocarcinomas. In the treated group as well as in the control group the age distribution shows a significant peak between the ages of 60 and 65 in both sex groups. Only a few patients older than 70 years of age were operated on. The male-female ratio was 1 : 5.

The percentage of asymptomatic patients (Feinstein category 1 shown in Tables 1 and 2) is quite similar to that of the original distribution recorded by Feinstein (1964), indicating that no particular measures of early diagnosis were effective. No explanation relevant to the statistical analysis can be given for the unequal number of 289 controls and 229 treated patients.

Table 3 summarizes the infusions given to only 219 of the 229 randomized patients, as 10 randomized patients died postoperatively before chemotherapy.

Detailed information is provided in Figures 1 through 5, where the occurrence of leucopenias is also documented. Alopecia, cystitis, and infections have been rare, so that they have been omitted from this preliminary evaluation. No second primary neoplasm has yet been observed.

The treatment was well tolerated, causing only minor side effects such as vomiting and nausea for 1–2 days. Loss of hair and diarrhea were also rare. No patient required hospitalization due to side effects. Most of the patients stayed away from work only for the day of infusion. It seems particularly important that the rate of leucopenia appears lower than a comparably high-dosed single-drug therapy would cause. Table 3 and Figures 1–5 also demonstrate the important finding that only 25 of 219 patients developed leucopenia below the leucocyte level of 2000/mm^3. Spontaneous recovery from leucopenia was seen in most cases, and only in some cases was the administration of cortisone and/or a blood transfusion necessary. Only a few patients received antibiotics and gammaglobulin prophylactically. It seems important that the occurrence of leucopenia during one treatment period is often followed by normal acceptance of the same treatment given later (Figs. 1–5). Chemotherapy was always begun and administered according to the protocol in hospital after operation. Continuation of this intermittent chemotherapy was followed much more rigorously by those patients living in the city of Vienna than those living outside Vienna, as already mentioned above.

Regarding the relationship of the number of deaths caused by the tumor or on the other hand by other diseases, after careful consideration of deaths of unknown cause (all patients without autopsy) we feel that no further information significant for the conclusions of this preliminary evaluation is decisive. If the actual causes of death had been known, we would have subdivided these patients by of death. However, as the number of unknown causes of death (as seen in Tables 4 and 5) is so great, it was not meaningful to subdivide this group into individual causes of death for calculation of the life-table curves.

The crude survival rates of the patients are calculated according to the life-table method. The number of patients at the time of operation, 36, and 60 months thereafter represents the number of patients at risk at this given time. The survival rates of patients with combined treatment and those of the control patients are subdivided into TNM stages I–IV (Fig. 6) and A, B, C (Fig. 7) (see also Tables 6 and 7).

Table 3. Bronchial carcinomas treated by radical surgery: patients with or without leucopenia after chemotherapy

Leucocytes not below	TNM stages								Total	Grand total
	I		II		III		IV			
	No. of patients	Total no. of infusions	No. of patients	Total no. of infusions	No. of patients	Total no. of infusions	No. of patients	Total no. of infusions	Patients	Infusions
2000	71	892	47	545	40	380	36	326	194	2143
1500	3	17	5	79	–	–	5	41	13	137
1000	5	57	–	–	2	52	2	32	9	141
700	1	11	–	–	–	–	2	10	3	21
Total	80	977	52	624	42	432	45	409	219	2442

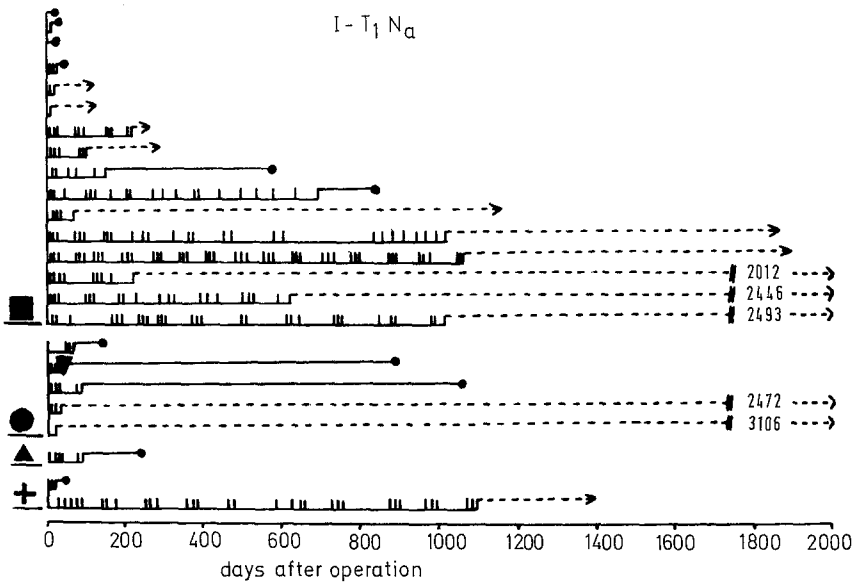

Fig. 1. Observation or survival time with number of infusions administered and length of intervals without treatment for each patient operated on for bronchial carcinoma in stage $I - T_1N_aM_0$

Key for Figs. 1–5: ⊥⊥⊥ Infusion; ——● Death; – – – → Observation period after chemotherapy; ■ Squamous-cell carcinoma; ● Adenocarcinoma; ▲ Oat-cell carcinoma; + Diverse carcinomas; ▲ Leucocytes below 2,000 but not below 1,500; ▼ Leucocytes not below 1,000; ! Leucocytes not below 700

