Thorax 1982;**37**:453–456

Outcome of carcinoma in situ and early invasive carcinoma of the bronchus

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ABSTRACT Seventeen patients in whom a squamous carcinoma in situ of the bronchus had been resected have been followed for up to 16 years. The crude mortality rate for these patients is remarkably high, with seven (41%) dead after five years and 14 (82%) after 10 years. Half the patients had died as a direct result of malignant disease by 10 years—because of recurrence, metastatic disease, or the development of a second tumour. A guarded long-term prognosis must be given in these patients owing to the many deaths (mainly from other respiratory diseases) besides those from recurrent cancer.

The diagnosis of carcinoma in situ is usually equated with a good prognosis. The lesion is most often recognised in the cervix of the uterus, where it is practicable to remove it completely with the other epithelium at risk, and thus to prevent the subsequent development of an invasive carcinoma at this site. In the case of the cervix in particular, the presence of very early microscopic invasion just beneath the epithelium (microinvasion) is also recognised to carry a good prognosis, similar to that of carcinoma in situ, and not normally to be associated with the risk of developing metastatic disease. These favourable prognoses do not necessarily apply to other sites, however, and the outlook is different when carcinoma in situ arises in an organ with an extensive epithelial covering, such as the urinary tract or the bronchial tree. Patients with carcinoma in situ or microinvasive carcinoma must therefore be followed for many years if the behaviour of the disease and thus its prognosis are to be determined. This paper is based on a long-term follow-up study of a series of such cases, originally reported by us in 1969.[1]

Methods

Sixteen men and one woman with carcinoma in situ or microinvasive carcinoma of the bronchus (aged 46–68 years, mean 58 years, at operation) were followed for up to 16 years. The presenting features are shown in table 1. Ten of these patients were reported in our earlier paper when we defined carcinoma in situ as a carcinoma confined to the epithelium, sometimes affecting the deeper glands and sometimes forming a large mass within the lumen of the bronchus. Microinvasion was described as the presence of minimal infiltration within the bronchial mucosa but not extending any deeper into the wall. All patients had undergone either pneumonectomy or lobectomy for their lesion and the diagnosis was not made until histological examination of the resected specimen had been completed.

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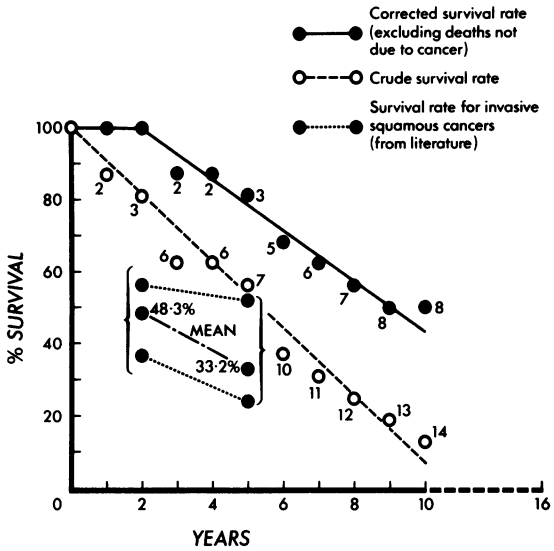
Results

The survival figures are shown in the figure, showing a crude survival rate at five years of about 50% and at 10 years of about 10%. For comparison, the two-to-five-year survival rates for patients with resected overt squamous carcinomas in previously reported series are included.[2–9] Fifteen of the 17 patients had died, six of these (40%) from causes other than cancer (table 2). Table 3 shows the nine patients who died of cancer (60% of all deaths)—three of them from carcinomatosis; a further four from what appeared to be a second primary bronchial carcinoma, which they had developed after various intervals; and two from a recurrence of the original lesion in the bronchial stump, where the original resection had not been complete. There are currently two men who have survived for a long time after their resection (12% of the total). One (case 7), who had no microinvasion, has survived 11 years 7 months, and the other (case 16), who did have microinvasion, has survived 8 years 1 month; both are well.

Table 1 *Presenting features of patients with carcinoma in situ and early invasive carcinoma of the bronchus*

Case No and sex	Age (y) at operation	Presenting symptom and duration	Smoking habits
1 M	59	Hoarseness: 6 weeks	20 cigarettes/day
2 M	63	Cough and haemoptysis after acute bronchitis: 6 months	Not known
3 M	67	Cough and chest pain: 5 months	20 cigarettes/day
4 M	61	Chest pain: 6 weeks	30 cigarettes/day
5 M	68	Cough: 6 weeks	50 cigarettes/day
6 M	56	Chest injury from a recent fall	20 cigarettes/day
7 M	58	Chest pain and cough: 3 weeks	30 cigarettes/day
8 F	46	Chest pain and cough: 8 weeks	Not known
9 M	60	Recurrent haemoptysis: 6 weeks	Pipe smoker, 3 oz/week
10 M	52	Cough, sputum, and haemoptysis: 5 months	30 cigarettes/day
11 M	57	Lesion seen on routine radiograph	Not known
12 M	64	Productive cough: 8 months	20 cigarettes/day
13 M	48	Dyspnoea, chest pain: 2 months	Not known
14 M	55	Cough, chest pain: 2 months	20 cigarettes/day
15 M	62	Cough, dyspnoea: 2 years; weight loss: 2 months	20 cigarettes/day
16 M	56	Cough, haemoptysis: 6 weeks	Not known
17 M	57	Cough, fever: 1 month	Pipe smoker, 4 oz/week



Survival after operation of patients with bronchial carcinoma in situ, compared with reported crude two-year and five-year survival rates for patients with resected invasive squamous carcinoma.[2–9] The numbers indicate those who had died. The slopes within the brackets show the best and worst of these reported survival figures with the mean.

