

## A 10 year follow-up of semi-annual screening for early detection of lung cancer in the Erfurt County, GDR

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**ABSTRACT:** A prospective and controlled study for early detection of lung cancer in the county of Erfurt with a follow-up of 10 years is presented. A collective of 41,532 males born between 1907 and 1932 was screened by chest fluorography at 6 month intervals and compared with a control group consisting of 102,348 males of the same age, who were screened at intervals of about 18 months. No significant reduction of overall mortality and of lung cancer mortality was achieved. Semi-annual screening brought about a higher detection rate (9%/6.5%), an increase in the resection rate (28%/19%) and higher 5 and 10 year survival rates (52%; 27%/39%; 19%) of resected patients than screening in 18 month intervals. Among those patients who refused resection or were surgically untreatable, the difference in survival rates between the two investigation groups lasted only up to the 12 months barrier. This is regarded as the effect of the lead-time bias. Fluorographic screening is effective only in patients with peripheral cancers. Patients resected for central lung cancers did not show differences in the survival rates. In both investigation groups considered together surgical therapy was possible mainly in those patients who had been detected by screening (resection rate: 48%; 5 yr survival rate: 26.9%). The resection rate of all the others amounted to 9%, the 5 yr survival rate to 1.4%. Therefore we consider fluorography to time as the only chance for lung cancer control of high risk groups in spite of the absence of reduction of lung cancer mortality.

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Lung cancer is the most frequent malignant neoplasm in the male population in most industrial nations and a challenge to physicians and medical science. Primary prevention, *i.e.* non-smoking and health education, has met with very limited success so far. Considering the limited therapeutical possibilities, efforts for early detection are the logical medical and health-political measures. Most previous investigations have shown that screening programs for lung cancer are ineffective. However, recent experiences and analysis of earlier results threw doubts upon their relevance [1].

Improved conditions in technique and management led to new investigations of the same problem. Prospective studies of the value of screening of high-risk individuals were begun in the United States [2-8] in 1972. At about the same time we started a controlled prospective study with the goal of determining the efficacy of fluorographic screening at semi-annual intervals as compared to screening performed at intervals of 1-2 years. The results of this study, with a follow-up of 10 years, are presented here.

### Patients

The male population of the Erfurt county, a political and economic region with about 1 million inhabitants,

was the object of investigation. Epidemiological studies revealed similar consumption of cigarettes per head of population, similar smoking habits and comparable economical structure in the 14 districts of the Erfurt county. All males, who lived in the district towns of Erfurt, Weimar, Gotha and Eisenach (40 to 65 years) on 31 December 1971 and were born between 1907 and 1932-41, 532 males underwent semi-annual chest fluorography in the years 1972-1977. All males of the same age, who lived on 31 December 1971 in the other 10 districts of the Erfurt county - 102,348 males - formed the control group. Control individuals underwent chest fluorography at intervals of 1-2 years. At that time annual fluorography of all male and female persons older than 15 years was on a statutory footing. Thus, there were prerequisites to start the investigation with equal conditions of prevalence for study and control districts. A retrospective analysis of lung cancer incidences of the years 1963 and 1968 revealed comparable numbers in the planned study and control districts [9, 10].

### Methods

Chest fluorographs were interpreted by a team of specialists. All suspected cases, no matter by what method they had been detected, were diagnosed and treated in

the Central Clinical for Heart and Lung Diseases, Bad Berka. Clinical follow-up was also performed there. The histological classification was made according to WHO Geneva 1967 [11] and was under the responsibility of Dr. Haenselt, a renowned specialist. He also determined the localization of the tumour on the resected lung. For differentiation between peripheral and central tumours we used the definition by WALTER and PRYCE [12]. Staging was performed according to the pTNM classification of Deutsche AG Bronchialkarzinom 1968/UICC 1968 [13]. Information on those who died, and on patients who could not be transported, was gathered from the district pulmonologists or oncologists, to whom we are indebted for their active cooperation.