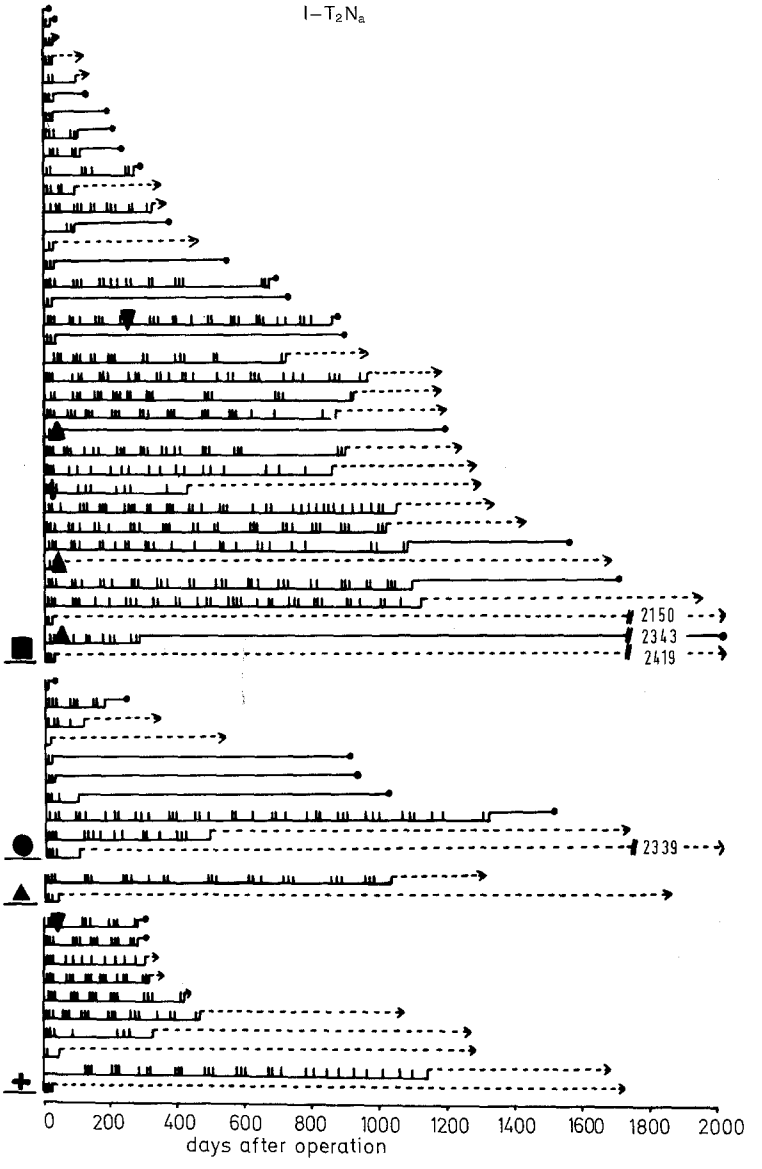

Fig. 2. Observation or survival time with number of infusions administered and length of intervals without treatment for each patient operated on for bronchial carcinoma in stage $I - T_2N_aM_0$

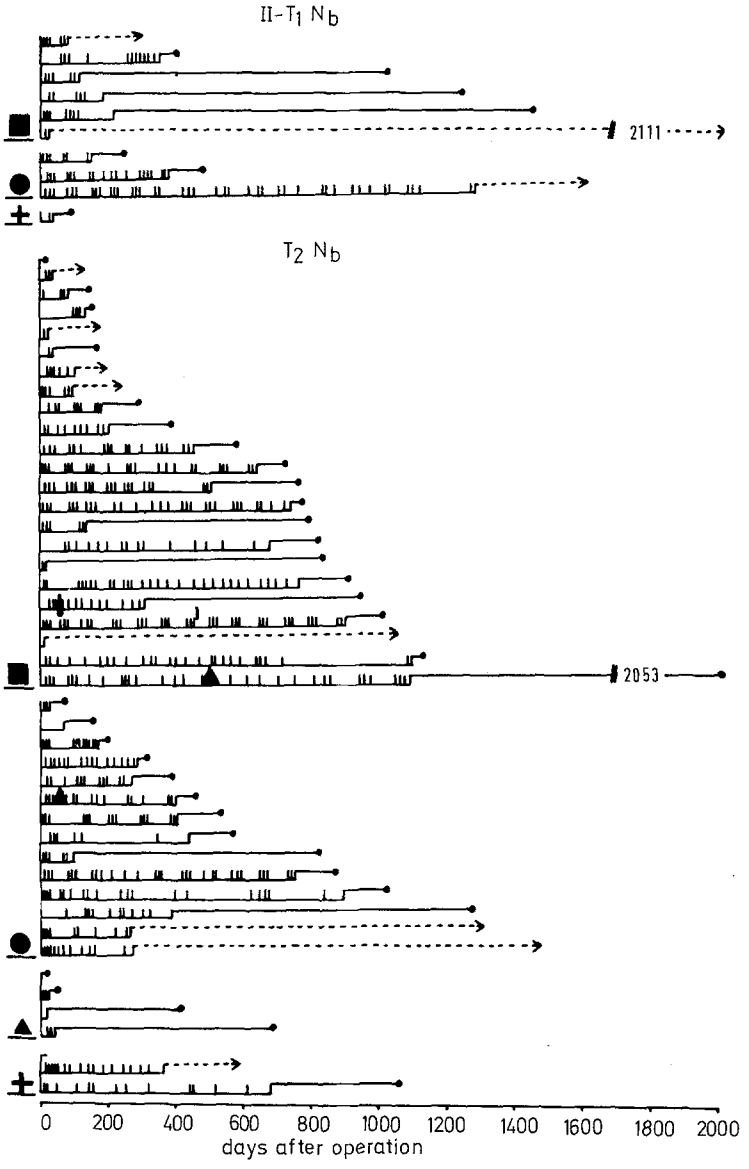

Fig. 3. Observation or survival time with the number of infusions administered and length of intervals without treatment for each patient operated on for bronchial carcinoma in stage II – $T_1N_bM_0$, $T_2N_bM_0$

