Second primary lung carcinoma

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Abbey Smith, R., Nigam, B. K., and Thompson, Joan M. (1976). Thorax, 31, 507–516. Second primary lung carcinoma. Fifty-five patients suffering from second primary lung carcinoma, 10 synchronous and 45 after resection for lung carcinoma (metachronous), have been observed from 1400 resections. The first manifestation of a second carcinoma in this series has always been the appearance of a new shadow in the follow-up radiograph. In our experience, second primary lung carcinoma is a disease affecting only heavy cigarette smokers. Heavy cigarette smokers suffering from squamous-cell carcinoma are at special risk. The results of re-operation, the significance of the time interval between the original operation and the appearance of the second primary carcinoma, and the slow growth rate of some second primaries are briefly discussed. No clear-cut methods exist for distinguishing a second primary from a metastasis from the original carcinoma.

In discussing second primary lung carcinoma, the main difficulty is definition. The arguments for and against considering a new shadow in a patient’s follow-up chest radiograph, after resection for lung carcinoma as a second primary, have continued since Warren and Gates’ (1932) report and the surgical reports of Robinson and Jackson (1958), Hughes and Blades (1961), and le Gal and Bauer (1961).

From a study of radiographic changes no one can distinguish extension or metastasis from the first carcinoma from a fresh primary lung carcinoma. The histopathological features of the fresh lesion are not available at the time the new radiological shadow first appears. A second operation, leading to histopathological diagnosis of the new lesion, is possible in less than one-third of patients who develop a second primary after resection—17 patients re-operated on from 55 in our series; 10 from 41 in the series of Shields and Robinette (1973), and 12 from 34 in the report of Razzuk et al. (1974).

Necropsy findings in a patient who develops a fresh lesion, which is inoperable and, by extending, causes the patient’s death, are equivocal. Metastases at necropsy may be due to either the original or a fresh lesion. Auerbach et al. (1967) described the difficulty in confirming independent primary lesions at necropsy. In Chaudhuri’s (1971) view, a fresh lesion can be established as a second primary carcinoma only if the histopathological features of the original and new carcinomas are different. Struve-Christensen (1971) emphasizes the importance of clinical factors in differentiating a metastasis from a second primary. A fresh lesion may with conviction be described as a second primary if the time interval between the appearance of the original and the new lesion is long.

Microscopic multiple primary bronchial carcinomas are relatively common, and the time taken for a microscopic primary to become a clinically apparent carcinoma varies. Other things being equal, we see no overriding reason for rejecting a fresh lesion which appears within one year of resection as a second primary solely on the grounds that the time interval is short. We have excluded examples of stump recurrence of carcinoma, extension of residual carcinoma of the lung following a too conservative resection, or extension of carcinoma in hilar lymph nodes. For purposes of patient management the single shadow (and the second primaries we have seen have all presented as single shadows), which appears in the chest radiograph at variable times after resection and has the same clinical, radio-
logical, and bronchoscopic characteristics as the original tumour, we regard as a second primary lung carcinoma.

Neptune, Woods, and Overholt (1966) state . . . ‘From a practical viewpoint we do not believe it makes any difference in management whether new-found disease is primary or recurrent. All such cases require careful evaluation and if the new lesion appears localized and is amenable to surgical excision, then this should be the procedure of choice’. We have followed this practice for the last 18 years.

Some may think that we have diagnosed second primary lesions too frequently, particularly when the time interval is short. Stump recurrence after resection has been excluded by bronchoscopy and slow progress of carcinoma in hilar nodes by mediastinoscopy. In local extension of the tumour the fresh shadow develops at the site of the previous resection.

These sequelae of resection may be rapidly fatal, but we have seen untreated patients survive eight years with stump recurrence, six years with increasing local hilar node involvement, and 12 years with extension locally in the lung at the resection site.

A metastasis from the original lesion is the difficult differential diagnosis. It is unusual to find extrathoracic manifestations of carcinoma at the time a second primary first shows radiologically. The long period during which the second primary seems confined to the lungs is a feature of the disease. Diffuse spread of carcinoma to both lungs after resection has an unmistakable radiological appearance.

