METASTATIC PATTERN IN ADENOCARCINOMA OF THE LUNG

An autopsy study from a cohort of 137 consecutive patients with complete resection

A cohort of 137 patients with completely resected stage I or II adenocarcinoma of the lung was observed from the time of operation; the metastatic pattern determined at autopsy is described in relation to clinical, histologic, and laboratory variables. The pretreatment variables evaluated were performance status, age, gender, lactate dehydrogenase, stage, degree of differentiation, and histologic subtype of adenocarcinoma of the lung. Patients who survived longer than 30 days after operation were eligible for analysis, and 35 autopsies were performed in this patient group (autopsy rate: 39.8%). The most common intrathoracic metastatic sites were mediastinal lymph nodes (43%), lung (31%), pleura (20%), pericardium (9%), and heart (6%). The most common extrathoracic sites were liver (37%), brain (33%), bones (21%), adrenals (17%), and kidneys (17%). Patients undergoing resection for stage I disease had significantly fewer intrathoracic metastases than patients with stage II disease ($p = 0.01$). Patients who survived less than 1 year had significantly more extrathoracic metastases than patients who survived for a longer period ($p = 0.01$). Patients with highly differentiated tumors had fewer extrathoracic metastases than patients with less differentiated tumors. No other statistically significant differences were observed. Overall, patients with stage I adenocarcinoma of the lung had better local control of the disease at autopsy than those with stage II disease, but distant metastases are a large problem despite the favorable prognosis of this patient group. The extrathoracic metastatic potential was greatest for less differentiated tumors. An active adjuvant systemic therapy after resection is needed in selected patients with poorly differentiated adenocarcinomas of the lung, even in those with stage I disease. (J THORAC CARDIOVASC SURG 1995;110:1130-5)

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Surgery is the treatment of choice in patients with stage I or stage II non-small-cell lung cancer (NSCLC) and it should be performed if the patient is physically fit for the operation. Even with complete resection, the risk of recurrence of the disease is high. Adenocarcinoma of the lung (ACL) attracts increasing attention because the incidence of ACL is increasing faster than that of other major histologic types of lung cancer.[1] Some reports suggest that ACL is now the most frequent histologic type.[2] The prognosis and treatment results of ACL may differ from those of the other major types of NSCLC,[3,4] although this is not a uniform observation.[5] The five-year survival after apparently complete resection has been reported to be 40% to 69% for patients with stage I ACL and 25% for patients with stage II,[6] which emphasizes the need for adjuvant treatment. A detailed knowledge of the metastatic pattern in this disease is necessary to design appropriate programs for detection of relapse. It is also important to know whether any clinical variables predict specific metastatic patterns and may therefore be used in the selection of patient groups for adjuvant treatment.

Several studies, most of which were published three to four decades ago, have focused on autopsy findings in NSCLC.[7-12] Most of these studies included very heterogeneous patient populations, with

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Table I. *Pretreatment characteristics for patients surviving less than and more than 30 days after operation*

	Patients surviving <30 days postoperatively (n = 8)	*Patients surviving ≥30 days postoperatively and autopsy performed (n = 35)*	*All patients undergoing resection (n = 137)*
Male/female	7/1	19/16	68/69
Age in years: median (range)	65 (58-74)	61 (42-75)	60 (37-79)
LDH (U/L): median (range)	399 (280-420)	356 (138-1110)	341 (138-1110)
Survival in days: median (range)	17 (0-29)	702 (36-2238)	960 (0-2560+)
Histologic subtypes			
Acinar	3	15	78
Papillary	2	7	16
Bronchioloalveolar	3	6	24
Solid carcinoma with mucus formation	0	7	19
Degree of differentiation			
High	0	8	29
Moderate	2	9	36
Poor	6	18	72
Performance status (WHO)			
0	2	18	77
1	5	14	53
2	1	3	7
Stage (AJC)			
I	4	22	111
II	4	13	26

AJC, American Joint Committee on Cancer; *WHO,* World Health Organization.

all stages and different treatment modalities, making firm conclusions difficult. Autopsy of patients with cancer has previously been a routine procedure in many countries. More recently, the autopsy rate has declined substantially because of changes in the legal basis and also in the attitude of the population,[13-15] so that autopsy studies are increasingly difficult to obtain.

