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Bronchial carcinoma and long-term survival

Retrospective study of 433 patients who underwent resection

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Freise, G., Gabler, A., and Liebig, S. (1978). *Thorax*, **33**, 228–234. **Bronchial carcinoma and long-term survival: Retrospective study of 433 patients who underwent resection.** The long-term follow-up of patients with bronchial carcinoma treated by surgery is presented. Of 471 patients who underwent thoracotomy, the tumour could not be resected in 38 (8%). Sixty-three (13·4%) died within the first four weeks; 125 (28·9%) survived more than five years. A high percentage developed either late metastases, late recurrences, or a second primary lung carcinoma. The results of surgical resection for bronchial carcinoma cannot be considered satisfactory, although resection remains the best treatment even in those patients with an apparently unfavourable prognosis.

In spite of reservations regarding retrospective studies, conclusions can be drawn regarding diagnosis, therapy, and prognosis. Questions concerning histological type, size, and site of tumour, and tumour stage can be answered only after an adequate postoperative interval. Five years after operation the patient who has apparently been successfully treated may die from a second primary carcinoma.

Patients under review

During the period from 1953 to 1968 471 patients at Heckeshorn Hospital had a thoracotomy for bronchial carcinoma (Table 1). Thirty-eight patients (8%) had tumours which were not resectable. Sixty-three (13·4%) died within the first four weeks after operation. Follow-up was not possible after discharge from hospital in 10 cases. The remaining 398 patients were followed up at outpatient consultations or from information sent by practitioners or other hospitals. One hundred and twenty-five patients (28·9%) survived five years; this survival rate is similar to those in other published studies.

Results

The incidence of bronchial carcinoma in women is less than in men. In our series, females represented 10% of all thoracotomies, which is an average rate (Buchberger and Jenny, 1967; Sriboonma, 1967; Kutschera, 1968). The reason why women have a better prognosis (Berndt, 1965; Watson, 1965) is uncertain. Our five-year survival rate in women is 34% and in men 27%. The women

Table 1 *Cell type, operation, and five-year survival rate*

Histological type	*All operated patients*	*Exploratory thoracotomy*	*Resection*	*Postoperative deaths*	*Five-year survival*	
					Total	*Resected*
Squamous-cell	275	12 (4·4)	263	40 (14·5)	(29·1)	80 (30·4)
Adenocarcinoma	56	5 (8·95)	51	6 (17·2)	(32·2)	18 (35·3)
Alveolar-cell	16	1 (6·25)	15	2 (12·5)	(25·0)	4 (26·9)
Undifferentiated	65	5 (7·7)	60	7 (17·5)	(29·2)	19 (31·6)
Oat-cell	49	15 (30·3)	34	8 (16·3)	(8·1)	4 (11·7)
Without histology and follow-up	10					
Total	471	38 (8·08)	433	63 (13·4)	(26·5)	125 (28·9)

Percentages are given in parentheses.

operated upon were younger and adenocarcinoma was more frequent in them, both factors improving the results.

The worse prognosis in men, especially in the 60–70 age group (Table 2), cannot be due only to a higher death rate during this decade. Loss of lung function caused by operation is a factor (Hamelmann 1968). This conclusion is partly confirmed by the superior results of lobectomy over pneumonectomy. The difference is clear in squamous-cell carcinomas; 19% survived five years after pneumonectomy but 30% after lobectomy. In addition to the preservation of lung as a cause for the better prognosis after lobectomy, the tumour treated by lobectomy is likely to be sited in the periphery of the lung and the lymph nodes to be free of invasion. When lobectomy can be performed a favourable tumour stage is present, and an exact comparison between lobectomy and pneumonectomy is possible only if these facts are taken into consideration.

INFLUENCE OF CELL TYPE

The opinions of pathologists often differ regarding classification. Therefore, comparisons of the histological categories of pathologists in different hospitals are difficult (Jones *et al.*, 1967). Jenny (1972) described two histological groups only: epidermoid and small-cell carcinomas, with a five-year survival rate of 30% and 14% respectively, much the same as in our cases (Table 1). In our series, the best five-year survival rate was in patients with squamous-cell carcinoma and adenocarcinoma. Alveolar-cell carcinoma is apparently in a low survival group (Table 2). Most authors have pointed out that the best treatment for small-cell carcinoma is irradiation only. But peripheral cases resected early have a reasonable chance after lobectomy (37·5% five-year survival, see Table 2). When pneumonectomy was necessary because of the extent of the tumour no patient survived five years.