### Statistics

The results have been combined in two- or three-dimensional contingency tables. In case of refusal of the hypothesis of independence between 2 or 3 factors, we tested the details. The decision concerning the significance was performed by comparing the calculated 2 I-values with the  $(1-\alpha)$  quantile of the  $\chi^2$  distribution with corresponding degrees of freedom  $\chi^2$  (df;  $1-\alpha$ ). In the life tables we calculated the probabilities by actual estimation. We compared two life tables using the log rank test according to PETO and PIKE [14]. The significance criterion was  $\chi^2(1;0.99)=6.64$  or  $\chi^2(1;0.95)=3.84$ .

I am much obliged to Dr. E. Lüdde for the mathematical statistical calculations.

Table 1. — Deaths and drop outs of the study

Deaths and drop outs	Study population	Control population
Males at start	n=41,532	n=102,348
Cause of loss		
Deaths	3,143 (12.6%)	8,038 (13.1%)
movers and refusers	1,492	5,011
Final number of living males 1977	36,897	89,299

### Results

During the on-going study from 1972 to 1977 3,142 males out of the study population died (see table 1). Among the control subjects 8,038 died in the same time. That means a mortality of 12.6% per year in the study group and of 13.1% per year in the control population. There is no statistical difference. Table 1 shows still more dropouts, people who moved from the area or who refused medical control: 1,492 in the study group and 5,011 in the control group. The lung cancer mortality amounted to 0.6% (control group) and to 0.8% (study group) per year during 1972–1977. There was no statistical difference.

During the 6 years of input, 374 (9%) of lung cancers were detected in the study collective. In 104 (28%) patients resection was performed. The number of detected lung cancers among the controls amounted to 667 cases, *i.e.* 6.5%. There were 125 (19%) patients surgically treated. The differences are statistically significant, both for detection rate and for resection rate (see table 2). In the study collective 47% of patients were detected by screening, 45% due to clinical findings. In the control collective the relations were 27% and 66% respectively. The frequencies of lung cancer detected at autopsy were 3 and 4 per cent respectively.

Table 2 illustrates the detected and surgically treated patients with lung cancer in the different age cohorts. It is significant that screening at short intervals will lead to a greater number of detections, in particular within the younger age groups (the percentage of more detection in the younger cohorts against the 3 older cohorts is significant at  $4.39 > \chi^2(1;0.95)=3.84$ ). In parallel to this, we found that the resection rate was remarkably higher in the younger patients, but not significantly higher in the older cohorts. There was also no difference in the post-operative mortality between study (2.9%) and control (4.0%).

If the methods of detection having become active in the two groups are checked (see table 3), then it is shown that the X-ray picture detected 27% of all lung cancer patients in the control districts; in case of the semi-annual screening 47% were detected in this way.

66% of the patients of the controls were diagnosed by means of symptoms. The share of the patients detected in such a manner in the study group amounted to 45%.

Table 2. — Distribution of patients detected and resected for lung cancer during the progress of the study in 1972 to 1977 among age cohorts per 10,000 in each group per year

Age cohorts born in	Study districts		Control districts		Resection rates	
	detected per 10,000	resected per 10,000	detected per 10,000	resected per 10,000	2 I	$\chi^2(1;0.99)$
1928 to 1932	3.4	1.6	2.1	0.6	19.0	6.64
1923 to 1927	7.1	3.5	4.5	0.8	112.6	6.64
1918 to 1922	16.0	4.2	8.3	1.8	7.7	6.64
1913 to 1917	17.8	6.4	16.6	3.5	94.1	6.64
1908 to 1912	31.4	6.5	22.2	3.9	7.8	6.64
1907	25.4	2.9	25.2	2.7	0.7	6.64

2 I=1 202.47  $> \chi^2(16;0.99)=32.0$ . The postoperative mortality amounted 2.9 per cent in study group and 4 percent in the control group.