The purpose of the current study was to evaluate the metastatic pattern in relation to a variety of clinical, histologic, and laboratory parameters at the time of operation in a well-described cohort of patients with completely resected stage I or stage II ACL. Prognosis and determinants of survival in this patient group have been described previously.[16]

Patients and methods

A cohort of patients in eastern Denmark who underwent complete resection of ACL stage I or stage II lesions during the period February 1981 through July 1985 were analyzed for prognostic variables. Preoperatively staging with mediastinoscopy or computed tomography of the mediastinum, or both, was done in all patients. Biopsy-proven disease spread to the mediastinum (stage III) was regarded as a sign of inoperability, and these patients were not included in the clinical trial. Lymphadenectomy or lymph node sampling was not routinely performed.[16] If a patient had symptoms related to metastatic disease, further examinations were performed before the patient was included in the operative trial and analyses.[16] All patients were subsequently followed up for survival and for metastatic pattern in case of autopsy.

Histopathologic subtyping of ACL and degree of differentiation was performed according to criteria of the World Health Organization[17] by one pathologist, who did not know the clinical results.

ACL was divided into acinar adenocarcinoma, papillary adenocarcinoma, bronchioloalveolar carcinoma, and solid carcinoma with mucus formation. Differentiation was divided into high, moderate, and low degrees of differentiation. Bronchioloalveolar carcinoma was defined as highly differentiated, and solid carcinoma with mucus formation was defined as poorly differentiated.[17]

The pretreatment and treatment variables recorded included stage of disease, operation type, pulmonary symptoms, performance status, weight loss, age, gender, hemoglobin, leukocyte count, lactate dehydrogenase, aspartate aminotransferase, and alkaline phosphotases.[16, 18] Patient survival was recorded, and autopsy reports were requested in case of death. No patients were lost to follow-up.

The autopsy records were reviewed for organs with macroscopic or microscopic evidence of metastasis. Each organ, including sites in the central nervous system, was regarded as one site of metastasis; the specific number of metastases to each organ was not recorded.

The clinical part of the study was performed according to the Helsinki II declaration.

Nonparametric methods were used, with the χ^2 test used for comparison of proportions and the Mann-

Table II. *Organs with metastatic involvement at autopsy among 35 patients surviving more than 30 days after complete resection of stage I or II ACL*

	Stage I		*Stage II*		*Total*	
Site	*No. positive/ No. examined*	*%*	*No. positive/ No. examined*	*%*	*No. positive/ No. examined*	*%*
Mediastinum	7/23	30.4	8/12	66.7	15/35	42.9
Liver*	5/23	21.7	8/12	66.7	13/35	37.1
Brain	7/14	50	0/7	0	7/21	33.3
Secondary lung	5/23	21.7	6/32	50.0	11/35	31.4
Primary lung†	4/23	17.4	7/12	58.3	11/35	31.4
Bones	3/32	13.0	4/11	36.7	7/34	20.6
Pleura	2/23	8.7	5/12	41.7	7/35	20.0
Kidney	3/23	13.2	3/12	25.0	6/35	17.1
Adrenal glands	2/23	8.7	4/12	33.3	6/35	17.1
Meninges	2/13	15.4	1/7	14.3	3/20	15.0
Spinal cord	1/1	100	1/1	100	2/2	100
Abdomen	2/13	8.7	1/12	8.3	3/35	8.6
Pericardium	0/23	0	3/12	25.0	3/35	8.6
Spleen	2/23	8.7	1/12	8.3	3/35	8.6
Heart	0/23	0	2/12	16.7	2/35	5.7
Skin	1/22	4.5	0/11	0	1/33	3.0
Urinary bladder	0/23	0	1/12	8.3	1/35	2.9
Esophagus, stomach	1/23	4.3	0/12	0	1/35	2.9
Trachea	1/23	4.3	0/12	0	1/35	2.9
Thyroid gland	0/23	0	0/12	0	0/35	0
Pulmonary artery	0/23	0	0/12	0	0/35	0
Aorta	0/23	0	0/12	0	0/35	0
Pancreas	0/23	0	0/12	0	0/35	0
Testis/ovary	0/23	0	0/12	0	0/35	0

*Significant difference between stage I and II, $p = 0.03$, Fisher's exact test.
†Significant difference between stage I and II, $p = 0.04$, Fisher's exact test.