**Patients Under Review**

Between 1953 and 1973 a second primary lung carcinoma has been diagnosed in 55 patients from a total of 1400 patients who have undergone resection. The follow-up, including twice-yearly chest radiographs of each of these 1400 patients, has, with one exception, been complete. This large number of second primaries has been revealed by the follow-up method, and their development is not due to an unusual preponderance of one cell type or exposure to carcinogen (except tobacco smoke). The time interval between the original operation and the appearance of the second primary is shown (in Table I). The means of diagnosis or presumptive diagnosis of the original tumour and the second primary are shown (Table II). The low incidence of malignant cells in the sputum may be explained by this method of investigation not being pursued when the diagnosis seemed obvious. We do not believe that a low incidence of malignant cells in the sputum is a characteristic of multiple primary carcinomas.

Of the 55 patients who developed a second primary, six synchronous primary lesions were not operated on: 32 patients had the original operation only; 15 were operated on a second time, and two were operated on a third time. The type of original and subsequent operation is shown in Table III.

**Table I**

<table>
<thead>
<tr>
<th>Time Interval between Original Primary and First Radiological Appearance of Second Primary</th>
<th>Simultaneous</th>
<th>Table I</th>
<th>Table I</th>
<th>Table I</th>
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<tr>
<td></td>
<td>&lt;1</td>
<td>1-3</td>
<td>4-12</td>
<td>13+</td>
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<tr>
<td>Simultaneous</td>
<td>10</td>
<td>8</td>
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<td>28</td>
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**Table II**

<table>
<thead>
<tr>
<th>Method of Diagnosis or Presumptive Diagnosis of Original and Second Primary Lung Carcinomas</th>
<th>Radiological and positive bronchoscopic</th>
<th>Radiological and positive cells in sputum</th>
<th>Radiological only</th>
<th>Necropsy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original carcinoma</td>
<td>28</td>
<td>1</td>
<td>26</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>Second primary</td>
<td>17</td>
<td>3</td>
<td>31</td>
<td>4</td>
<td>55</td>
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</table>

**Table III**

<table>
<thead>
<tr>
<th>Type of Operation</th>
<th>Pneumonectomy</th>
<th>Lobectomy</th>
<th>Segmental</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Original operation</td>
<td>15</td>
<td>32</td>
<td>2</td>
<td>49</td>
</tr>
<tr>
<td>Second operation</td>
<td>0</td>
<td>10</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Third operation</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
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</table>

Six patients with synchronous primaries were not operated on

Specimens for histopathological examination were obtained from either the first operation, the subsequent operation, bronchial biopsy in patients not operated on a second time, or at necropsy. Sixty-eight specimens were reported as squamous-
cell carcinoma, four as adenocarcinoma, three undifferentiated, and two oat-cell carcinoma.

Confirmation of a difference in histology between the original and second primary carcinoma was obtainable in only four patients. Lymph-node invasion was present in five patients at the original operation and in three different patients at the second operation. The second primary carcinoma appeared on the contralateral side in 43 of the 55 patients. In six patients with synchronous primaries, the lesions were bilateral.

RESULTS OF RE-OPERATION
In each of the 15 second operations resection of the second primary was possible. Every diagnosis of a new radiological shadow was confirmed as a second primary at operation. There were no hospital deaths following re-operation; neither radiotherapy nor cytotoxic drugs were used before or after operation. No patient who had had a pneumonectomy was re-explored.

Of the 15 patients who underwent a second operation, 11 died before the end of the third postoperative year, three with third primaries, and the remainder with extension of the carcinoma. Three patients have survived between three and five years from the date of the second operation. Of these, one is alive four-and-a-half years after the second operation with a third primary present; one died from a myocardial infarct without gross evidence of carcinoma at necropsy; and the other died from a third primary. Only one patient survived for more than five years after the second operation. This patient died following resection of a primary carcinoma of the colon five-and-a-half years after a second operation on the contralateral side, and at necropsy a third primary was detected in the originally affected lung.

The two patients who underwent a third operation survived less than two years. One of these had, at approximately two-year intervals, a right middle lobectomy, a left upper lobectomy, and segmental resection of the right lower lobe and died five months after the third operation from a paraplegia of uncertain cause. An isolated microscopic fourth primary was present in the bronchial epithelium but there was no clinical or radiological evidence of its existence. The other patient had a left upper lobectomy and a local removal of tracheal carcinoma two years later, followed after 18 months by a residual left lower lobectomy. She died within a year of this third operation from extension of the carcinoma. All patients living more than three years after re-operation had squamous-cell carcinoma and were heavy smokers. Two smoked more than 60 cigarettes daily before the first operation.

