Papers and Originals

South London Lung Cancer Study*

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Introduction

Bronchial carcinoma kills more people than any other cancer in England and Wales. In 1966 carcinoma of lung, bronchus, pleura, and trachea (International Nos. 162 and 163) caused the death of 22,610 men—a proportion of 386 per 1,000 total male cancer deaths (967 per 1,000,000 living males). Each year the deaths continue to increase (Annual Report of Chief Medical Officer of Ministry of Health, 1966).

Survival rates are very poor: for men in England and Wales perhaps 1,400 of each year's victims live five years. The situation today is no better than when Barrett (1958) wrote: "The present position is summarized as follows: the average span of life between the first symptom and death is about one year; of this short time three to four months elapse before a diagnosis is made, and two more before a surgeon is consulted. When the patients are first seen by a surgeon 80% are judged to be inoperable and to them there is nothing but palliation to offer. The prognosis for all cases is that 5% will live for five years from the day the disease is diagnosed."

In southern England in 1961 4,190 males with this disease were registered at the South Metropolitan Cancer Registry (in part of whose area the present study was conducted). Only 6% of these men were alive three years later.

Present Study

Against this background of increasing mortality and poor prognosis the South London Lung Cancer Study was undertaken. It was a serial routine six-monthly chest survey by photofluorography from January 1959 to June 1963 on male volunteers aged over 45. The questions to be answered by such a survey have been discussed elsewhere (Nash, 1958).

Organization and Procedure.—The S.E. and S.W. London Mass *X*-ray Services offered six-monthly chest radiography to all men over 45 years of age (except those referred by general practitioners) who attended the units during the radiological phase of the study (from 1 January 1959 to 30 June 1963). The aims of the routine were explained in a leaflet at each man's first examination. The procedure was entirely voluntary. Six months after his latest attendance each man was sent a new appointment and a simple questionary. Examinees with findings suspicious of neoplasm were referred to chest clinics or thoracic outpatient departments for further investigation.

Records.—Three types of record were kept: (1) one master card was prepared for each man. It recorded the results of every examination during the period of the study. At each examination the answers to the questionary were coded and entered on the same card. (2) Ministry of Health standard mass radiography cards were issued on every attendance. (3) From documents (1) and (2) a data card was punched every time a man was examined.

Examinees.—A total of 67,400 master cards were issued, this being the number of men aged over 45 who attended at least once from 1 January 1959 to 30 June 1963. Of these 55,100 lived inside the South Metropolitan Cancer Registry area, while 12,300 lived outside the area. Altogether 264,900 Ministry of Health cards were issued and the same number of data cards

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TABLE I.—*Analysis of Repeat Examinations According to Age and Smoking Habits With Yield of Primary Lung Cancer*

	All Cigarette Smokers	Cigarette Amounts (per day)									Pipe	Pipe & Cigs.	Other	Not Known	Non-Smoker*	Total
		1–4	5–9	10–14	15–19	20–24	25–29	30–39	40+	Not Known						
Age 45–54:																
Examinations	72,038	3,042	7,749	19,919	11,955	18,122	4,273	4,333	1,527	1,118	10,962	3,631	984	1,419	33,823	122,857
Cases found	25	1	2	2	2	9	4	3	2	0	3	0	0	1	3	32
Rate/1,000 examinations	0·3	0·3	0·3	0·1	0·2	0·5	0·9	0·7	1·3	—	0·3	—	—	0·1	0·09	0·3
Age 55–64:																
Examinations	36,584	1,892	5,296	11,331	5,303	8,419	1,664	1,534	617	528	6,569	2,048	552	2,313	16,884	64,950
Cases found	65	2	11	13	11	16	3	5	4	0	6	3	2	1	7	84
Rate/1,000 examinations	1·8	1·1	2·1	1·1	2·1	1·9	1·8	3·3	6·5	—	0·9	1·5	3·6	0·4	0·4	1·3
Age 65+:																
Examinations	4,291	416	892	1,404	479	793	90	126	19	72	1,401	362	135	267	3,237	9,693
Cases found	21	1	3	6	2	6	1	1	0	1	4	0	0	0	6	31
Rate/1,000 examinations	4·9	2·4	3·4	4·3	4·2	7·6	11·0	8·0	—	(14·0)	2·9	—	—	—	1·9	3·2
Total																
examinations	112,913	5,350	13,937	32,654	17,737	27,334	6,027	5,993	2,163	1,718	18,932	6,041	1,671	3,999	53,944	197,500
Total cases	111	4	16	21	15	31	8	9	6	1	13	3	2	2	16	147
Rate/1,000 examinations	1·0	0·7	1·1	0·6	0·8	1·1	1·3	1·5	2·8	0·6	0·7	0·5	1·2	0·5	0·3	0·7

* Includes ex-smokers

punched—that is, there was a total of 264,900 attendances for examination. Of these 67,400 were first visits and 197,500 were repeat examinations. Table I shows an analysis of the *repeat* attendances by age and smoking habits (made from the questionary filled in each time a man attended). Over 80% of repeat examinations were made at an interval of 32 weeks or less.