Whitney U test for comparison of discontinuous numeric variables between groups.

Results

A total of 137 patients with stage I or stage II ACL underwent complete resection during a 4½-year period from February 1981 through July 1985; by October 1993, 108 of these patients had died. Forty-three autopsies were performed, corresponding to an autopsy rate of 39.8%. Eight patients died within 30 days after operation, and autopsies were performed on all. These patients were excluded from the general description of the metastatic pattern and analysis in relation to clinical parameters. No metastatic sites were found at autopsy in any of these eight patients. Results of pretreatment characteristics for these eight patients are given in Table I, together with those of the 129 patients who survived more than 30 days. The pretreatment characteristics did not differ significantly between the eight patients with early perioperative death and the patients with longer survival times.

The metastatic pattern observed at autopsy for 35 patients who survived longer than 30 days after operation is given in Table II. The most common sites of metastasis were intrathoracic, with lung metastases, mediastinal lymph node involvement, and involvement of pleura, heart, and pericardium as frequent manifestations. Significant differences in frequency of organ involvement between stage I and stage II ACL were observed for primary lung ($p = 0.04$) and liver ($p = 0.03$). The most common among the extrathoracic metastatic sites were liver, brain, bones, adrenal glands, and kidneys. The median number of organs with tumor involvement was 2 (range 0 to 10); the median numbers of intrathoracic and extrathoracic sites with tumor involvement were 1 (range 0 to 5) and 1 (range 0 to 7), respectively.

The influences of clinical variables on the metastatic pattern are shown in Table III. The analyses were performed both for total number of metastatic sites and for intrathoracic (regional) sites and extrathoracic (distant) sites separately. Significant differences were observed between initial stage I and stage II disease, both with respect to the total

number of metastases and the number of intrathoracic metastases, but not for the number of extrathoracic metastases. Patients with stage I disease had fewer metastases (median 1; range 0 to 10) than did those with stage II disease (median 5; range 0 to 8; $p = 0.015$). They also had fewer intrathoracic metastases (median 0; range 0 to 4) than those with stage II disease (median 3; range 3 to 5; $p = 0.012$). Patients surviving less than 1 year had significantly more extrathoracic (distant) sites than patients with longer survival times. Furthermore, patients with lesions having highly differentiated histologic features had fewer extrathoracic metastatic sites (median 0; range 0 to 3) than did patients with moderate or poorly differentiated tumors (median 1; range 0 to 7) but did not have more regional sites. No other significant differences were seen regarding other pretreatment variables such as gender, age, lactate dehydrogenase, performance status, histologic subtype, or degree of differentiation.

Table III. *Autopsy findings of metastases in relation to pretreatment variables for 35 patients surviving more than 30 days after complete resection for stage I or II ACL*

	No. of metastatic sites		
Test size	*Total: median (range)*	*Intrathoracic: median (range)*	*Extrathoracic: median (range)*
Age (yr)			
Below	1 (0-8)	1 (0-5)	1 (0-6)
Median (60.8), *p*	0.53	0.56	0.29
Above	2 (0-10)	1 (0-4)	2 (0-7)
Survival (mo)			
Below	2 (0-8)	0 (0-5)	1 (0-4)
Median (23.4), *p*	0.18	0.59	0.11
Above	2 (0-10)	1 (0-5)	1.5 (0-7)
≤6	4 (1-7)	1,5 (0-3)	2,5 (1-4)
vs, *p*	0.71	1.00	0.41
All	2 (0-10)	1 (0-5)	1 (0-7)
≤12	2 (1-10)	1 (0-4)	1 (0-7)
vs, *p*	0.07	0.66	0.01
All	2 (0-8)	0.5 (0-5)	1 (0-4)
Lower quartile	2 (1-10)	1 (0-4)	2 (0-7)
vs, *p*	0.22	0.34	0.19
Higher quartile	2 (0-5)	0 (0-4)	1 (0-4)