We would agree with Razzuk et al. (1974) that the prognosis following re-operation is grave. These authors, from a series of 12 re-operations, describe only one patient alive more than five years later. Neptune et al. (1966) report two patients alive more than five years after re-operation; both had a contralateral lobectomy following the original lobectomy, at intervals of 31 and 32 months. From five re-operations Struve-Christensen (1971) reported no five-year survivors.

DISCUSSION
INFLUENCE OF SMOKING A true assessment of how heavily a patient has smoked during his lifetime is extremely difficult, even by personal interview. With the shortcomings of all methods of collecting information retrospectively in mind, we carried out during 1971 a comparison between the smoking habits of patients with second primary lung carcinomas and those of a group of patients who after operation did not develop a second primary.

At the end of 1971, 39 patients with second primary lung carcinoma were interviewed, often on more than one occasion, concerning the duration and amount of cigarette smoking. If the patient had died, close relatives were interviewed. Only 39 of the total of 55 patients were investigated in this way because in nine adequate information was not available and seven developed a second primary after December 1971. The smoking habits of these 39 patients were compared with those of a larger group of 124 patients, 60 of whom had survived less than two years and 64 more than 10 years with no second primary. It had been shown that there was no significant difference in the age or smoking habits of these two groups of single primaries.

The 124 patients with single primaries included eight non-smokers and one who smoked a pipe only, while the 39 patients with multiple primaries were all smokers. However, this difference was not statistically significant. All the patients with multiple primaries smoked 10 or more cigarettes a day, while three of those with single primaries smoked less than 10 cigarettes a day, in addition to the nine non-cigarette smokers specified above. This seems to indicate that patients with multiple primaries are heavier smokers than those with
To counteract the difference in the sizes of the two groups, 39 of the single primaries group were matched for age and sex with the 39 multiple primaries and their smoking habits were again compared. These 39 smoked an average of 27 cigarettes per day, so that there was no significant difference between them and the group of 115 single primary smokers from which they were chosen. There was still a significant difference between the average number of cigarettes smoked per day by the multiple primaries group and these selected single primaries. The distributions of numbers of cigarettes smoked in the two groups are illustrated in Figure 2.

Owing to the small numbers, the patients were grouped into those who had smoked less than 20, 20–49 or 50+ cigarettes per day. As one would expect, there was no significant difference between

### TABLE IV

<table>
<thead>
<tr>
<th>Factors</th>
<th>Single Primaries (n=124)</th>
<th>Multiple Primaries (n=39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at resection (yr)</td>
<td>54.6 ± 8.51</td>
<td>55.3 ± 6.94</td>
<td>NS</td>
</tr>
<tr>
<td>Extent of operation:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pneumonectomy</td>
<td>74</td>
<td>11</td>
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<tr>
<td>Lobectomy</td>
<td>50</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Occupational dust exposure</td>
<td>50/124</td>
<td>12/39</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cigarettes smoked per day</td>
<td>28.4 ± 14.48 (n=115)</td>
<td>36.5 ± 17.58 (n=39)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>No. of years smoked up to resection</td>
<td>35.1 ± 10.60 (n=113)</td>
<td>35.5 ± 10.90 (n=37)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking given up after resection</td>
<td>56/124</td>
<td>18/39</td>
<td>NS</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oat cell</td>
<td>14</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>94</td>
<td>33</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Node invasion at operation</td>
<td>36/124</td>
<td>5/39</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Data for multiple primaries refer to first primary
18 non-smokers and 1 pipe only excluded
3 multiple primaries included twice because of double histology – squamous and adenocarcinoma
Second primary lung carcinoma

the 39 selected single primaries and the total
group of 115 single primaries \( (x^2=0.04) \). The 39
patients with multiple primaries smoked signifi-
cantly more cigarettes per day than the 115
patients with single primaries \( (x^2=7.44, p<0.05) \),
and also more than the selected 39 patients with
single primaries \( (x^2=5.57, 0.05<p<0.10) \).