INFLUENCE OF SPREAD OF CARCINOMA OUTSIDE LUNG

The most accurate information concerning extension of bronchial carcinoma is obtained by the TNM system of the Committee on Clinical Stage Classification and Statistics of the UICC (International Union Against Cancer, 1968) (Table 3).

In spite of some shortcomings (a classification proposed by Dold *et al.* (1972) is now in clinical use), the TNM system enables comparisons to be made of results in different countries. As is seen in Table 4, the five-year survival rate of bronchial carcinoma varies from 45 to 5·7%, depending on classification. The T_1 N_1/T_1 N_2 and T_4 N_1 cases are not considered because of the small numbers.

By using the TNM formula, comparable groups of patients in relation to prognosis and operability can be obtained and more accurate comparisons made. Thus, in our patients, five-year survival rates of 43% in stages I and II were found. A deterioration in long-term survival is evident from the 19·3% survival in stage III and 6·4% in stage IV. Taking this classification as a basis for comparison, our results accord with those of Salzer (1971).

If classification by extent of tumour (Table 5)

Table 2 *Type of operation and five-year survival (male patients)*

		Age at operation (years)					
Histological type	*Operation*	*< 39*	*40–50*	*51–60*	*61–70*	*71*	*Total*
Squamous-cell	Pneumonectomy	1/2[1]	2/20 (10)	24/80 (30)	11/57 (19·3)		38/159 (24·2)
	Lobectomy		2/5 (40)	13/34 (38·2)	14/46 (30·4)		29/85 (34·1)
	Miscellaneous			1/1	1/6		2/7
Adenocarcinoma	Pneumonectomy		0/1	2/5 (40)	0/3		2/9 (22·2)
	Lobectomy		0/1	7/17 (41·2)	1/5 (20)		8/23 (34·8)
	Miscellaneous				1/3		1/3
Alveolar-cell	Pneumonectomy			1/1	0/1		1/2
	Lobectomy			2/2	1/2		3/4
	Miscellaneous				0/2	0/1	0/3
Undifferentiated	Pneumonectomy		2/5 (40)	4/17 (23·5)	4/8 (50)	0/1	10/31 (32·3)
	Lobectomy		1/3 (33·3)	1/6 (16·7)	0/7	0/1	2/17 (11·8)
	Miscellaneous			1·2	3·5 (60)		4/7 (57·1)
Oat-cell	Pneumonectomy		0/4	0/11	0/6		0/21 (0)
	Lobectomy		0/1	1/4	2/3		3/8 (37·5)
Total	Pneumonectomy	1/2	4/30 (13·3)	31/114 (27·2)	15/75 (20)	0/1	51/222 (22·9)
	Lobectomy		3/10 (30)	24/63 (38·1)	18/63 (28·6)	0/1	45/137 (32·8)
	Miscellaneous			2/3	5/16	0/1	7/20 (35·0)

[1]Numerator = 5-year survival. Denominator = resected patients.
Percentages in parentheses.

Table 3 *TNM classification*

T	*Primary tumour*
T_0	No evidence of primary tumour
T_1	Tumour confined to segmental bronchus or to a segment of one lobe
T_2	Tumour confined to lobar bronchus or to one lobe
T_3	Tumour involving main bronchus or more than one lobe
T_4	Tumour extending beyond the lung

M	*Distant metastases*
M_0	No distant metastases
M_1	Distant metastases

N	*Regional lymph nodes*
N_0	No lymph node involvement
N_1*	Involvement of bronchopulmonary lymph nodes
N_2*	Involvement of mediastinal lymph nodes, especially those of the tracheobronchial and paratracheal group

Staging	
I	$T_1 N_0$
II	$T_1 N_1$, $T_2 N_0$, $T_2 N_1$
III	all T_3-cases, all N_2-cases
IV	all T_4-cases, all M-cases

*Modification, not yet generally accepted.