Table 4. Bronchial carcinomas treated by radical surgery and subsequent chemotherapy, subdivided into TNM stages and classed according to cause of death

	TNM stages				Total
	I	II	III	IV	
Total no. of patients	83	54	43	49	229
Alive	45	11	15	8	79
Died of:					
Postoperative complications	6	4	3	4	17
Tumor	10	17	13	12	52
Cachexia	1	3	–	6	10
Suicide	2	–	–	–	2
Other diseases not connected with the tumor	3	2	2	5	12
Unknown	16	17	10	14	57

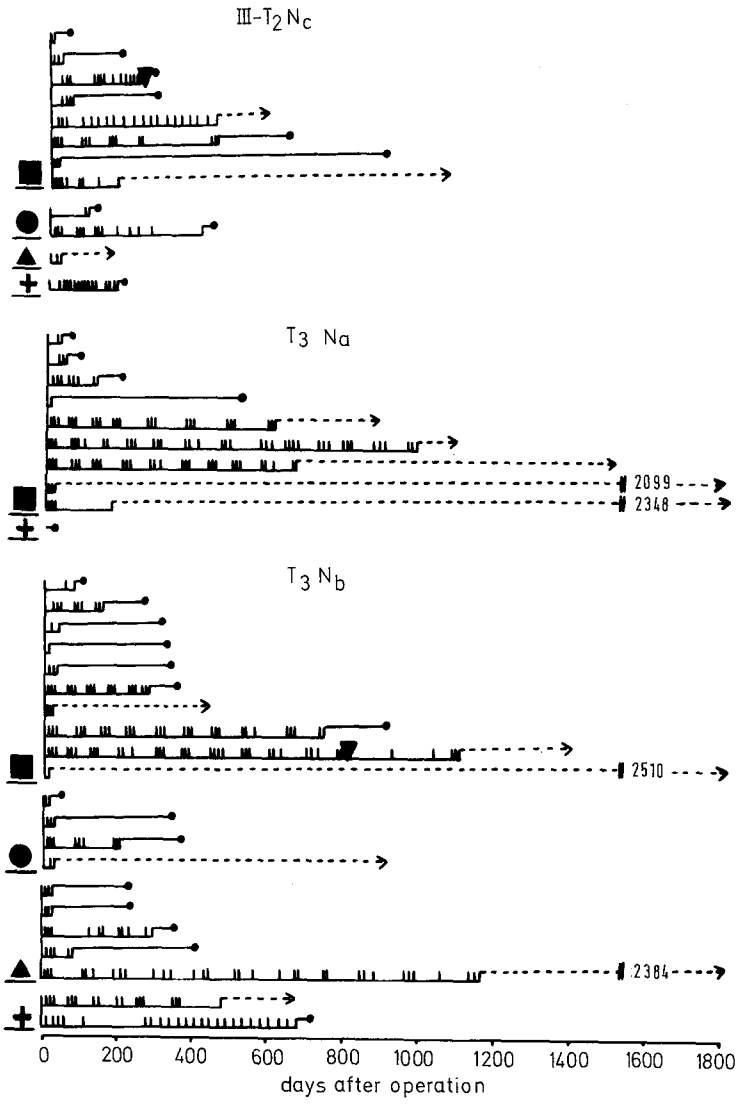

Fig. 4. Observation or survival time with number of infusions administered and length of intervals without treatment for each patient operated on for bronchial carcinoma in stage III – $T_2N_cM_0$, $T_3N_aM_0$, $T_3N_bM_0$

Table 5. Bronchial carcinomas treated by radical surgery but without subsequent chemotherapy, subdivided into TNM stages and classed according to cause of death

	TNM stages				Total
	I	II	III	IV	
Total no. of patients	149	50	53	37	289
Alive	92	15	17	3	127
Died of:					
Postoperative complications	12	2	7	9	30
Tumor	21	15	10	9	55
Cachexia	1	3	1	–	5
Suicide	–	–	–	1	1
Other diseases not connected with the tumor	3	3	5	4	15
Unknown	20	12	13	11	56