The part which excessive cigarette smoking
appears to play in the development of a second
primary has not been emphasized in some surgical
reports. Auerbach et al. (1961) clearly described
the nature and extent of changes in the bronchial
epithelium from cigarette smoking. Glennie,
Harvey, and Salama (1964) mention smoking in
relation to multiple primary carcinoma of the
bronchus. Watson (1965), discussing 56 patients
surviving more than 10 years after surgery, noted
that nine continued to smoke and three of these
developed a new primary lung cancer. Abbey
Smith (1966) stated 'Some heavy smokers with
squamous cell carcinoma develop second primaries
but many do not.' Each of the 15 patients of
Neptune et al. (1966) who were re-operated on for
carcinoma (not all for second primary lesions)
were male cigarette smokers.

Our interest in the importance of smoking arose
from the fact that, as new patients with a second
primary lung carcinoma presented, it was evident
from their history that each was a heavy smoker.
So far we have not diagnosed a second primary
carcinoma in a patient smoking less than 10 ciga-
ettes each day.

TIME INTERVAL BETWEEN ORIGINAL AND SECOND
LUNG PRIMARY It is necessary to differentiate
three distinct time intervals—the time between
the original operation and the initial radiographic
appearance of the second primary, the time be-
tween operation and confirmation of the diagnosis
of the same second primary, and the time between
the first operation and the second operation. These
three intervals may differ by as much as five or
more years. The time interval between the original
operation and the first radiological appearance of
the second primary can be ascertained only by
frequent chest radiographs. On the other hand, an
abnormality may be present in the chest radiog-
raph and the patient may not present for diagno-
sis for a period of several years. An exact
definition of the time interval may be important.
We have not seen a fresh primary appear in a
patient's radiograph later than 12 years after the
original operation. Twenty-five years ago it was
incorrectly assumed that if a patient survived five
years from the date of operation he was unlikely
to die from lung carcinoma. We now believe that
it is unusual for a patient to die of lung carcinoma
if the chest radiograph is normal at the end of the
twelfth year after operation.

Second primaries occurring more than 12 years
after resection are recorded, although it is not
always clear whether the interval under considera-
tion is the time of first radiological appearance of
the new shadow, the time of final diagnosis of the
second primary, the time between the original and
a second operation, or the interval between the
first operation and necropsy. Nor is a distinction
between a fresh primary and a metastasis always
made. Possible ambiguities in the time interval
actually being described and also in the pathology
of the second lesion must be accepted in reports
of long time intervals. Brock (1964) reported 15
years between right lower and left upper lobec-
tomy for primary tumours; Clifton, Das Gupta,
and Pool (1964) 13 years between left lower lobec-
tomy and wedge resection of the right upper lobe;
Watson (1965) fresh carcinoma in 6 of 56 patients
surviving resection by more than 10 years; Bel-
cher and Anderson (1965) two patients with fresh
lesions 10 and 12 years after resection; le Roux
(1968) six patients surviving 9 to 12 years after
pneumonectomy with fresh carcinoma; Struve-
Christensen (1971) one second primary at 10 years;
Chaudhuri (1971) three second primaries at 13, 11,
and 10 years after resection; Shields and Robinette
(1973) eight second primaries diagnosed after the
tenth year from a total of 41 post-resection second
primaries; and Razzuk et al. (1974) second pri-
maries at 15, 14, 12, 12, and 10½ years after resec-
tion from a total of 29 patients with multiple
primary carcinoma.

We have no evidence whatsoever for assuming,
when the intervals exceed 12 years, that the lesion
was radiologically present during or before the
twelfth year. C. A. Jackson, of Harefield Hospital,
one of the first to draw attention to the clinical
importance of multiple primary carcinomas of the
lung (Robinson and Jackson, 1958), has shown us
the notes and radiographs of a patient whose chest
radiograph was normal during the fifteenth year
after resection and who developed a second sec-
nary carcinoma during the sixteenth year. We
recollect isolated reports of even longer intervals
without being able to provide references. Intervals
exceeding 12 years between operation and detect-
ion of the second primary must be accepted.
However, because the appearance of a fresh pri-
mary between eight and 12 years after resection
is so relatively common, and after the twelfth
year so rare, some significance might be attributed to this observation. Second primary lung carcinoma accounts for about a quarter of deaths between the eighth and twelfth years after resection, but never for deaths after the twelfth year, in our series.