Table 4 *TNM formula and five-year survival rate*

TNM formula	*All resected patients*	*Surviving more than 5 years*	%
$T_1 N_0 M_0$	42	18	42·85
$T_1 N_1 M_0$	1	0	0
$T_1 N_2 M_0$	5	0	0
$T_2 N_0 M_0$	140	63	45·00
$T_2 N_1 M_0$	22	8	36·36
$T_2 N_2 M_0$	32	3	9·37
$T_3 N_0 M_0$	52	15	28·85
$T_3 N_1 M_0$	19	2	10·52
$T_3 N_2 M_0$	57	12	21·05
$T_4 N_0 M_0$	23	2	8·69
$T_4 N_1 M_0$	5	0	0
$T_4 N_2 M_0$	35	2	5·71
Total	433	125	28·86

Table 5 *Extension of primary and five-year survival rate*

Tumour	*All resected patients*	*Surviving more than 5 years*	%
T_1	48	18	37·50
T_2	194	74	38·14
T_3	128	29	22·66
T_4	63	4	6·35
Total	433	125	28·86

and involvement of lymph nodes (Table 6) is made, it becomes clear that the T_4 cases (tumour extending beyond the lung) have the worst prognosis. Nevertheless, 6% of T_4 patients have a five-year survival. Therefore, it can be stated, contrary to the opinion of Dittrich (1971), that there is a chance of cure in some T_4 cases (Wassner and Hauser, 1967; Zeidler and Linder, 1973).

The influence of lymph node metastasis on survival is clearly shown by using the TNM formula. Although some authors (Rienhoff *et al.*, 1965) have reported that lymph node metastases are not of major importance to survival, it must be noted that in several reports an exact distinction between lymph node stages (N_1 and N_2 or N_3) is not made (Maassen, 1967). Long-term results are better

Table 6 *Lymph node involvement and five-year survival rate*

Lymph node involvement	*All resected patients*	*Surviving more than 5 years*	%
N_0	257	98	38·13
N_1	47	10	21·28
N_2	129	17	13·18
Total	433	125	28·86
N_2 without T_4	94	15	15·88

when bronchopulmonary nodes only are involved. The greater the distance of involved lymph nodes from the primary carcinoma the worse the survival rate.

In spite of this we do not refuse resection to these patients (Gabler and Freise, 1971). Although our early results with a 22% survival in N_2 cases could not be reproduced, we emphasise the five-year survival rate of 21·5% in T_3 N_2 cases. The poorer survival rate in our T_2 N_2 cases might be explained by the statement of Dittrich (1971) who interpreted his results to imply that lobectomy was an inadequate operation in stage II. Lobectomy was performed in some stage II cases because of reduced lung function; on the other hand, in most T_3 N_2 patients pneumonectomy with resection of all lymph nodes was done. We believe that involvement of mediastinal lymph nodes is not a contraindication to resection in bronchial carcinoma and many authors agree with this viewpoint (Overholt and Bougas, 1956; Konrad and Schulte, 1969; Pearson *et al.*, 1972).

INFLUENCE OF SITE OF CARCINOMA

In our 433 resected cases the tumour was central in 223 patients and peripheral in 210. No difference in long-term survival between the two groups was noted, although differences have been reported by other authors. Jenny (1972) found central bronchial carcinomas to be more frequent (ratio 3 : 1) and the chance of long-term survival better. This

is explained by the fact that central lesions produce symptoms earlier (Buchberger and Jenny, 1967). Bergmann's (1971) patients show a ratio of central to peripheral carcinomas of 1 : 1·6. His better three-year survival rate for peripheral carcinoma is due to earlier detection of peripheral carcinomas during the later years and to the fact that central carcinomas more frequently require pneumonectomy.

One-fifth of Salzer's (1971) cases had peripheral carcinomas. He considers that improved radiographic diagnosis will reveal an increased number of peripheral carcinomas. Long-term survival rates in his material are similar in both groups.

Dittrich (1971) considers that classification into central and peripheral carcinomas is not necessary because misinterpretations of antero-posterior radiographs may occur. He considers tumour staging by the TNM classification at thoracotomy to be decisive. In our opinion, this concept should be followed.

The site of origin of the carcinoma in our 433 resected cases is shown in the Figure. The best results (34·3% five-year survival) were obtained from resection when the carcinoma was situated in the right upper lobe. The five-year survival rate was 31·2% for tumours of the left lower lobe, 26·4% for the upper lobe, 26·8% for the right lower lobe, and 18·8% for tumours situated in the middle lobe.