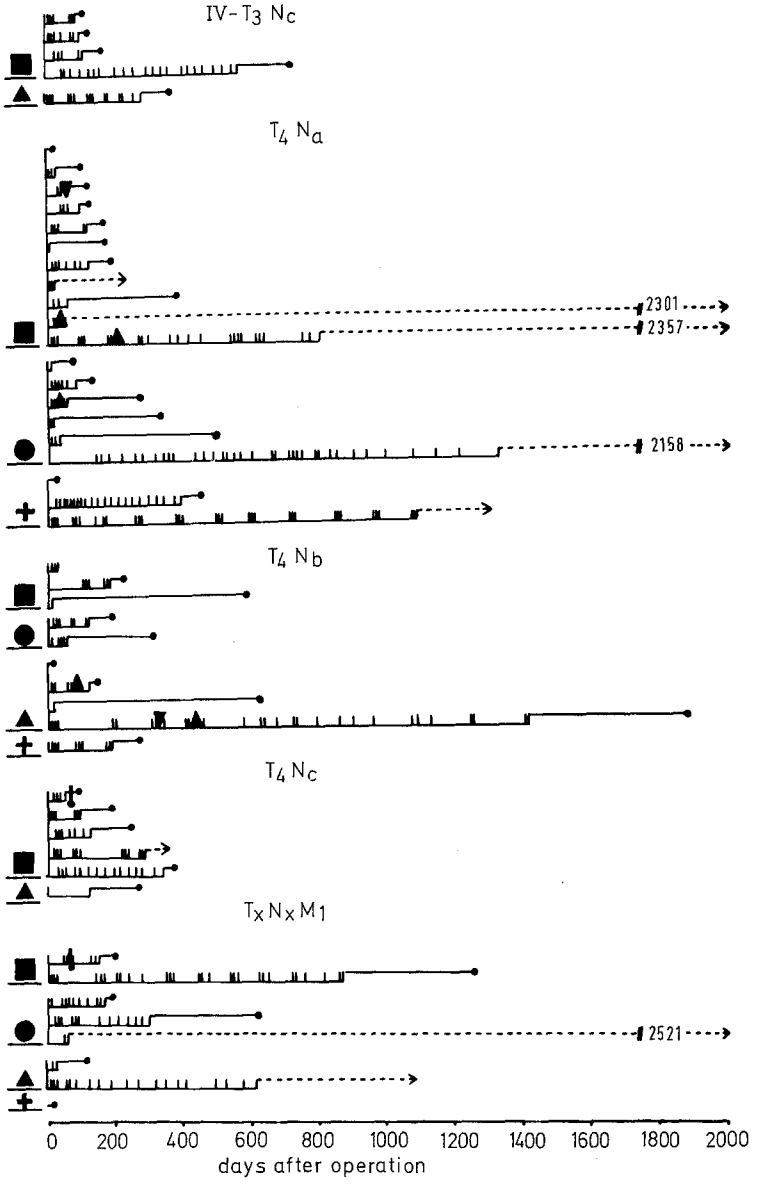

Fig. 5. Observation or survival time with number of infusions administered and length of intervals without treatment for each patient operated on for bronchial carcinoma in stage IV – $T_3N_cM_0$, $T_4N_aM_0$, $T_4N_bM_0$, $T_4N_cM_0$, $T_xN_xM_1$

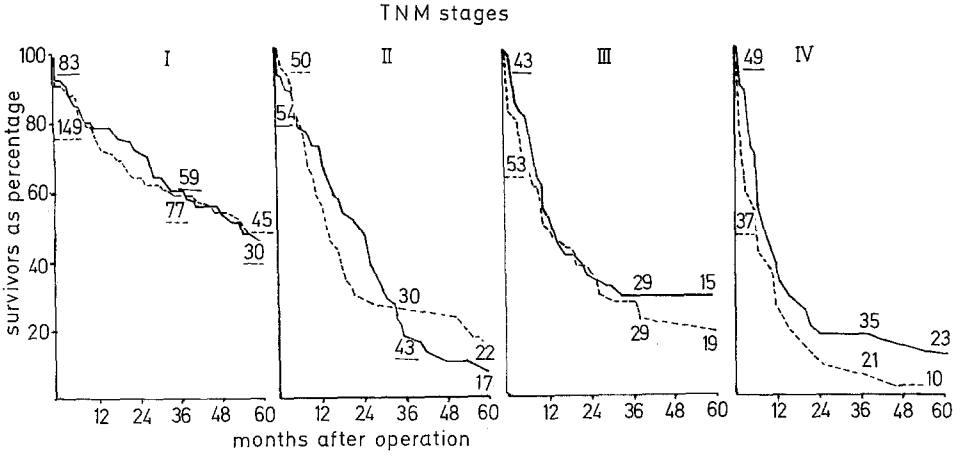

Fig. 6. Comparison of life-tables from patients receiving/not receiving adjuvant chemotherapy after radical surgery for bronchial carcinomas: —— chemotherapy group; – – – randomized controls

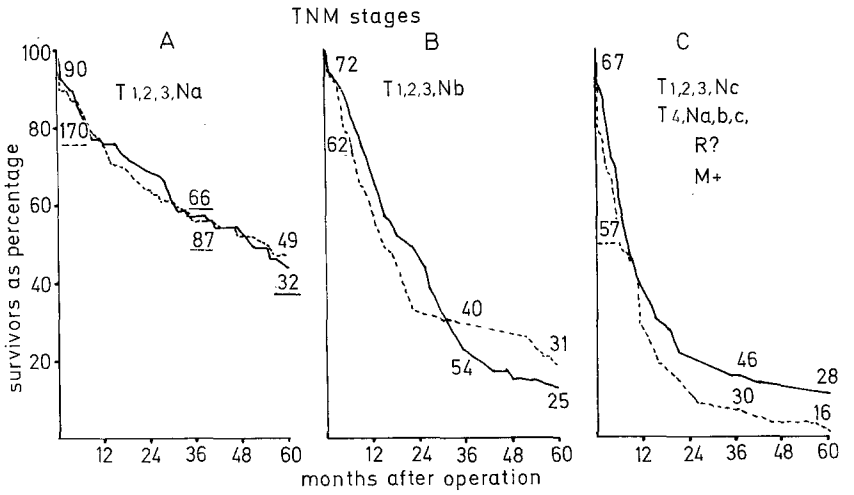

Fig. 7. Comparison of life-tables from patients receiving/not receiving adjuvant chemotherapy after radical surgery for bronchial carcinomas: —— chemotherapy group; – – – randomized controls

Table 6. Numbers of patients operated on 60 months or more ago and numbers and percentages of survivors at 60 months after surgery

Group	Treated			Controls			P value[a]
	Patients	Survivors	%	Patients	Survivors	%	
To Figure 6							
TNM I	30	13	43.3	45	20	44.4	> 0.1
TNM II	17	2	11.8	22	4	18.2	> 0.1
TNM III	15	4	26.7	19	5	26.3	> 0.1
TNM IV	23	5	21.7	10	0	0	> 0.1
To Figure 7							
TNM A	32	15	46.9	49	21	42.9	> 0.1
TNM B	25	4	16.0	31	5	16.1	> 0.1
TNM C	28	5	17.9	16	1	6.3	> 0.1

[a] P value according to the Fisher-test (Fisher, 1969)

Table 7. Numbers of living patients and their median observation time and numbers of deceased patients and their median survival time