Table 3. - Distribution of patients detected and resected for lung cancer among the different modes of detection

mode of detection	Study districts				Control districts			
	detected		resected		detected		resected	
	n	%	n	%	n	%	n	%
by screening	175	47	89	86	182	27	81	65
by symptoms	169	45	12	11	440	66	36	29
occasional	10	3	1	1	14	2	4	3
by control of healthy people with known lesions	5	1	2	2	11	2	4	3
by autopsy	15	4	-	-	20	3	-	-
	374	100	104*	100	667	100	125*	100
Prevalence cases:								
1972								
1st screening:	32		6		68		10	
2nd screening:	22		10		-		-	

2 I=279.52 >  $\chi^2$  (13;0.99)=6.64; \*: resection rate: 2 I=11.5 >  $\chi^2$  (1;0.99)=6.64.

Table 4. - Patterns of pTNM stages (Deutsche AG Bronchialkarzinom/ UICC 1968) see HERMANEK and GALL [13]

pTNM stages	study population	control population
T <sub>1</sub> NaMo	33	34
T <sub>1</sub> NbMo	5	2
T <sub>2</sub> NaMo	32	34
T <sub>2</sub> NbMo	11	9
	81	79
T <sub>3</sub> NaMo	11	21
T <sub>3</sub> NbMo	4	13
T <sub>1</sub> NcMo	1	1
T <sub>2</sub> NcMo	2	5
T <sub>3</sub> NcMo	3	4
T <sub>4</sub> Na-bMo	2	2
	23	46

2 I=5.91 >  $\chi^2$ (1;0.95)=3.84

The percentage of incidentally detected persons and the lung cancers detected during the autopsy corresponded with each other in both groups. If the detection methods of the resected patients of the two groups are compared, then 65% of the surgically treated patients of the control group were discovered by means of X-ray screening in an interval of 18 months. There were 86% in the study group that had been detected through semi-annual X-ray screening. Only 11.5% of the resected patients of the study group had been clinically detected. This share amounted to 29% in the control group. Neglecting the difference of screening intervals of both groups there are 357 out of 966 lung cancer patients (without autopsy cases), who had been detected by fluorography. 649 patients had been detected by symptoms or other occasions. The corresponding resection rates were 48% against 9% (170 : 59 patients).

The distribution of stages in both collectives are shown in table 4. Twenty three patients (22%) of the study group who have been surgically treated were classified in stage III but from the resected patients of the controls 46 (37%) had stage III cancers. The difference is significant (2 I=5.91 >  $\chi^2$  (1,0.95)=3.84).

Table 5 demonstrates the histological type patterns. Real differences between the two collectives are found only in the frequency of adenocarcinomas, together with the bronchioloalveolar cancers: 28% in the study group and 21% in the control group. The tumour localization of the resected cancers is shown in table 6. There were no statistically significant differences between the two groups.

Table 5. - Histological classification of resected tumours (WHO 1967)

	Study group		Control group	
	n	%	n	%
Squamous cell carcinoma	53	51	64	51
Adenocarcinoma	27	26	21	17
Bronchiolo-alveolar cell carcinoma	2	2	6	5
Small cell carcinoma	14	13	21	17
Large cell carcinoma	8	8	10	8
Mixed type	-	-	3	2
$\Sigma$	104	100	125	100

2 I=7.74 <  $\chi^2$ (5;0.95)=11.1.

Table 6. - Localization of resected tumours

Localization of tumours	Study group		Control group	
	n	%	n	%
central	35	34	51	41
peripheral	57	55	64	51
intermediate	12	11	10	8
$\Sigma$	104	100	125	100

2 I=1.65 <  $\chi^2$ (2;0.95)=5.99.

The analysis of life tables of all patients with lung cancer detected during 1972 to 1977 shows a significant difference between the two collectives of investigation. Over the whole time of follow-up we find a survival difference of statistical significance ( $T=9.1 > \chi^2(1;0.99)=6.64$ ) (see table 7). To clarify the causes of this effect we differentiated between surgically treated and untreated patients. Fig. 1 shows the life tables of tumour resected patients of both groups. In the follow-up of 10 years a parallel course of both curves becomes discernible, with a significant difference of  $>10\%$  ( $T=3.9 > \chi^2(1;0.95)=3.84$ ).