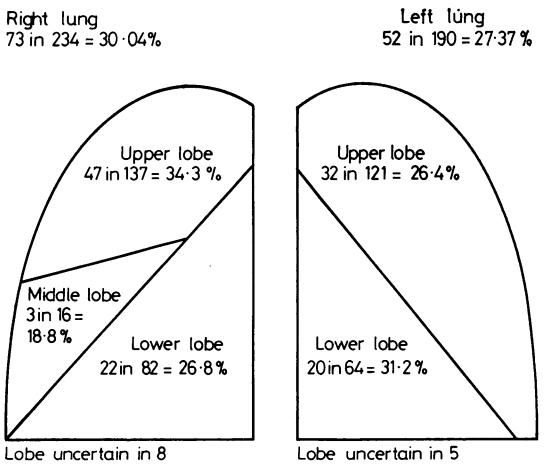


Figure *Tumour site and five-year survival rate.*

Schoen and Stoehr (1971) have pointed out that the upper lobes are affected more often than the lower, and the right lung more often than the left. Similar observations have been made by Hoffmann *et al.* (1969). Huwe (1959) has reported a 17·8% five-year survival for right upper lobe tumours. Salzer (1971) has reported that the most favourable long-term survival rates are for carcinoma in the right upper lobe, as we have noted. Other authors (Sriboonma, 1967; Hoffmann *et al.*, 1969; Schoen and Stoehr, 1971) have described favourable long-term survival rates for bronchial carcinoma in the left upper lobe. Carcinoma of the left lower lobe is considered to have an unfavourable prognosis (Sriboonma, 1967, 12·7%; Schoen and Stoehr, 1971, 14·5% five-year survival rates). Schoen and Stoehr (1971) and Hoffmann *et al.* (1969) consider that the frequency of contralateral lymph-node involvement in the left lower lobe tumours is responsible for the worse result. Hoffmann *et al.* (1969), moreover, point to frequent abdominal metastases in carcinoma of the left lower lobe and recommend preliminary exploration of the abdomen in left lower lobe carcinoma. Our data, however, do not support this view of the poor prognosis of left lower lobe carcinoma.

INFLUENCE OF SIZE OF TUMOUR

The frequency of metastases in cases of resected peripheral bronchial carcinoma is shown in Table 7. Whereas there is no statistically significant difference in the frequency of metastases between the first and second groups, there is a significant difference between groups 2 and 3 and a highly significant difference between groups 1 and 3. These results in our series relate to a tumour stage without proof of lymph node metastasis at the time of operation, that is, stage $T_1/T_2\ N_0\ M_0$. Our experience confirms the general opinion that, in patients with large tumours, the chances of cure are less than when the tumour is small. Resection of large peripheral tumours may be considered a palliative procedure to prevent complications caused by tumour necrosis, such as excessive sputum or severe bleeding.

Table 7 *Tumour size and development of metastases after operation*

Diameter of tumour (cm)	*No. of patients without proof of lymph node metastasis at time of operation*	*No. of patients developing metastasis after operation*	*Frequency of metastasis*
1–4 (Group 1)	105	44	42%
4·1–5 (Group 2)	42	21	50%
5·1–11 (Group 3)	63	46	73%

INCIDENCE OF LATE RECURRENCE AFTER OPERATION

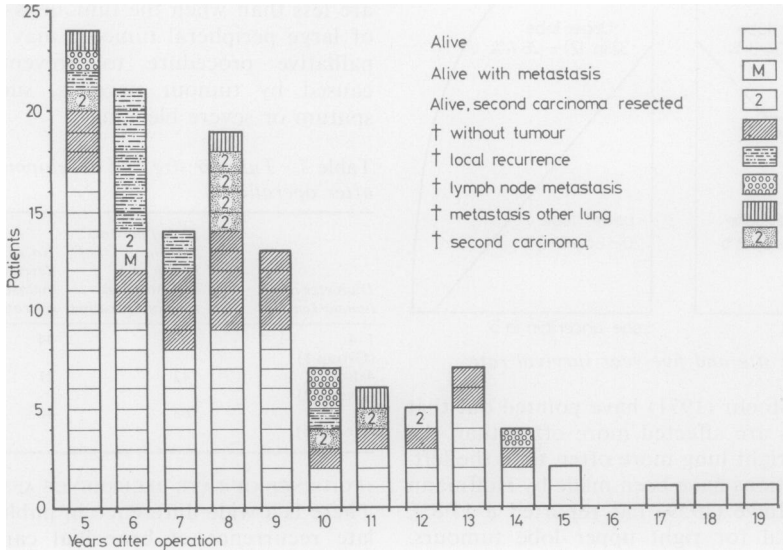
There is a wide difference in published data about late recurrence of bronchial carcinoma. Regele