Group	Deceased patients					Living patients				
	No. of patients	Median survival time in months before demise		No. of patients	P value[a]	No. of patients	Observation time in months after operation		No. of patients	P value[a]
		Treated	Controls				Treated	Controls		
To Figure 6										
TNM I	38	15	11	58	> 0.1	45	41	28	91	> 0.1
TNM II	43	18	11	35	> 0.1	11	11	15	15	> 0.1
TNM III	28	9	8	36	> 0.1	15	32	20	17	> 0.1
TNM IV	41	6	6	34	> 0.1	8	56	6	3	> 0.1
To Figure 7										
TNM A	41	12	11	69	> 0.1	49	41	28	101	> 0.1
TNM B	54	14	11	43	> 0.1	18	30	17	19	> 0.1
TNM C	55	6	6	50	> 0.1	12	35	6	7	$0.05 > P > 0.01$

[a] P value according to the Wilcoxon-test (Wilcoxon et al., 1969)

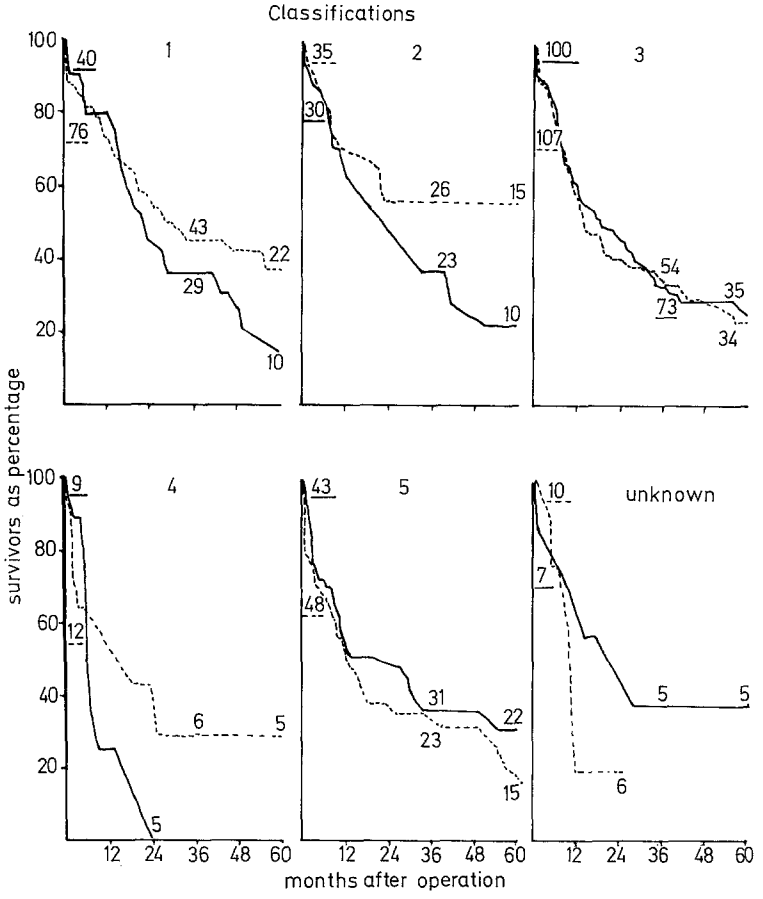

Fig. 8. Comparison of life-tables from patients receiving/not receiving adjuvant chemotherapy after radical surgery for bronchial carcinomas: Feinstein classification 1–5 and the category "unknown" —— chemotherapy group; – – – randomized controls

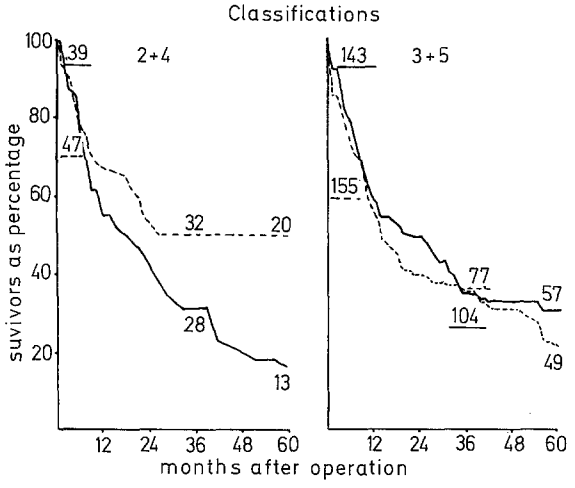

Fig. 9. Comparison of life-tables from patients receiving/not receiving adjuvant chemotherapy after radical surgery for bronchial carcinomas. Feinstein classification: 2 + 4 and 3 + 5 —— chemotherapy group; – – – randomized controls

The steepness of the curves (Figs. 6 and 7) demonstrates that the prognosis worsens with advancing TNM stage. These findings permit no significant statistical difference, but do support a passing tendency of improvement in some of these patients.

Figures 8 and 9 show the survival curves of the groups of the same patients, subdivided into Feinstein categories 1–5 and the 6th category termed "unknown".

As seen in Figure 8, in the first group (Feinstein 1), i.e., in the patients randomly diagnosed as tumor-bearing, no positive trend can be seen in patients who received adjuvant chemotherapy. In the second group (Figs. 8 and 9) (Feinstein 2 and 2 + 4), i.e., that of patients with slow-growing tumors, this therapy seems to decrease the survival rate of the treated group. The third group (Feinstein 3 and 3 + 5), i.e., patients with fast-growing tumors, shows a slightly positive trend favoring the group who received the combined therapy.

This demonstrates that there is a correlation between the Feinstein categories and differences in prognosis and in sensitivity to the chemotherapy given.

As seen in Figures 8 and 9, the slower-growing tumors (Feinstein categories 2 and 4) have a better prognosis than the faster-growing tumors (Feinstein categories 3 and 5). However, the sensitivity to the chemotherapy used shows the opposite.