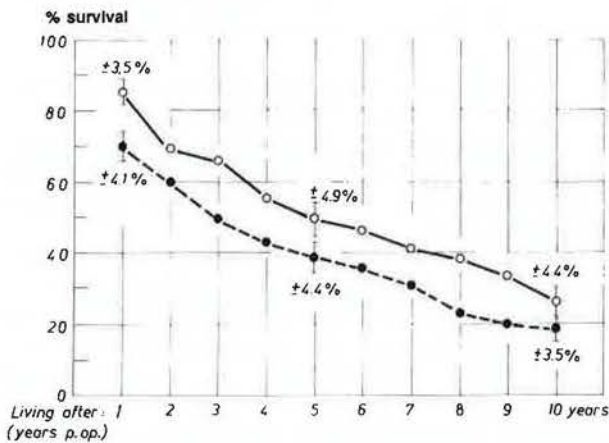
Fig. 2 depicts the life tables of surgically untreated patients of the same groups. During the first year of follow-up there is a declining difference of survival of about 15–10%. After the first year there is a similar course of both curves. There is no significant difference ( $T=0.8 < \chi^2(1;0.95)=3.84$ ).

As a rule, fluorography is only adapted to early detection of peripheral cancers. Therefore, we analysed separately the chances of survival of patients with central and with peripheral tumours. For central cancers there was no difference between the survival rates of resected

Table 7. – Life table of all patients with lung cancer detected during 1972 to 1977

Living after: years p. diagn.:	1	2	3	4	5	6	7	8	9	10
<i>Study group</i>										
L	374	165	90	74	59	54	49	44	40	35
D	209	75	16	15	5	5	5	4	5	7
P%	44	24	20	16	14	13	12	11	9	7.5
%SE(P <sub>n</sub> )	2.6	2.2	2.1	1.9	1.8	1.7	1.7	1.6	1.5	1.4
<i>Control group</i>										
L	667	178	107	76	62	51	47	40	30	26
D	489	71	31	14	11	4	7	10	4	1
P%	27	16	11	9	8	7	6	4.5	4	4
%SE(P <sub>n</sub> )	1.7	1.4	1.2	1.1	1.0	1.0	0.9	0.8	0.8	0.7

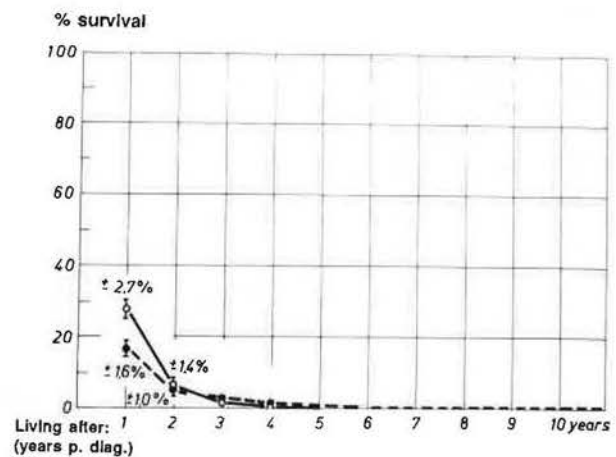
In the study group  $n=374$  and in the control group  $n=667$  (according to Peto and Pike 1973). Result of log rank test:  $T=9.1 > \chi^2(1;0.99)=6.64$ . L: living patients in the beginning of the year; D: deceased patients on the end of the year; P%: probability (in percent) of survival; %SE(P<sub>n</sub>): standard error in percent.



<i>Study group</i>										
L	104	88	73	70	58	54	49	44	40	35
D	15	16	7	12	4	5	5	4	5	7
P%	86	70	67	56	52	47	42	39	34	27
%SE(P <sub>n</sub> )	3.5	4.5	4.6	4.9	4.9	4.9	4.8	4.8	4.6	4.4

<i>Control group</i>										
L	125	88	75	62	54	49	45	39	29	25
D	37	13	13	8	5	4	6	10	4	1
P%	70	60	50	43	39	36	31	23	20	19
%SE(P <sub>n</sub> )	4.1	4.4	4.5	4.4	4.4	4.3	4.1	3.8	3.6	3.5

Fig. 1. – Surgically treated patients. Life tables of study group ( $n=104$ ) and of control group ( $n=125$ ). L: living patients in the beginning of the year; D: dead patients at the end of the year; P%: probability (in percent) of survival; %SE(P<sub>n</sub>): standard error in percent.