Primary Cancer of Lung Discovered by Repeat Examination

It should be noted that the first *repeat* examination occurs at an examinee's second visit. From 197,500 repeat examinations conducted during the survey period 147 cases of primary lung cancer were discovered. The principal ground for confirmation of each diagnosis is given in Table II. The discovery rate per 1,000 repeat examinations is 0.7—that is, about 1.4 per 1,000 man-years surveillance.

TABLE II.—*Principal Ground for Confirmation of Each Diagnosis of Primary Lung Cancer in 147 Cases Picked up by Six-monthly Routine Repeat Radiography*

	Cases	4-Year Survivors
Operation { Resection	83	39
Operation { Thoracotomy	20	—
Post-mortem examination { Micro	6	1
Post-mortem examination { Macro	3	—
Bronchoscopic biopsy	12	—
Sputum	5	—
Biopsy of neck glands { Definite	2	—
Biopsy of neck glands { Probable	0	—
Biopsy—other { Definite	4	—
Biopsy—other { Probable	0	—
Radiological and clinical	8	—
Radiological only	4	—
Clinical only	0	—
Total	147	40

Table I shows how the discovery rate increases tenfold with age and almost as much by the number of cigarettes smoked. A much more striking picture results when the effects of variations in age and amounts smoked are combined (see Chart).

Treatment

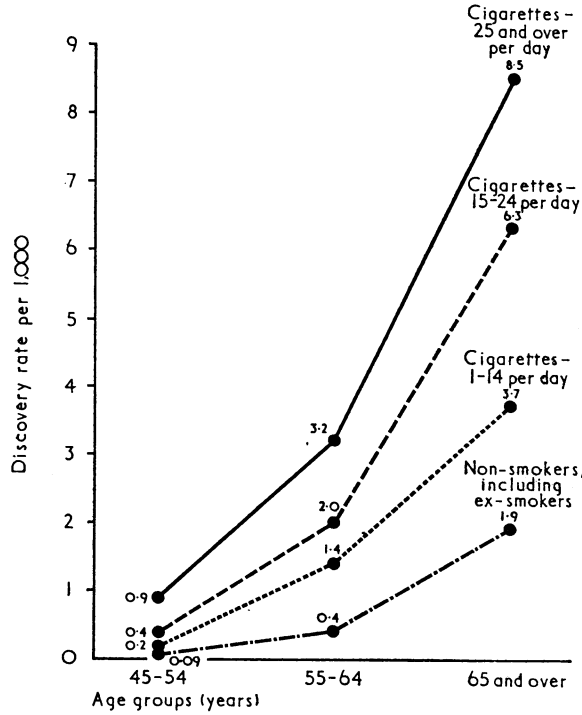
The average time from "pick-up" film to lobectomy or pneumonectomy was 13 weeks, the most common duration being five weeks, and the range varied between one week and two and a half years. These times, of course, include the interval necessary to make the diagnosis. Table III shows by histology and by age groups the resectability and survival of 147 cases of primary lung cancer picked up by six-monthly routine repeat radiography. Of 147 cases 83 (56%) were resected. Of those aged 45 to 54 and of those aged 55 to 64 the proportion resected was 60%. Of 31 men aged over 65 13 were resected.

The proportion resected varied with some cell types—15 out of 18 with adenocarcinoma and 75% of all squamous-celled growth were resected. In anaplastic, undifferentiated, and oat-cell growth taken together 43% (19 out of 44) were resected.

Survival

As four years have passed since the last case in the radiographic phase of the study was discovered, survival figures for this minimum period are now available. No case discovered by serial radiography has been lost during the follow-up.

Of 147 confirmed cases of bronchial carcinoma picked up at routine six-monthly radiography 40 (27%) survived four years or longer. Survival has been measured from the date of radical treatment, or, if no radical treatment was undertaken, from the date of diagnosis at hospital.



Yield of primary lung cancer at repeat examinations according to age and number of cigarettes smoked.

TABLE III.—*Histology By Age Groups Showing Resectability And Survival of 147 Cases of Primary Lung Cancer Picked Up By Six-monthly Routine Repeat Radiography*

Cell Types	Age 45–54				Age 55–64				Age 65+				Total								
													Resected Cases		Not Resected Cases		Total Cases		4-Year Survivors		
	Resected	Not Resected	Total	4-Year Survivors	Resected	Not Resected	Total	4-Year Survivors	Resected	Not Resected	Total	4-Year Survivors	No.	%	No.	%	No.	%	Cases	% of Cell Type Surviving	% of Total Survivors
Adeno-carcinoma	2	0	2	1	12	2	14	9	1	1	2	0	15	18	3	5	18	12	10	55	25
Anaplastic	0	1	1	0	3	3	6	0	0	1	1	0	3	4	5	8	8	6	0	—	—
Oat cell	5	6	11	0	4	5	9	1	1	0	1	0	10	12	11	17	21	14	1	5	(2·5)
Squamous	8	0	8	1	28	9	37	17	10	6	16	8*	46	55	15	24	61	42	26*	43	65
Undifferen-tiated	3	1	4	1	2	7	9	1	1	1	2	0	6	7	9	14	15	10	2	19	5
Miscellaneous and not known	1	5	6	0	2	7	9	1	0	9	9	0	3	4	21	32	24	16	1	4	(2·5)
Total	19	13	32	3	51	33	84	29	13	18	31	8*	83	100	64	100	147	100	40*	27	100

* Includes one case not resected.