Discussion

The observed difference in total number of metastases between initial stage I and stage II disease could result from different biologic characteristics of the tumors. The more aggressive, poorly differentiated tumors had a higher stage at the time of diagnosis and also had a higher number of involved organs at the time of death, despite an apparently complete resection. In addition, the presence of more extrathoracic sites in short-term survivors could be explained by a higher metastatic potential, corresponding to a more aggressive behavior of the tumor. New molecular biology techniques, such as detection of epithelial cytokeratin component 18 by monoclonal antibodies, could give further information about this characteristic.[19]

The fewer extrathoracic sites in highly differentiated tumors compared with moderate and poorly differentiated tumors may explain the previously reported observation that these tumors have a better prognosis with a slower clinical progression and longer survival.[16]

A high confidence for perioperative staging procedures is suggested by the observation that no sites of residual disease were found in the eight patients who died within 30 days after operation.

The general pattern of metastatic sites observed in this study is in accordance with previously published large, nonconsecutive series.[10, 20-22] The most frequent sites of metastatic involvement in the present study and in previous studies are shown in Table IV.

Discordance between the frequencies of metastatic organ involvement in the present study and those in previously reported studies are probably caused by imbalance in the frequency of the major histologic types of the tumors treated and also by different treatments for the study populations, including treatment modalities such as surgery, radiotherapy, and chemotherapy. Accordingly, the figures cannot be directly compared. However, some conclusions can be extracted from the data. Among these is that regional intrathoracic disease activity, including metastasis to mediastinal lymph nodes, lungs, heart, and pericardium, is common of the time of death in spite of an apparently complete resection.

Local rate of metastasis in 140 patients who died within 30 days after resection has been reported to be 28.5%, and in those with adenocarcinoma up to 43%.[23] Later studies based on pattern of metastasis with clinical implications on treatment of relapse reported local recurrence rates from 11% to 18%.[6, 24, 25] Compared with autopsy data, these figures are smaller because they include the inaccuracy of the diagnostic tools and clinical decisions and

Table IV. *Metastatic pattern in the present study and in previous studies*

	Involvement (%)				
Organs	*Present study*	*Gulluzzi et al.*[10]	*Feld et al.*[20] *(site of first relapse)*	*Oehler et al.*[22]	*Notter et al.*[21]
Mediastinum	42.9	nr	4	NR	NR
Liver	37.1	39.3	NR*	13.0	38.5
Brain/central nervous system	33.3	25.7	22	6.0	21.4
Lung (secondary)	31.4	NR	14	NR	24.8
Bones	20.6	14.6	12	12.4	26.7
Adrenals	17.1	33.5	NR*	7.6	29.4
Kidney	17.1	15.4	NR*	8.8	18.1
Spleen	8.6	5.3	NR*	NR	NR
Heart/pericardium	8.6	nr	NR*	NR	9.3

nr, Not reported; no values given in the material.
*Total percentage of "other distant sites" = 23.

Table V. *Extent of surgical treatment and summary of metastatic pattern in 43 autopsies of patients with stage I and stage II adenocarcinoma of the lung*

	*Lobectomy**	*Bilobectomy**	*Pneumonectomy**	*Total**
Autopsy summary				
Stage I				
Local (only)	3	0	0	3
Distant	6	0	1	7
Both	4	0	3	7
None	5 (2)	2 (1)	3 (1)	10
Total	18 (2)	2 (1)	7 (1)	27 (4)
Stage II				
Local (only)	1	0	1	2
Distant	0	0	3	3
Both	2	3	1	6
None	2 (1)	0	3 (3)	5
Total	5 (1)	3	8 (3)	16 (4)

*Total number of patients (number of perioperative deaths in parentheses).

represent an earlier step in the progression of the disease than the present autopsy data did. Only 5 of the 35 patients who survived more than 30 days after operation and had an autopsy died with local recurrence only, and our data did not allow firm conclusions on the relation of metastasis to the extent of the surgical procedure (Table V). Of the 15 patients who died without metastatic disease, 8 died in the postoperative period. The remaining 7 patients died of concurrent diseases: 3 of acute myocardial infarction, 1 of pulmonary embolism, 1 of acute pericarditis, 1 of pneumonia and acute pleuritis, and 1 of a new primary cancer (squamous cell carcinoma in the esophagus).