<i>Study group</i>										
L	270	76	17	4	1	0	0	0	0	0
D	194	59	13	3	1	0	0	0	0	0
P%	28.1	6.3	1.5	0.4	0	0	0	0	0	0
%SE(P <sub>n</sub> )	2.7	1.4	0.7	0.4	0.3					

<i>Control group</i>										
L	542	90	32	14	8	2	2	1	1	1
D	452	58	18	6	6	0	1	0	0	0
P%	16.6	5.9	2.6	1.5	0.4	0.4	0.2	0.2	0.2	0.2
%SE(P <sub>n</sub> )	1.6	1.0	0.7	0.5	0.3	0.3	0.2	0.2	0.2	0.2

Fig. 2. – Life tables of surgically untreated patients of study group ( $n=270$ ) and control group ( $n=542$ ). According to Peto and Pike 1973). See legend to figure 1.

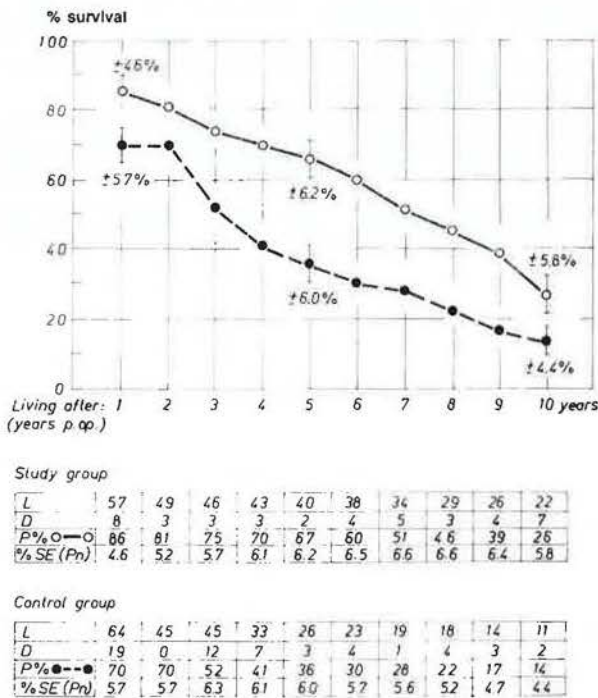


Fig. 3. - Life tables of peripheral tumour patients of study group (n=57) and control group (n=64). According to Peto and Pike 1973. See legend to figure 1.

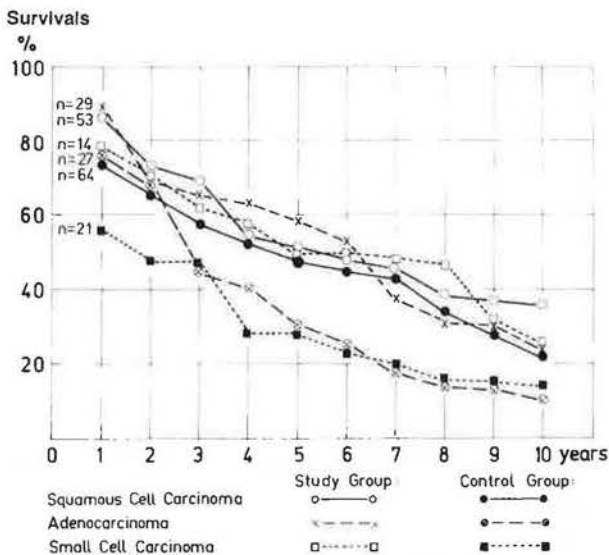


Fig. 4. - Prospective study of Erfurt county 1972-1977, follow-up 10 yrs. Life table of resected patients according to histological types, without large cell carcinomas.

patients of the study and the control population. The same result was obtained in the few cases of intermediate cancers. Fig. 3 reflects the life tables of patients resected for peripheral lung cancers. The significant difference of survival curves ( $T=6.3 > \chi^2(1;0.95)=3.84$ ) is demonstrable

at 5 year survival rates of 67% in the study group and 36% in the control group. The 10 year survival rates are 26% and 14%. The life tables of patients of both groups who were not surgically treated we differentiated also among the localization. The results were similar to those shown in fig. 2. The difference in the first time after diagnosis lasted for maximal 12 months.