Factors Affecting Survival

Histology.—The most favourable histologies for survival are in the squamous and adenocarcinomatous groups (Table III): 43% of those with squamous-celled histology lived at least four years, and 10 out of 18 with adenocarcinoma lived at least four years. Results for other cell types are depressing.

Age.—The prognosis improves with age. There was no evidence to suggest that men aged 45 to 54 were helped to survive by six-monthly radiography: 3 (9%) out of 32 lived four years. Of men aged 55 to 64 29 (35%) out of 84 were alive after four years. Of 31 men aged 65 and over eight were alive four years later.

Resectability.—Survival without resection was rare. Only one man out of 64 without resective surgery was alive at four years, and he died within five years of discovery. Of 83 men who underwent resection 39 (47%) were alive four years later. Survival in the age group 45 to 54 after resection was bad; only 3 out of 19 were alive four years after operation. Men aged 55 to 64 fared much better: 29 (57%) out of 51 were alive four years later. Though men aged 65 and over had a lower resection rate (42%) than younger men, 7 out of 13 who were resected were alive four years after operation. The four-year survival after resection was 56% (36 out of 64) in men over 55.

Presence or Absence of "New Chest Trouble."—Of 142 men who answered the questionary at the time of their pick-up examination 38 said they had new chest trouble. Only 6 (16%) of the 38 were alive at four years. Of 104 who said they had no new chest trouble 34 (33%) were alive at four years (see Table IV).

TABLE IV.—*Analysis of Answers to "Have You Had Any New Chest Trouble Recently?" on Pick-up Questionary for 147 Men With Primary Lung Cancer Found by Six-monthly Routine Repeat Radiography.*

Answer to Questionary	Interval From Previous Film						Total All Intervals		
	28 Weeks or Less			Over 28 Weeks					
	Cases	4-Year Survivors		Cases	4-Year Survivors		Cases	4-Year Survivors	
		No.	%		No.	%		No.	%
Yes	25	6	24	13	0	—	38	6	16
No	64	24	38	40	10	25	104	34	33
Not answered	1	0	—	4	0	—	5	0	—
Total ..	90	30	33	57	10	18	147	40	27

Interval Between Routine Examinations.—Of 90 men with primary bronchial neoplasm who had their discovery film taken not more than 28 weeks after a previous satisfactory one, 30 (33%) were alive four years after treatment. Of 57 cases picked up on a routine film taken more than 28 weeks after a previous satisfactory film, only 10 (18%) were alive four years after treatment. The proportions in different histological types in these longer and shorter examination interval groups do not explain this difference in survival.

Effect of Early Diagnosis on Short-term Survival.—Six-monthly radiography, by bringing to light cases of lung cancer in a presymptomatic or preclinical stage, produces an early recognition effect. This might improve the observed short-term survival prospects without altering the eventual prognosis. Some idea of the magnitude of such an effect can be found by comparing the mean survival period of 98 general-practitioner referred cases[1] and 42 cases picked up by six-monthly routine radiography, none of either group of patients having undergone surgery and all of whom died less than four years after radiological diagnosis. The mean survival for the general-practitioner referred patients was 36 weeks. For the 42 patients found by six-monthly radiography who had no surgery the mean survival was 53 weeks. From this comparison the "precognition effect" would seem to be only about four months.

Though 40 men out of 147 picked up by six-monthly routine repeat radiography lived at least four years 71% of the remaining 107 who died lived less than one year. In fact, the most common survival period of the fatal cases was six months.

[1] A series not containing any of the volunteer population for six-monthly radiography.

Effects of Combinations of Above Factors on Survival

Prognosis After Resection in Relation to Interval Between Mass X-ray Examinations.—Though the interval between examinations has but a small effect on the proportion resectable, the survival of men over 55 *after resection* was strikingly related to the interval between the previous satisfactory film and the pick-up film as shown in Table V. In the group of men whose cancer was picked up at an interval between 24 and 28 weeks after a film passed as normal 76% (25 out of 33) were alive at least four years after resection. Only 6 (32%) out of 19 men whose cancer was picked up 29 to 52 weeks after a film passed as normal were alive four years or more after resection. An exact test on these percentages shows that their difference is significant at a level where P lies between 1/400 and 1/500—that is, P (one tail) = 0.00225. To the surgeon perhaps the most encouraging part of the present study is the finding that the prognosis in the cases he will resect can be improved by ensuring that the interval between routine films is six months or less.