It could be argued that commonplace reasons for failure to diagnose a second primary after the twelfth year exist, such as the few patients who survive into and after the thirteenth year, the difficulty in obtaining frequent chest radiographs of patients of advancing years, and the fact that the survivors after the thirteenth year are those who gave up smoking after operation. Fifty-seven patients have survived 13 to 22 years after operation, and 56 of these have twice-yearly chest radiographs. In none has a second primary carcinoma been detected. Twenty-one of these 56 patients did not give up smoking after operation and four have died—one from cardiac infarction, two from cardiorespiratory failure, and one from a contralateral pneumothorax. At necropsy these patients showed no gross carcinoma. These 21 patients smoked less over a shorter period than those who developed second primaries, but they included three patients who regularly smoked 30 cigarettes each day, two patients 40 a day, one 50, and one 60 cigarettes daily since adolescence. Until the outcome is known in each of these patients the importance of not finding a second primary after 12 years must be speculative. Four patients who developed second primaries in the 8 to 12-year interval stopped smoking at the time of their original operation.

DIFFERENCES IN RATE OF GROWTH OF SECOND PRIMARIES The rate of growth of a second primary carcinoma is unpredictable, which makes patient management difficult. The rate of growth can be different for carcinomas of a similar cell type and is independent of the extent and nature of the first operation. Four patients from the 40 not operated on have lived more than five years after the first radiological evidence of a second primary without any treatment. Not only have they survived for five years but they have remained in sufficiently good health to continue working. The radiographs of a patient surviving more than five years were reported (Fig. 3 in Abbey Smith [1970]). Radiographs of two other patients, both heavy smokers (50+ per day) surviving more than five years without treatment, are shown (Figs 3–4).

CASE 1 A man aged 56 had a right upper lobectomy in 1966 for a squamous-cell tumour of the right upper lobe (Fig. 3). In 1969 a small shadow appeared in the left upper zone (Fig. 4a). The patient remained symptom free and at work although the lesion slowly increased in size (Fig. 4b). In 1974 the small lesion in the left upper lobe was resected by segmental resection and found to be a squamous-cell carcinoma with the histopathological features of a primary. The patient was discharged from hospital on the fourteenth day and has remained well since.

CASE 2 A man aged 57 had a right pneumonec-tomy for a squamous-cell carcinoma of the right main bronchus in 1968. In 1969 a small shadow was visible in the left upper lobe. No treatment was given. The patient remained symptom free and at work. In 1970 (Fig. 5a) the lesion had grown, and the radiographs in 1972 and 1973 are shown (Fig 5b and c). Figure 5d shows the radiographic appearance in 1975. The lesion continues to grow. The patient is virtually symptom free and remains at work in spite of being advised to curtail his activities. Squamous-cell carcinoma cells are present in the sputum.

These radiographs show the slow rate of growth of some second primaries and also the differences in the size reached by a second primary during the same time interval. It is not possible to compare the rates of growth of a first with a second primary because the first primary is resected, if operable, as soon as the radiological shadow appears. It is, of course, well known that some carcinomas grow slowly (Abbey Smith, 1954); our impression is that a second primary is more likely to grow slowly than the first primary. These case reports show how silently the second primary may progress and illustrate how a second primary first diagnosed 15 years after operation may have been present at 12 years or even earlier and not recognized, unless regular chest radiographs are taken.

We have not seen a patient with a second primary appearing more than eight years after operation survive for five years. An explanation that when the time interval is long the patient will be older, and more likely to die from cardiorespiratory complications, is not wholly convincing.

Whether to treat a second primary lesion actively is a difficult decision. A slow rate of growth is not to be depended upon. Exploration should be advised for any patient whose chest radiograph shows a new shadow 1 cm or more in diameter which has been present over a period of one month, if the general condition of the patient is satisfactory. A persistent single new shadow in
the chest radiograph after resection for carcinoma is almost invariably malignant.

Whether a patient with squamous-cell carcinoma who has regularly smoked more than 40 cigarettes a day should have a segmental resection (when this achieves total macroscopic removal of carcinoma) instead of lobectomy is a question still not resolved. The risks of development of a second primary lesion must be set against the risks of local recurrence of tumour from an inadequate local resection.

REFERENCES


FIG. 5. (a) Case 2. Detail of left upper zone of chest radiograph in 1970. The shadow was first visible in 1969. (b) Appearance in 1972. (c) Appearance in 1973. (d) Appearance in May 1975 (compare size with Fig. 4d).


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