and Wagner (1966) found a frequency of 1% in their extensive necropsy material. Other authors report a higher incidence; Watson (1968) reported 21 in 93, Elmendorff and Albsmeier (1969) 23 in 49, and Jones *et al.* (1967) 11 in 89 cases. The absolute criterion for accepting late recurrence is the development of carcinoma in the bronchus or parenchyma adjacent to the site of resection. If the histological type of the primary tumour and the recurrence is the same, it seems unwarranted to consider them as two separate primary tumours. For more than five years after operation we observed 11 out of 125 patients in whom tumour tissue was found close to the site of the resected primary and of a similar histological type. Two of our patients had late recurrences at the site of resection only, four had developed metastases in regional lymph nodes, four showed generalised metastases, and one had a metastasis in the other lung. The time interval before late recurrence was on average six years, and the maximum 14 years after operation (Table 8). All histological types of bronchial carcinoma were found and there was no relation between tumour stage at the time of operation and late recurrence.

The late development of malignant tissue in regional lymph nodes indicates metastasis (Regele and Wagner, 1966). There should be no doubt about associating the resected tumour with the nodes when they are situated in the drainage area of the resected carcinoma, when the same histological type is observed, and no primary is found. We have not observed late metastasis limited to local lymph nodes only. In our four cases with late lymph node metastasis occurring between the sixth and the tenth year after operation, metastasis was also found in the lung. It was not certain where the first evidence of late metastasis had occurred. In spite of finding the same histological type of tumour in all four cases, it was difficult to decide whether a late metastasis or a new primary with regional lymph node metastasis was present. The opinon of the pathologist may help in deciding between late metastasis and a second primary. The same difficulty applies to four other cases in which tumours in other parts of the lung developed between the sixth and the tenth year after operation. If the histological type corresponded to that of the original tumour the new development was considered as a late metastasis. In our eight cases of late metastasis, all cell types of tumours were found. With regard to the tumour stage, even the most favourable one, T_2 N_0, was represented six times.

The diagnosis of a second primary in the lung is sometimes justified. The increasing number of successfully resected tumours will increase the number of patients developing a second primary (Chaudhuri, 1971). Considering also the influence of inhaled carcinogenic substances on the bronchus (Hughes and Blades, 1961; Ott and Titscher, 1969) and presuming an organ disposition for developing

Table 8 *Late recurrence, late metastasis, and second carcinoma in 125 patients who underwent resection for bronchogenic carcinoma*



carcinoma in some patients (Warren and Gates, 1932; Steele, 1963), the occurrence of a second bronchial carcinoma is not surprising. Women with carcinoma of the breast develop a second carcinoma after mastectomy in the other breast six times more frequently than do controls (Desaire, 1949). On these criteria we have diagnosed two second carcinomas of the lung. In both patients eight and 11 years after resection of the primary a second bronchial carcinoma of another histological type developed in the lung, and with its own lymph node metastasis. The incidence of 2 in 125 cases is low. But the occurrence of a second carcinoma of the lung is no longer to be considered a rarity (Brock, 1964; Smith, 1966; Cacers and Felson, 1972).

Altogether 20 of 125 patients (16%) surviving more than five years after operation died of a late manifestation of their bronchial carcinoma. Two developed a new primary in the lung. Moreover, two patients developed an extrapulmonary malignancy before the late manifestation of lung carcinoma appeared. In six other patients a second malignancy was diagnosed up to 12 years after lung resection (Table 8).

Conclusions

Depending on the stage of the tumour, 6–46%—on average 28·9%—of all patients operated upon have survived five years and, of these, a high percentage are not cured. One cannot be satisfied with these results. With regard to the operative procedure, it has been proved that even unfavourable cases have a chance of long-term survival and, even if it is small, the chance should be taken (Smith, 1970; Ashor *et al.*, 1975). Large tumours, lesions involving the mediastinum or thoracic wall, or carcinomas with mediastinal lymph node metastasis can be operated upon successfully. In our opinion, the decision to operate on these patients is limited only by the risks of a thoracotomy in unresectable cases. In our patients, the rate of exploratory thoracotomy without resection is relatively low, namely, 8% with a mortality of 3%. From our experience, survival is decreased only slightly by exploratory thoracotomy. These facts indicate the value of resection even in patients with an unfavourable prognosis in order to give the only chance of cure.

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