TABLE V.—*Fate After Resection of 64 Men Aged 55 and Over, Showing Relation of Survival to Interval Between Ultimate and Penultimate Miniature Films*

Interval From Previous Miniature Film	Alive 4 Years After Surgery	Dead
23 weeks and under	2	2
24–28 weeks	25	8
29–52 weeks	6	13
53 weeks and over	3	5

Prognosis in Relation to Interval Between Examinations and Presence of "New Chest Trouble."—Of the 38 men who said they had new chest trouble 25 were picked up at an examination 28 weeks or less after a previously satisfactory film and six of them were alive four years later. Of the remaining 13 picked up at an interval of 29 weeks or more after a previously satisfactory film there were no four-year survivors.

Prognosis in Relation to Age and Histological Type.—The combined proportion of undifferentiated, oat-celled, and anaplastic histologies reported in our series is highest in the youngest age group. These cell types together account for half the cancers in the 45 to 54 age group, for 29% in the 55 to 64 age group, and for only 12% in the men aged 65 and over. Squamous cell histology was reported in 25% of men aged 45 to 54, but in 44% and 52% of the two older age groups. This distribution may partly account for the poor survival in the youngest age group.

Cost of Survival

The cost effectiveness of selective six-monthly serial routine radiography for the production of long-term survivors can be examined. An analysis of the cost and number of *x*-ray examinations required to "produce" a four-year survivor is given in Table VI. It shows that the number of examinations required per four-year survivor falls dramatically as the number of cigarettes smoked per day increases (column 6). Column 7 shows the cost of finding a potential four-year survivor at a unit operating expenditure of £30 per hundred miniature examinations. A four-year survivor aged 55 or over may be salvaged for as little as £180 in heavy smokers.

TABLE VI.—*Cost Per Four-year Survivor According to Smoking Habits and Age*

Age Group	1 Examinations	2 Cases of Primary Lung Cancer	3 4-Year Survivors	4 No. of Films per 4-Year Survivors	Middle and Old Age Groups Only: 5 4-Year Survivors	6 No. of Films per Survivor	7 Cost per Survivor at £30 per 100 Films
Non-smokers 45-54	33,823	3	—	>33,800			
Non-smokers 55-64	16,884	7	3	5,600	6	3,300	£990
Non-smokers 65+	3,237	6	3	1,100			
1-14 cigarettes per day 45-54	30,710	5	—	>30,700			
1-14 cigarettes per day 55-64	18,519	26	7	2,600	9	2,400	£720
1-14 cigarettes per day 65+	2,712	10	2	1,400			
15-24 cigarettes per day 45-54	30,077	11	1	30,100			
15-24 cigarettes per day 55-64	13,722	27	10	1,400	12	1,200	£360
15-24 cigarettes per day 65+	1,272	8	2	650			
25+ cigarettes per day 45-54	10,133	9	2	5,100			
25+ cigarettes per day 55-64	3,815	12	7	500	7	600	£180
25+ cigarettes per day 65+	235	2	—	>200			
Other and not known	32,361	21	3	10,800			
Total	197,500	147	40	4,900			

The data in Table VI allow a calculation to be made of the expected output of survivors from a mass radiography unit practising selective radiography based on age and smoking habits. Thus a unit with an output of 50,000 examinations per annum could, if working with examinees aged over 55 who smoked 15 or more cigarettes daily, be expected to produce 50 four-year survivors as a result of one year's work. The output of survivors, if heavy smokers only were examined, could be expected to be still higher.

An Incomplete Picture

The cases found by mass radiography are a part only of the whole population or set of lung cancers occurring in co-operating volunteers. It is necessary to answer the following questions:

(1) What proportion of all cases of lung cancer becoming manifest in the co-operating volunteers will be either (*a*) found at the six-monthly routine *x*-ray examinations or (*b*) fall ill and be found by clinical means independently of the routine mass radiography service and between these repeat examinations? The cases in (*a*) we call "pick-up cases" and the cases in (*b*) "intersurvey clinical fall-out cases." Cases type (*a*) and (*b*) occur only in co-operating volunteers.

(2) What was the survival prospect of the pick-up cases and the intersurvey clinical fall-out cases considered as a complete (global) set of carcinomata occurring in co-operating volunteers?

Definition.—The set or globality of primary lung cancers in co-operators consists of all such cancers discovered at routine repeat mass radiography at an interval not exceeding 40 weeks from a previous satisfactory film, together with all intersurvey clinical fall-out cases medically referred to a clinic or hospital within 40 weeks[2] of a "normal" repeat film and including all cases so referred in the period January 1959 up to 40 weeks after the end of the radiographic phase of the study, which was 31 June 1963—that is, to April 1964.