Figure 10 demonstrates the different effectiveness of this adjuvant chemotherapy on the patients of histo-

Table 8. Numbers of patients operated on 60 months or more ago and numbers and percentages of survivors at 60 months after surgery

Group	Treated			Controls			P value[a]
	Patients	Survivors	%	Patients	Survivors	%	
To Figure 8							
F 1	10	3	30.0	22	4	18.2	> 0.1
F 2	10	3	30.0	15	11	73.3	$0.05 > P > 0.01$
F 3	35	11	31.4	34	9	26.5	> 0.1
F 4	3	0	0	5	1	20.0	> 0.1
F 5	22	5	22.7	15	4	26.7	> 0.1
F unknown	5	2	40.0	4	0	0	> 0.1
To Figure 9							
F 2 + 4	13	3	23.1	20	12	60.0	$0.05 > P > 0.01$
F 3 + 5	57	16	28.1	49	13	26.5	> 0.1

[a] P value according to the Fisher-test

Table 9. Numbers of living patients and their median observation time, and numbers of deceased patients and their median survival time

Group	Deceased patients					Living patients				
	No. of patients	Median survival time in months before demise		No. of patients	P value[a]	No. of patients	Observation time in months after operation		No. of patients	P value[a]
		Treated	Controls				Treated	Controls		
To Figure 8										
F 1	26	16	12	38	> 0.1	14	26	27	38	> 0.1
F 2	22	11	7	16	> 0.1	8	40	67	19	> 0.1
F 3	65	9	8	62	> 0.1	35	41	13	45	$0.01 > P > 0.005$
F 4	7	6	4	7	> 0.1	2	9	15	5	> 0.1
F 5	26	8	8	33	> 0.1	17	36	25	15	$0.1 > P > 0.05$
F unknown	4	12	8	5	> 0.1	3	47	5	5	$0.1 > P > 0.05$
To Figure 9										
F 2 + 4	29	9	7	23	> 0.1	10	37	57	24	> 0.1
F 3 + 5	91	9	8	95	> 0.1	52	41	18	60	$0.001 > P > 0.0001$

[a] P value according to the Wilcoxon-test

logically different groups without regard to TNM staging or Feinstein categories (cf. Tables 10 and 11).

In Figure 11 only those patients are included who underwent radical surgery according to histological evidence, i.e., with no tumor at the cut surface, with (N_+) or without (N_0) tumor cells in the regional lymph nodes and with no evidence of distant metastases.

In the upper row the life-table curves of the group of patients with histologically proven evidence of the absence of any tumor-cell involvement of the regional lymph nodes (N_0) are demonstrated, subdivided according to the three main categories of histology: squamous-cell, adeno-, and all other types of carcinomas. In the lower row the corresponding life-table curves of the group of patients with tumor-cell involvement of the regional lymph nodes (N_+) are shown.

The benefit of combined treatment in patients with oat-cell carcinomas and with the other different histological types ("diverse") of carcinomas can be seen. However, no beneficial effect can be seen in the group of patients with squamous-cell or adenocarcinomas.

Figure 12 depicts the life-table curves of the selected patients in Feinstein categories 3 and 5, i.e., fast-growing tumors, subdivided into TNM stages I, II, III, and IV.

Within the subgroups demonstrated in Figure 12, a tendency for the treatment to be beneficial can be seen

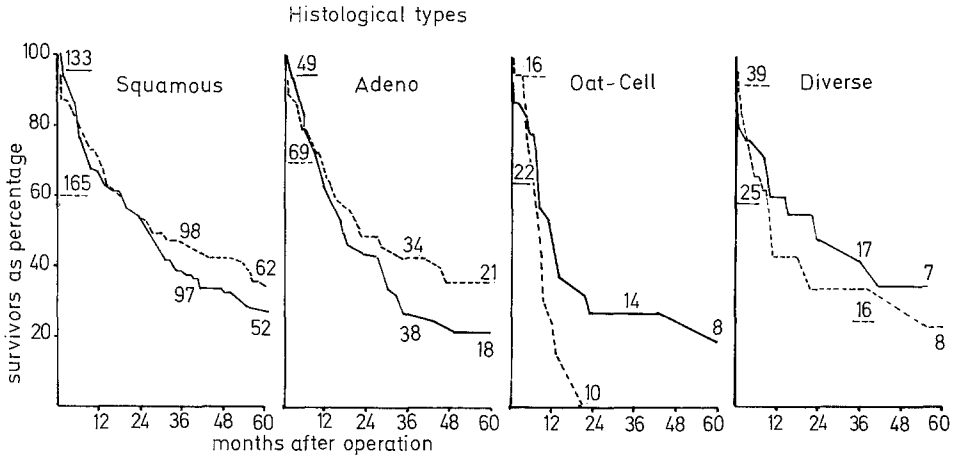

Fig. 10. Comparison of life-tables from patients receiving/not receiving adjuvant chemotherapy after radical surgery for bronchial carcinomas: Histological types: —— chemotherapy group; – – – randomized controls