Discussion

Carcinoma in situ is not a lesion necessarily confined to a surface epithelium: in the case of the uterine cervix, "epidermidisation" of the endocervical glands with the cellular features of squamous carcinoma but no breach of the basement membrane is commonly seen in association with the lesion on the surface. The presence of a tumour mass within the bronchial lumen is not considered to preclude a diagnosis of carcinoma in situ provided that there is no infiltration; the development of the mass is possibly the result of the different conditions within the bronchial lumen. The characterisation of "microinvasion" is more difficult and we arbitrarily decided that very limited microscopic submucosal invasion could be categorised in this way. The number of patients is too small for us to draw any firm conclusion about the significance of the different types and amounts of lesion that were found.

Patients with bronchial carcinoma in situ are clearly a group with a high death rate despite the fact that their carcinoma is removed at an apparently early stage in its evolution—altogether about two-thirds of the patients will have died seven years after resection of their tumour. The corrected mortality rates, including only those patients who died from malignant disease, would be expected to show good survival; but in practice this is true only for the first two years after operation: thereafter there is a steady increase in the deaths directly due to cancer, and half the patients will have died after nine years. Almost one-third of the patients did not die from malignant disease but succumbed to some other condition, usually a non-malignant respiratory disorder. The nine patients who died from malignant disease followed one of three patterns. Three patients, all with microinvasive lesions as defined here, developed carcinomatosis without any other apparent local lesion in the lung. This suggests either that the infiltration was more extensive than had been recognised or, more probably, that despite the very limited amount of infiltration that was found the patients nevertheless had had a highly malignant tumour that spread rapidly. The second pattern was

Table 2 *Deaths not due to cancer*

Case	*Sex*	*Microinvasion*	*Survival*	*Cause of death*
1	M	Yes	11 m	Bronchopneumonia
2	M	Yes	28 m	Bronchopneumonia
3	M	No	69 m	Lobar pneumonia, intestinal obstruction
6	M	Yes	23 m	Cerebral haemorrhage
8	F	No	2 w	Pulmonary insufficiency (postoperative)
13	M	Yes	122 m	Bronchopneumonia

Table 3 *Deaths due to cancer*

Case	*Sex*	*Microinvasion*	*Survival*	*Cause of death*
10	M	No	16 y	2nd cancer (squamous) after 16 y
12	M	Yes	56 m	Carcinomatosis
14	M	Yes	29 m	Carcinomatosis
17	M	Yes	64 m	Cerebral metastases
4	M	Yes	61 m	2nd cancer (oat-cell) after 4 y
5	M	No	73 m	2nd cancer (squamous) after 4 y 4 m
11	M	Yes	96 m	2nd cancer (squamous) after 7 y
9	M	Yes	9 y	Recurrent cancer in stump
15	M	Yes	25 m	Recurrent cancer in stump

seen in the four patients, a quarter of the series, who developed a second malignant tumour apparently distinct from the first. This is an event that could be anticipated if the theory that the whole of the bronchial mucosa is at risk of developing malignant change is correct. The most detailed study of the bronchial tree in cigarette smokers was that of Auerbach *et al,*[10] who found a high frequency of epithelial abnormalities and dysplasia throughout the bronchial tree, increasing in proportion to the number of cigarettes smoked. The examination of the rest of the available bronchial tree in the patients in the present series showed widely scattered foci of squamous metaplasia or dysplasia in the mucosa, and in two patients there were two distinct separate carcinoma-in-situ or microinvasive lesions present in the specimens taken at operation. The interval before the development of a second tumour varied considerably from case to case, the longest being 16 years. The development of a second primary tumour in the bronchial tree after resection of a carcinoma is now being recognised with increasing frequency, mainly in heavy cigarette smokers.[9 11]

Finally, in this group there were two patients who had an incomplete removal of the carcinoma in situ because it extended on to the carina. These patients provided an opportunity to observe the behaviour and natural history of such a lesion. One of them (case 15) had a microinvasive lesion that rapidly progressed to produce an invasive carcinoma at the bifurcation, with death two years later. The other patient (case 9) also had a microinvasive lesion at the time of his initial resection. He was subsequently followed with regular cytological examinations of his sputum, and later with bronchoscopy and biopsy. Malignant cells reappeared in his sputum eight months after the resection of his first tumour and a carcinoma in situ was confirmed by biopsy at this stage. Three and a half years later the mucosa had the characteristic granular appearance of carcinoma in situ and by six years microinvasion was apparent. Eight years after operation he finally developed a fully infiltrating tumour and died the following year.

There is thus great variation in the prognosis of these lesions. The presence of microinvasion within the bronchial mucosa as defined here may still be associated with long survival, as many of the patients in this series with this feature survived over five years; nevertheless, as all three patients who died of carcinomatosis had microinvasive lesions, its presence is an added reason for a cautious prognosis. We should remember that occasionally there may be long-term survival even with overt tumours which have metastasised.[9] The degree of any accompanying lung disease and the smoking habits of the patient must be considered when the doctor is trying to arrive at a prognosis, since these appear to be the most important factors in determining the outlook in patients who have a slowly growing tumour. Some squamous carcinomas in the bronchus moreover appear to be biologically highly malignant and to carry a poor prognosis even though they are found at an apparently early stage and are histologically well differentiated. From this series it appears that after five years the survival in patients who have had a squamous carcinoma in situ removed is little better than that reported (see figure) for those patients who have had an overt invasive squamous bronchial carcinoma resected.

We are grateful to Dr MR Baker for his helpful comments and to the department of medical illustration, St James's Hospital, for the illustrations.

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