A man with bronchial carcinoma is regarded as an intersurvey clinical fall-out case if his cancer, though not found by mass radiography, produces an illness which causes him to be referred to hospital or clinic (or for a chest *x*-ray examination) within 40 weeks of a satisfactory routine film in the study survey, or if, though not attending hospital within 40 weeks of a satisfactory film, he could be ascertained to have been prevented by his cancerous illness from attending his unkept next appointment for routine repeat chest film.

(3) What evidence is there that mass radiography is doing any more than creaming off the patients with slow-growing tumours who would be curable, irrespective of whether they were found before clinical presentation—that is, by mass radiography or when clinically mature? If this creaming off (or selection) of curable cases is found to occur is its magnitude sufficient to account completely for the apparently good results obtained?

What follows is an account of a search for the intersurvey clinical fall-out cases. These and the pick-up cases will together provide a series with its case fatality rate unaffected by factors accompanying selection due to case-finding technique.

Without the new facility of cancer registration this task would be very difficult, particularly in the tracing of unknown survivors from bronchial carcinoma. (Deaths are relatively easy to trace through several agencies.) Therefore *the rest of this study is confined to the 41,800 residents (and their cancers) in the South Metropolitan Cancer Registry area who attended for at least one repeat examination.* The age composition of these men was in the same proportion as all examinees given in Table I.

Means by which Unfound Cases were Traced

Using Cancer Registry Records

The South Metropolitan Cancer Registry index was used to find whether any registered cases of primary lung cancer had had a chest *x*-ray examination during the period of the South London Lung Cancer Study—that is, between January 1959 and June 1963.

A Complete Survival or Death Follow-up

To safeguard against possible omissions in cancer registration a survival follow-up of all volunteers was carried out, firstly by direct contact with each examinee or his firm to establish whether he was alive at June 1964. All not so traced were sought through the National Health Service executive councils and the Registrar General's Office, including the Cancer Registration Section at Titchfield and the registers of deaths at Somerset House, London.

Out of 41,800 men aged over 45, resident originally in the South Metropolitan Cancer Registry area, who had at least one repeat examination during the study, 99.5% have been traced either as alive at June 1964 or later, or as dead, with date and certified cause of death. The number untraced is only 203, which includes 41 untraced emigrants. The 162 non-emigrants, though untraced, can be inferred to have the following attributes: (1) they are not in the index of the South Metropolitan Cancer Registry; (2) *they were not registered as being dead* from any cause under their own names at the Registrar General's Office at Somerset House; and (3) *if* they had lung cancer they could be assumed to be alive at June 1964, having moved outside the area of the South Metropolitan Cancer Registry.

Global Picture

The methods of search discovered 87 intersurvey clinical fall-out cases of primary lung cancer. These 87 cases, together with the 110 cases which had been picked up at a routine mass

[2] That is, six months to next appointment plus three months' grace before classification as a defaulter.

x-ray examination not more than 40 weeks after a previous satisfactory film, form the global set of 197 primary bronchial carcinoma cases in the 41,800 co-operating volunteers resident in the South Metropolitan Cancer Registry area. So far as the 99.5% follow-up was able to ascertain, this constitutes a set of lung cancers clinically or radiologically consecutive and complete. Firmest grounds for confirmation of the diagnosis of lung cancer in this global set are given in Table VII. Six-monthly radiography picked up 56% of the global set. The proportion therefore that it failed to find was 44%.

TABLE VII.—*Principal Ground for Confirmation of Each Diagnosis of Primary Lung Cancer in Global Set of Cases in Volunteers Resident in South Metropolitan Cancer Registry Area*

Grounds for Diagnosis	Pick-up Cases		Intersurvey Clinical Fall-out Cases	
	No.	Survivors At 4 Years	No.	Survivors At 4 Years
Operation { Resection	59	29	18	4
Operation { Thoracotomy	15	—	9	—
Post-mortem examination { Micro	4	1	15	—
Post-mortem examination { Macro	2	—	8	—
Bronchoscopic biopsy	12	—	10	—
Sputum	4	—	2	—
Biopsy of neck glands { Definite	2	—	2	—
Biopsy of neck glands { Probable	0	—	1	—
Biopsy—other { Definite	3	—	3	—
Biopsy—other { Probable	0	—	1	—
Radiological and clinical	7	—	15	—
Radiological only	2	—	1	—
Clinical only	0	—	2	1
Total	110	30	87	5

Table VIII gives the age distribution, histology, and four-year survival of the global set. It shows that of 87 intersurvey clinical fall-out cases only 5 (6%) lived four years or more. Of the 110 pick-up cases 30 (27%) lived four years or more. The effect of adding these two groups together is to give a set of 197 cancers with a global four-year survival of 18% (35 men).

We may now examine the hypothesis that mass radiography obtains its comparatively favourable prognosis by "creaming off" or selecting a disproportionate number of curable cases from a large population of cancers with the usual case fatality rate of 94 or 95%. If under this hypothesis the 35 global survivors were assumed to represent, say, 6% of a global population of cancers the set would contain about 600 members. But the global set ("pick-ups" plus "intersurvey clinical fall-outs") contains only 197 members—that is, one-third of the estimated number. This failure of the estimated global set to coincide with that which existed renders the "creaming off" hypothesis untenable.