The differentiation of survival rates according to the histological types is shown in fig. 4. The survival chances in cases of squamous carcinoma do not differ in the two collectives, but there are remarkable differences between the small cell cancers and the adenocarcinomas from the two groups. The small numbers, however, do not allow mathematically significant results with the log rank test.

### Discussion

The goal of the Erfurt study was to compare the effectiveness of semi-annual fluorographic screening as against an interval of 1-2 years. Cytological screening, tested in 1974 and 1975, had been stopped due to ineffectiveness and high expense [15]. In 1971 all males from study districts as well as from control districts above an age of fifteen years had been called for an obligatory mass screening in 1972, which was attended by approximately 80%. Therefore, initial screening in 1972 did not yield a higher number of detected cases, (see table 3), and our yields in this point are not comparable with that of the lung cancer projects of the National Cancer Institute [2-9].

The results of our study after a follow-up of 10 years lead to the following conclusions:

1. No significant decrease of overall mortality and of lung cancer mortality could be achieved by screening in short intervals.
2. A significantly higher number of lung cancers were detected in semi-annual fluorography.
3. The resection rate in the group of semi-annually screened patients was 28% and significantly higher than that of patients who were screened at intervals of about 18 months (19%).
4. The 5 and 10 year survival rates of patients of both groups were significantly different over the whole time of follow-up. But the separated analysis of resected and of surgically untreated patients showed different curves of survival rates over the whole time of follow-up only for the surgically treated patients of both collectives. The surgically untreated patients of study participants and of controls had different survival rates only in the first 12 months. This difference is considered to be due to lead time bias.
5. There was no significant difference in the patterns of histological types, so we could not find any argument for a length-time bias.
6. By the analysis of life tables of restricted patients with special regard to the localization of tumour we found a significant difference of life tables of individuals with peripheral cancers between both groups but not between patients resected for central cancers.

The lack of control of lung cancer mortality, which is in agreement with earlier literature [1], was surprising to

us. In the analysis of details we found a higher number of detected lung cancers in the screened group with short intervals, and also an increase in the resection rate as well as in the 5 and 10 year survival rates. But all that did not cause a decrease in lung cancer mortality. The higher number of detected lung cancers, also observed in the Mayo Lung Project [16] and in a Japanese study [17], as well as in the study of KUBIK and POLAK [18], leads to speculations. The suspected figure of non-detected lung cancers obviously is so high that a considerable number of patients will die due to either a false diagnosis or a concurrent sickness. HEASMAN and LIPWORTH [19] and others [20, 21] found a false negative diagnosis of lung cancer in up to 30 per cent of the cases. The rate of autopsy in our population amounted to 50 per cent. The figures of lung cancer patients primarily detected in autopsy did not differ for the two groups.

The postsurgical stage patterns of our patients demonstrate that screening in 6 month intervals leads to a high rate of stage I and stage II. Similar relations were found by others [16, 18].

The patterns of histological types among resected patients in both groups differ only in the incidence of adenocarcinomas. SAXÉN and HAKAMA [22] and VEEZE [23] pointed out that reducing the screening intervals will increase the number of tumours with short doubling time. We could not give any proof of this. In the study group we found a higher percentage of adenocarcinomas, interpreted as slowly growing tumours but with early dissemination and, therefore, with high grade of malignancy [13, 24-29]. Among our patients those with adenocarcinomas had the best prognosis. We consider this as a result of continuous screening, that has been practised in our country for a long time. In this way small coin lesions will be detected before they have metastasized.

Comparing the life tables of the two groups according to histological types of lung cancer, it becomes apparent that the survival rates of patients with adenocarcinomas as well as with small cell carcinomas out of the study group take their course through the whole time of follow-up 15 to 20 per cent above the survival curve of the control group (there is no significance for the small number of cases).