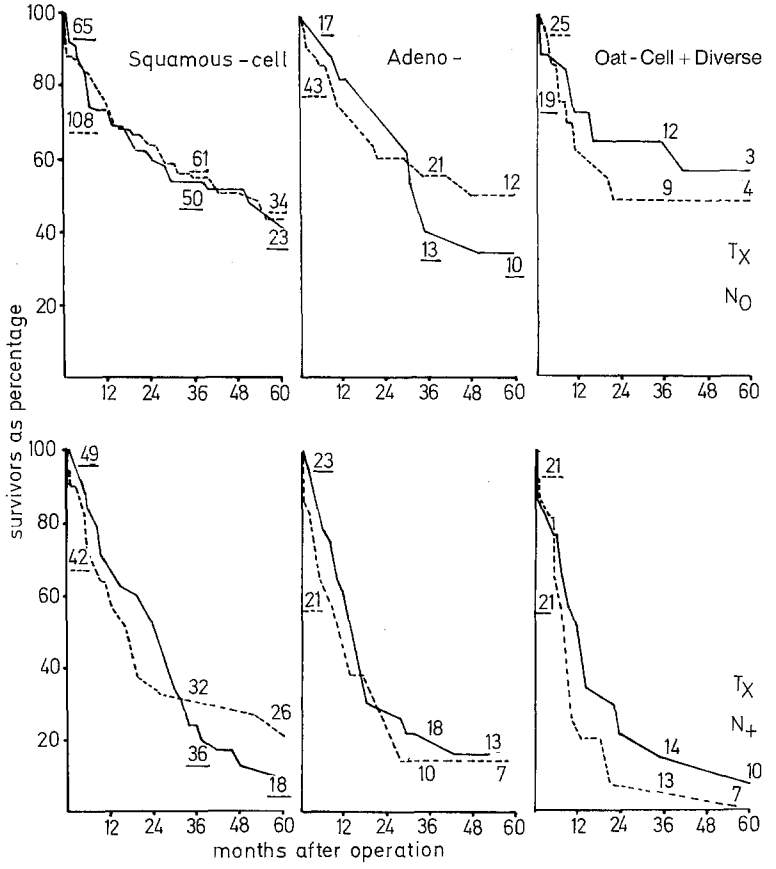

Fig. 11. Comparison of life-tables from patients receiving/not receiving adjuvant chemotherapy after radical surgery for bronchial carcinomas, subdivided by histological type and according to N_0 or N_+: —— chemotherapy group; – – – randomized controls

in all stages. Figure 13 shows the same patients as in Figure 12, but subdivided into the three histological main groups. See also Tables 12 and 13.

It is of interest that there seems to be a positive tendency, even in the groups with squamous-cell carcinomas. The subdivision of the squamous-cell carcinomas by degree of histological differentiation expressed by the presence or absence of keratinization results in an apparent difference between these two groups. The group with keratinization shows a more favorable prognosis, whereas it shows a lower sensitivity to the chemotherapy used.

Table 10. Numbers of patients operated on 60 months or more ago and numbers and percentages of survivors at 60 months after surgery

Group	Treated			Controls			P value[a]
	Patients	Survivors	%	Patients	Survivors	%	
To Figure 10							
Squamous-cell	52	16	30.8	62	23	37.1	> 0.1
Adeno	18	5	27.8	21	4	19.0	> 0.1
Oat-cell	8	3	37.5	5	0	0	> 0.1
Diverse	7	0	0	8	2	25.0	> 0.1
To Figure 11							
T_xN_0 Squamous-cell	23	12	52.2	34	15	44.1	> 0.1
Adeno	10	4	40.0	12	4	33.3	> 0.1
Oat-cell + Diverse	3	1	33.3	4	2	50.0	> 0.1
T_xN_+ Squamous-cell	18	3	16.7	26	8	30.8	> 0.1
Adeno	5	0	0	7	0	0	> 0.1
Oat-cell + Diverse	10	2	20.0	7	0	0	> 0.1

[a] P value according to the Fisher-test

Table 11. Numbers of living patients and their median observation time and numbers of deceased patients and their median survival time

Group	Deceased patients					Living patients				
	No. of patients	Median survival time in months before demise		No. of patients	P value[a]	No. of patients	Observation time in months after surgery		No. of patients	P value[a]
		Treated	Controls				Treated	Controls		
To Figure 10										
Squamous-cell	83	10	11	93	> 0.1	50	38	33	72	> 0.1
Adeno	37	12	9	34	> 0.1	12	54	21	35	$0.005 > P > 0.001$
Oat-cell	16	8	9	14	> 0.1	6	39	6	2	> 0.1
Diverse	14	8	6	21	> 0.1	11	29	8	18	$0.05 > P > 0.01$
To Figure 11										
T_xN_0 Squamous-cell	32	8	12	50	> 0.1	33	40	33	58	> 0.1
T_xN_0 Adeno	10	23	9	16	$0.05 > P > 0.01$	7	64	24	27	$0.05 > P > 0.01$
T_xN_0 Oat-cell + Diverse	7	9	5	9	> 0.1	12	38	8	16	$0.05 > P > 0.01$
T_xN_+ Squamous-cell	36	20	14	31	> 0.1	13	13	33	11	> 0.1
T_xN_+ Adeno	19	12	7	14	> 0.1	4	46	9	7	$0.1 > P > 0.05$
T_xN_+ Oat-cell + Diverse	17	9	8	19	> 0.1	4	17	11	2	> 0.1

[a] P value according to the Wilcoxon-test

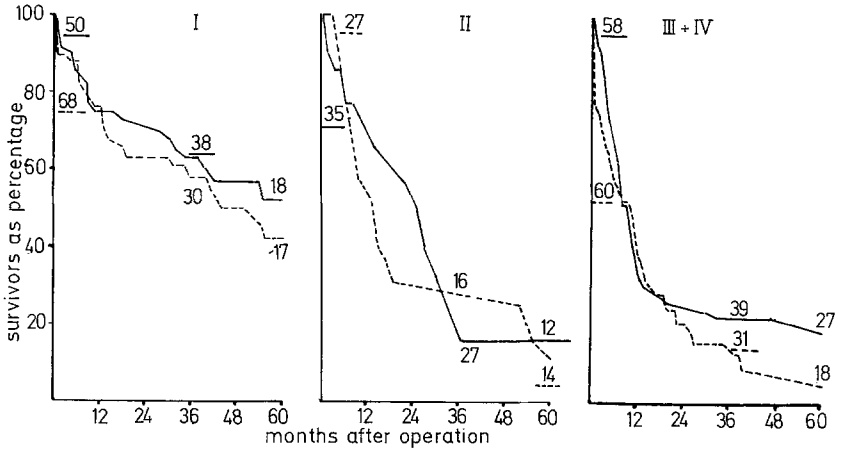

Fig. 12. Comparison of life-tables from patients receiving/not receiving adjuvant chemotherapy after radical surgery for bronchial carcinomas. Feinstein categories 3 and 5, subdivided into TNM stages: —— chemotherapy; – – – randomized controls