Global Survival and Experience in Region

Table IX shows the age and cell type distribution of the total recorded cases of primary lung cancer (4,190) in the South Metropolitan Cancer Registry area for 1961—the central year of the South London study period. It also gives *three-year* survival figures for the regional cases. A comparison of this Table with the data at the right-hand side of Table VIII shows that the age and histological composition in the mass radiography global set and the regional set differ.

Age.—No evidence was found that mass radiography at six-monthly intervals helped to improve the prognosis of men in the youngest age group: only 8% (4 out of 48) of men aged 45 to 54 lived four years or more (see Table VIII). In men aged 55 to 64 the *four-year* survival of the mass radiography volunteers, 20% (24 out of 118), is very much better than the *three-year* survival of 8% experienced by this age group in the region. Of the 31 men aged 65 and over 7 (23%) lived at least four years. The numbers are too small to form the basis of a conclusion about the value of the procedure for this group, but the results are encouraging when compared with a regional survival figure for this age group of 3%. However, the regional group of men aged 65 and over contained a higher proportion of very old men.

Histology.—The survival for the group containing together the anaplastic oat-cell and undifferentiated growths is the same in the mass radiography global set as for this histological set of lung cancers in the whole Cancer Registry area. It would therefore seem that these cell types progressed too quickly for six-monthly radiography to improve their prognosis. Squamous-cell growths, however, carried a survival figure of 31%, which

TABLE VIII.—*Histology and Survival of Global Set of Primary Lung Cancers in Volunteers Resident in South Metropolitan Cancer Registry Area*

Histology	Pick-up Cases in Age Groups									Intersurvey Clinical Fall-out Cases in Age Groups									Globality (Pick-up and Intersurvey Clinical Fall-out Cases)								
	45–54		55–64		65+		Total			45–54		55–64		65+		Total			45–54			55–64			65+			Total		
	Cases	4-Year Survivors	Cases	4-Year Survivors	Cases	4-Year Survivors	Cases No.	Cases %	4-Year Survivors	Cases	4-Year Survivors	Cases	4-Year Survivors	Cases	4-Year Survivors	Cases No.	Cases %	4-Year Survivors	Cases No.	Cases %	4-Year Survivors	Cases No.	Cases %	4-Year Survivors	Cases No.	Cases %	4-Year Survivors	Cases No.	Cases %	4-Year Survivors
Adenocarcinoma	1	1	10	6	2	0	13	12	7	2	0	1	0	1	0	4	5	0	3	6	1	11	9	6	3	10	0	17	9	7
Anaplastic, oat, and undifferentiated	12	1	20	2	2	0	34	31	3	8	0	18	0	2	1	28	32	1	20	42	1	38	33	2	4	13	1	62	31	4
Squamous	7	1	29	12	11	6	47	43	19	8	1	13	2	3	0	24	28	3	15	31	2	42	35	14	14	45	6	71	36	22
Miscellaneous and not known	5	0	5	1	6	0	16	14	1	5	0	22	1	4	0	31	35	1	10	21	0	27	23	2	10	32	0	47	24	2
Total	25	3	64	21	21	6	110	100	30	23	1	54	3	10	1	87	100	5	48	100	4	118	100	24	31	100	7	197	100	35

TABLE IX.—*Total Cases of Primary Lung Cancer for* 1961 *Registered at South Metropolitan Cancer Registry. Age and Histology with Three-year Survival*

Histology	Age 45–54			Age 55–64			Age 65+			Total		
	Cases	3-Year Survivors		Cases	3-Year Survivors		Cases	3-Year Survivors		Cases	3-Year Survivors	
		No.	%		No.	%		No.	%		No.	%
Adenocarcinoma	53	7	13	80	4	5	52	2	4	185	13	7
Anaplastic, oat cells	159	10	6	362	21	6	269	7	3	790	38	5
Squamous	176	39	22	391	71	18	341	31	9	908	141	16
Miscellaneous or not verified	273	16	6	738	27	4	1,296	23	2	2,307	66	3
Total	661	72	11	1,571	123	8	1,958	63	3	4,190	258	6

is nearly twice that of the squamous group in the regional registrations, even though the men aged 45 to 54 in the mass radiography set fared worse than those of a similar age in the regional set. In the adenocarcinomatous group the prognosis was extraordinarily good. More than half the number of regional survivors were produced from less than one-tenth of the regional total with this histology (Tables VIII and IX). It is in these two cell types that mass radiography appears to have a definite value in men aged 55 and over.

The overall regional survivor figure of 6% cannot be compared with the mass radiography figure of 18% for statistical significance, because of differences in age group and cell type composition. The expected number of survivors was therefore calculated by taking the number of *cases* in each cell type and age subgroup in the mass radiography series and by applying to them the regional survival *percentages* in these subgroups to obtain expected numbers of survivors. These were then added together to give the expected total number of survivors. This calculation showed that in the mass radiography series there would be an expected number of 17 three-year survivors. In fact there were 35 four-year survivors. This difference is significant at a level where P is less than 1/1,000 using the χ^2 test.