No such difference was found for squamous cell carcinomas; this type is in about 75 per cent localized in the central bronchi and there is not as much early metastasizing as in the other types. This fact corresponds to the observation that central lung cancers have no support for cure by a fluorographic screening in short intervals. Sputum cytological examinations represent an adapted but expensive method for early detection of central squamous cell cancers, as could be proved by recent studies of National Cancer Institute [3-8].

Figure 3 underlines that patients with peripheral lung cancers take most benefit from fluorographic screening. This fact was also stated in the conclusions of the NCI cooperative early lung cancer detection program [8]. The important matter, however, is that those people who will be found with a malignant lesion take the chance of a surgical therapy without delay. This group alone demonstrates the superiority of screening in short intervals

against longer periods. KUBIK and POLAK [18] hold the view that there is no difference in the effectiveness of screening between a semi-annual and a 3-year interval. KRECKLOW B. and KRECKLOW K. [30], however, observed by epidemiological investigations a clear shifting to a greater proportion of advanced tumour stages and a decrease of resection rates from 22.1 to 15.7 per cent during 15 years, when the interval of fluorographic screening of population changed from 12 to 24 months by a statutory footing.

The resection rates in the Erfurt study are remarkably lower than in other studies [1]. In particular, we had a resection quota of 51 (study group) and 48 (control group) per cent in the cases, detected by fluorography. These numbers are of the same magnitude as X-ray detected cases of recent studies [4, 16, 18]. The interval cases, that were detected by symptoms or special chances, influenced the results of our study. They amounted to 48 per cent in the study group and 68 per cent in the control group, and the corresponding resection rates come up to 9%. These percentages demonstrate the small chance for curing the patients detected by symptoms or special occasions.

Considering the chance of patients who were detected by symptoms - only 1.4% survived 5 years - we can recommend only in the interest of the individual patients, that in all male smokers, having consumed more than 200,000 cigarettes during their life, annual fluorography should be done, and if there is also an occupational risk and/or familial disposition, semi-annual screening seems to be indicated [31]. Without a regular control of high-risk persons there is no ingenious approach to initial lung cancers [4]. Primary prevention is a social mission that must be pushed on, but secondary prevention should not be neglected.

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*Suivi à 10 ans d'un dépistage semestriel pour la détection précoce du cancer du poumon dans le Comté d'Erfurt, GDR. J. Wilde.*

RÉSUMÉ: Présentation d'une étude prospective et contrôlée pour la détection précoce du cancer du poumon dans le Comté d'Erfurt, avec un suivi de 10 ans. Un collectif de 41.532 hommes nés entre 1907 et 1932, a fait l'objet d'un dépistage radiophotographique semestriel, et comparé à un groupe contrôle constitué de 102.348 hommes du même âge, qui furent examinés à des intervalles d'environ 18 mois. L'on n'a observé aucune réduction significative de la mortalité globale ou spécifique au cancer du poumon. Le dépistage semestriel a entraîné un taux de détection plus élevé (9% vs 6.5%), une augmentation du taux de résection (28% vs 19%), et des taux de survie plus élevés à 5 et à 10 ans (52% vs 27%; 39% vs 19%) chez les patients réséqués, que le dépistage à intervalles de 18 mois. Parmi les patients qui ont refusé la résection ou constituaient des contre-indications chirurgicales, les différences de taux de survie entre les deux groupes ne persistaient que pendant 12 mois. Ceci est considéré comme la conséquence de biais "lead-time". Le dépistage radio-photographique n'est efficace que chez les patients atteints de tumeurs périphériques. Les patients réséqués pour cancer central du poumon n'ont aucune différence dans les taux de survie. Si l'on considère les deux groupes ensemble, le traitement chirurgical a été possible principalement chez les patients détectés par dépistage (taux de résectabilité: 48%; taux de survie à 5 ans: 26.6%). Le taux de résection de tous les autres cancer s'élève à 9%, et le taux de survie à 5 ans à 1.5%. En prenant ce facteur en considération, la radio-photographie à intervalles nous paraît la seule chance pour le contrôle du cancer du poumon dans les groupes à haut risque, et ce malgré l'absence de réduction de la mortalité par cancer du poumon. *Eur Respir J.*, 1989, 2, 656–662.