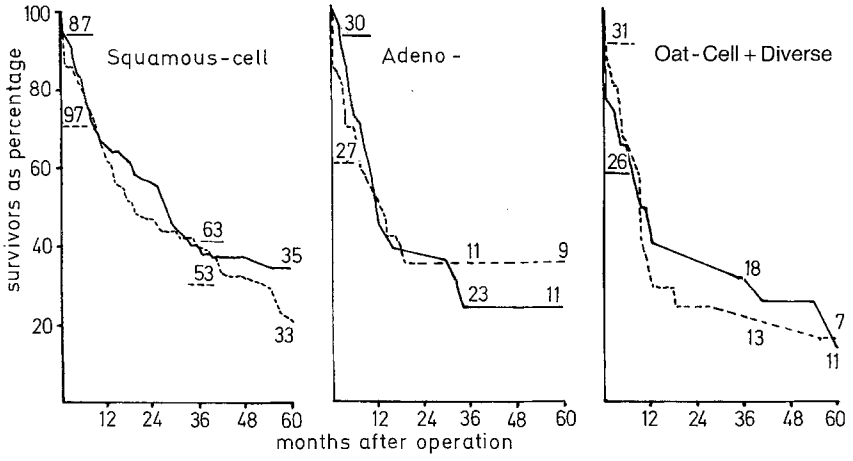

Fig. 13. Comparison of life-tables from patients receiving/not receiving adjuvant chemotherapy after radical surgery for bronchial carcinomas. Feinstein categories 3 and 5, subdivided into histological types: —— chemotherapy; – – – randomized controls

Table 12. Numbers of patients operated on 60 months or more ago and numbers and percentages of survivors at 60 months after surgery

Group	Treated			Controls			*P* value[a]
	Patients	Survivors	%	Patients	Survivors	%	
To Figure 12							
TNM I	18	9	50.0	17	8	47.1	> 0.1
TNM II	12	1	8.3	14	3	21.4	> 0.1
TNM III + IV	27	6	22.2	18	2	11.1	> 0.1
To Figure 13							
Squamous-cell	35	12	34.3	33	8	24.2	> 0.1
Adeno	11	2	18.2	9	3	33.3	> 0.1
Oat-cell + Diverse	11	2	18.2	7	2	28.6	> 0.1

[a] *P* value according to the Fisher-test

Table 13. Numbers of living patients and their median observation time and numbers of deceased patients and their median survival time

Group	Deceased patients					Living patients				
	No. of patients	Median survival time in months before demise		No. of patients	P value[a]	No. of patients	Observation time in months after operation		No. of patients	P value[a]
		Treated	Controls				Treated	Controls		
To Figure 12										
TNM I	21	9	10	27	> 0.1	29	42	21	41	$> 0.01 > P > 0.005$
TNM II	26	21	12	20	> 0.1	9	22	6	7	> 0.1
TNM III + IV	44	7	7	48	> 0.1	14	35	14	12	> 0.1
To Figure 13										
Squamous-cell	50	9	12	60	> 0.1	37	38	21	37	> 0.1
Adeno	22	10	4	14	$> 0.1 > P > 0.05$	8	51	8	13	$> 0.05 > P > 0.01$
Oat-cell + Diverse	19	7	8	21	> 0.1	7	36	14	10	> 0.1

[a] P value according to the Wilcoxon-test

Conclusion

The adjuvant chemotherapy described was well tolerated. In some cases the therapy was discontinued for other reasons, mostly because patients in Austria are not informed of their diagnosis.

This preliminary evaluation of combined treatment certainly encourages the continuation of this kind of study. Considering the variety of prognostic factors and the types of tumors involved, including differences in the sensitivity to a given drug combination and/or dose, it might become necessary and/or advantageous to select various other therapeutic agents, which act as specifically as possible on the different kinds of tumors. The results shown seem to support the hypothesis that the dose schedule used was not adequate for slow-growing tumors and for squamous-cell and adenocarcinomas.

Therefore, it seems advantageous to change the dose schedule or the combination of drugs used for the adjuvant treatment for this group of tumors. This does not necessarily mean that the dose used is optimal for faster-growing tumors.

The tendencies observable in the results of this pilot study suggest more promising findings from and the necessity of further protocols of larger cooperative international groups.

References

Arnal, M. L., Dold, U., Ehlers, C. Th., Gögler, E., Hamperl, H., Karrer, K., Oberhofer, G., Ott, G., Pascher, W., Proppe, A., Scheibe, O., Schmolling, E., Spiessl, B., Thurmayer, R., Wildner, E. P.: Zur Klassifizierung der Geschwulstkrankheiten. Der „gesicherte" TNM-Schlüssel (Erweiterungsvorschlag zu den „General Rules" der UICC). Meth. Inform. Med. **6,** 70 (1967)

Feinstein, A. R.: Symptomatic patterns, biologic behavior and prognosis in cancer of the lung. Ann. intern. Med. **61,** 27 (1964)

Fisher, R. A.: Fishers exakter Vierfeldertest. In: Statistische Auswertungsmethoden. Sachs, L., (Ed.), p. 365. Berlin-Heidelberg-New York: Springer 1969

Karrer, K., Denck, H.: Weitere Vorschläge zur chemotherapeutischen Rezidivprophylaxe des Bronchuskarzinoms. Wien. med. Wschr. **17,** 121 (1971)

Kreyberg, L., Liebon, A. A., Uehlinger, E. A.: International histological classification of tumors. 1. Histological Typing of Lung Tumors. Geneva: WHO 1967

Wilcoxon, F., Mann, H. B., Whitney, D. R.: U-Test. In: Statistische Auswertungsmethoden. Sachs, L. (Ed.), p. 293. Berlin-Heidelberg-New York: Springer 1969

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