Discussion

The pioneer work on six-monthly serial radiography was done by Boucot (1961). Brett (1966), in North London, gave a preliminary report on the mortality experience in a group of men aged 40 and over offered six-monthly mass radiography for three years, compared with a similar group radiographed at the beginning and end of the same three-year period. He found equal mortality rates for primary bronchial carcinoma in the two groups during the period. Survival after a known follow-up period—for example, three or four years from discovery or treatment of each case—is not given. A judgement of the life-saving value of six-monthly mass radiography by comparison of mortality rates in a group radiographed six-monthly and a similar group not so radiographed is warranted, provided that the case incidence in the two groups is equal. This equality cannot be assumed.

Heasman and Lipworth (1966) in a study from the General Register Office, concluded for malignant disease of the lung, *I.C.D.* Nos. 162 and 163, that there was considerable underdiagnosis of this condition, amounting probably to 13–17%. This underdiagnosis appeared to be unaffected by age. Any factors reducing the underdiagnosis effect will have a repercussive effect on mortality rates, as 95 out of 100 patients die. If, as seems likely, the close surveillance of six-monthly radiography in Brett's test group brought to light a number of cases that would otherwise have remained uncertified the effect would be to increase the recorded mortality in the group examined every six months. The magnitude of this underdiagnosis effect could completely obscure the modest decrease in mortality which might be expected from earlier diagnosis by six-monthly radiography (compare Tables VIII and IX). Whether or not six-monthly radiography reduced undercertification could be ascertained by comparison of case-incidence in Brett's two groups. Clearly, before judgement of the value of six-monthly mass radiography from the North London work is made knowledge of case-incidence and case-fatality must be awaited, as these cannot be assumed to be equal in the "test" and "control" groups.

The South London study has shown that six-monthly routine mass radiography appears to have little or no life-saving value in men aged under 55. The bulk of Brett's examinees (72%) were in this age group, where the main effect of mass radiography could well be to bring to light already doomed cases which would otherwise have been part of Heasman and Lipworth's underdiagnosed 13–17%.

Possible Applications of Present Findings

What benefits might be expected if the modest prospects of salvaging more survivors in the age group 55 plus which emerge from the findings of the South London study were applicable to men of this age in England and Wales? If all men aged 55 or over who smoke 15 or more cigarettes per day were examined by serial routine radiography at six-monthly intervals (say 700,000 men—that is, annually 1.4 million examinations—a task well within the capabilities of the existing mass radiography units) another 1,000 survivors over and above the 1,400 five-year survivors from each year's crop of cases might be salvaged.

Conclusions

The life-saving value, in terms of four-year survivors, of six-monthly mass radiography in lung cancer by age and cell type may be summarized thus:

Cell Type	Age Groups		
	45–54	55–64	65+
Adeno	Undetermined	High	Undetermined
Anaplastic, oat, undifferentiated	Probably nil	Probably nil	Undetermined
Squamous	Undetermined	High	High
All cell types combined	Probably nil	Moderate	Moderate

This *provisional* evaluation is based on comparison of regional survival (Table IX) with global survival—that is, pick-up cases plus intersurvey clinical fall-out cases (Table VIII)—in the co-operating mass radiography volunteers.

For men aged 55 and over earlier diagnosis of lung cancer leading to overall improvement in survival can be achieved by serial routine radiography. The prognosis of the cases discovered depends on the interval between examinations, which should not exceed six months.

In this disease prevention is possible and is better than cure. Therefore during the attendance of men in this high-risk group at mass radiography units the opportunity should be seized to try to bring them to realize the importance of cutting down or stopping cigarette-smoking, because, if they do, these are the men most likely to benefit from a reduction of their immediate risk of developing lung cancer.

Summary

To assess whether six-monthly routine chest radiography could improve the present poor prognosis of bronchial carcinoma, the South London Lung Cancer Study offered a service aimed at earlier diagnosis to men aged 45 and over by the mass *x*-ray units in South London. Of the 67,400 men attending for a first examination 75% came back at least once; 197,500 repeat examinations were carried out. These revealed 147 patients with confirmed primary bronchial carcinoma, 27% of whom lived four years or more.

Of 83 men undergoing resection 39 (47%) were alive four years later. Men aged 45 to 54 (though having as great a proportion of growths resected as the older men) did badly, but the experience with the 84 older men was encouraging. The interval between penultimate and ultimate routine films was found to affect survival, and even more striking was the relation of the interval between examinations to prognosis after resection.

Cancer Registry records revealed that six-monthly serial routine mass radiography picked up 56% of all cases in this series; 44% of cases had fallen ill, to be discovered clinically between the routine examinations. The overall four-year survival rate of the whole group was 18%, compared with 9% for all patients in the region, the difference being wholly in patients aged 55 and over.

These findings seem to confirm that prognosis is improved by early diagnosis, which can be improved if routine examinations are carried out at intervals not exceeding six months. Probably a mass *x*-ray unit concentrating on men aged 55 and over smoking 15 cigarettes a day could salvage four-year survivors at a cost of only £300 each. Every 1,000 films taken would pick up a potential four-year survivor.

This study was possible only with the help of many people. We are grateful to them all, particularly the staffs of the Registrar General's Office and of the National Health Service executive councils in England and Wales, the South Metropolitan Cancer Registry, the S.E. and S.W. London Mass *X*-ray Services, the medical and surgical staff of the Brompton Hospital, and the staff of the Brook Thoracic Surgical Unit. We thank the S.E. and S.W. Metropolitan Regional Hospital Boards for support from research funds. We thank Miss G. Whitworth for invaluable help with drafting this paper and for tabulations; Miss J. Higgs, Miss M. Ravenscroft, and Miss A. Taylor for help in the follow-up; and Mr. E. Uztups for the illustration.

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Renal Tubular Acidosis of Pyelonephritis with Renal Stone Disease

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Renal tubular acidosis was first described by Butler, Wilson, and Farber (1936) and subsequently by Albright, Consolazio, Coombs, Sulkowitch, and Talbot (1940). The essential feature of the syndrome as described by these workers was a hyperchloraemic metabolic acidosis associated with an inappropriately alkaline urine. The condition has often been considered to be congenital (Pitts, Schulte, and Smith, 1955; Huth, Webster, and Elkinton, 1960), and is sometimes associated with other tubular defects (Jackson and Linder, 1953). An important feature is a tendency to nephrocalcinosis and/or renal stone formation, which may be the presenting disorder, but renal tubular acidosis is generally considered to be a relatively rare cause of renal stone disease.

Wrong and Davies (1959) emphasized that the essential lesion of renal tubular acidosis was a failure of the distal tubule to produce a urine of normal acidity and simplified the diagnosis by developing a short ammonium chloride loading test. With this test they showed an acidifying defect not only in a group of cases with hyperchloraemic acidosis, but also in three patients with unexplained nephrocalcinosis without acidosis, and in several cases of renal disease of various causes.

In recent years increasing attention has been paid to the behaviour of the renal tubule in pyelonephritis (Brod, 1956; Kleeman, Hewitt, and Guze, 1960; Kaitz, 1961), but there has been little systematic examination of the renal handling of hydrogen ion in this condition. Several authors have noted a failure to conserve bicarbonate in cases of pyelonephritis, but they have tended to distinguish between this disorder and renal tubular acidosis as the term is generally used (Schwartz and Relman, 1957; Lathem, 1958). Others have stated that renal tubular acidosis may be a complication of pyelonephritis (Albright and Reifenstein, 1948; Wrong, 1965), but very few documented cases have actually been reported.

In the course of studying patients with renal stone disease we have routinely performed the short acid load test of Davies and Wrong (1957) and have found a substantial number of stone patients unable to acidify their urine to a normal degree. A feature of all these cases is the presence of active upper urinary tract infection, and this, combined with the absence of any other underlying condition, leads us to believe that the condition in these patients is acquired as a result of chronic pyelonephritis. The present paper gives the results obtained in 24 such cases collected over a period of five years and compares them with a further 24 patients with renal stone disease and pyelonephritis who could produce a urine of normal acidity.

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Clinical Material

Eighteen patients with renal stone disease (out of about 600 tested) were unable to acidify their urine to *p*H 5.4 (Davies and Wrong, 1957). All of them had a chronic urinary tract infection. From this group of 18 cases we have excluded five because of associated cystinuria (two cases), primary hyperoxaluria (one case), Cushing's syndrome (one case), and steroid therapy (one case).

Twelve additional patients who presented with kidney stones and infection were found to have medullary sponge kidneys on radiological and histological evidence and four of these failed to acidify their urine. They were not included in the present study.

Eleven patients from a similar clinic in Glasgow, selected on identical criteria, were added to the Leeds group to make a total of 24 cases (group A). In none of these 24 cases was there evidence of urinary tract obstruction, which is known to cause an acidification defect of the urine (Berlyne, 1961).

For comparison with this series we chose the first 24 of the total of 63 Leeds patients with pyelonephritis and renal stone disease who could acidify their urine below *p*H 5.4 (group B).

The diagnosis of pyelonephritis was made if at least three of the following criteria were fulfilled: a convincing history of recurrent urinary tract infections, repeated pyuria with positive bacterial cultures in midstream specimens of urine, radiological changes on intravenous pyelography (Edwards, 1965), histological evidence (Cotran, 1965), and a positive prednisone provocation test (Little and de Wardener, 1962). In no case was there a history of analgesic abuse (Dawborn, Fairley, Kincaid-Smith, and King, 1966) or evidence of hypertensive renal disease.

The stones were graded as staghorn, medium, and small. The term "staghorn calculus" referred to any stone which