These results point toward the need for better procedures for staging of minimal, locally advanced disease; the combination of computed tomography and mediastinoscopy is recommended in the preoperative evaluation.[26, 27]

Common distant sites of relapse, both in the present study and in previous studies,[10, 20-22] are liver, brain, bones, adrenals, and kidneys (see Table IV). These sites should be monitored in studies of adjuvant treatment of patients having complete resection to achieve accurate evaluation of relapse site and recurrence-free survival.

Metastatic spread to the spleen was more prevalent than previously reported and metastases to the pancreas and abdominal nodes were less prevalent. These differences may have been caused by real biologic differences between ACL and other histologic types of NSCLC, or they may be the result of stocastic variation caused by the limited number of patients in the studies compared in Table IV.

In conclusion, among patients with completely resected ACL, a highly differentiated histology and a survival time exceeding 1 year were associated with a significantly lower incidence of extrathoracic

spread. Inversely, patients with poorly differentiated tumors and a short survival time (less than 1 year) had a significantly higher incidence of extrathoracic metastatic disease, even those initially having stage I disease. Locoregional control of disease is recognized as a well-defined problem, and adjuvant treatment is needed in ACL to improve the prognosis.

Highly effective adjuvant chemotherapy regimens in ACL have not yet been defined, even though promising results have been obtained from phase II trials. Future aspects could be to evaluate treatment results from adjuvant, postoperative chemotherapy in completely resected stage I and II ACL, especially in patients with such prognostic factors as poor differentiation with a high risk of distant metastasis and thereby a short predicted survival time.

REFERENCES

1. Dodds L, Davis S, Polissar L. A population-based study of lung cancer incidence trend by histologic type, 1974–1981. J Natl Cancer Inst 1986;76:21-9.
2. Cox JD, Yesner RA. Adenocarcinoma of the lung: recent results from the Veterans Administration Lung Group. Am Rev Respir Dis 1979;120:1025-9.
3. Eagan RT, Frytak S, Creagan ET, Richardson RL, Coles DT, Jett JR. Different response rates and survival between squamous and non-squamous non–small cell lung cancer. Am J Clin Oncol 1986;9:249-54.
4. Mountain CF, Lukeman JM, Hammar SP, et al., and the Lung Cancer Study Group Pathology Committee. Lung cancer classification: the relationship of disease extent and cell type to survival in a clinical trials population. J Surg Oncol 1987;35:147-57.
5. Greenberg ER, Korson R, Baker J, Barrett J, Baron JA, Yates J. Incidence of lung cancer by cell type: a population-based study in New Hampshire and Vermont. J Natl Cancer Inst 1984;72:599-603.
6. Thomas PA, Rubinstein L, and the Lung Cancer Study Group. Malignant disease appearing late after operation for T1 N0 non–small cell lung cancer. J THORAC CARDIOVASC SURG 1993;106:1053-7.
7. Budinger JM. Untreated bronchogenic carcinoma. Cancer 1958;11:106-16.
8. Abrams HL, Spiro R, Goldstein N. Metastases in carcinoma: analysis of 1000 autopsied cases. Cancer 1950;13:74-85.
9. Engelman RM, McNamara WL. Bronchogenic carcinoma: a statistical review of two hundred and thirty-four autopsies. J Thorac Surg 1954;27:227-37.
10. Gulluzzi S, Payne PM. Bronchial carcinoma: a statistical study of 741 necropsies with special reference to the distribution of blood-bone metastases. Br J Cancer 1955;9:511-27.
11. Guillan RA, Zelman S, Alonso RA. Adenocarcinoma of the lungs: an analysis of 24 cases in men. Am J Clin Path 1967;47:580-84.
12. Onuigbo WIB. Some pathological data on 2000 adenocarcinomas and squamous cell carcinomas of the lung. Br J Cancer 1963;17:1-7.
13. Storm HH, Andersen J. Percentage of autopsies in cancer patients in Denmark in 1971-1980. Ugeskr Læger 1986;148:1110-14. [Danish]
14. Roberts WC. The autopsy: its decline and a suggestion for its revival. N Engl J Med 1978;299:332-8.
15. Geller SA. Autopsy. Sci Am 1983;2:124-36.
16. Sørensen JB, Badsberg JH. Prognostic factors in resected stages I and II adenocarcinoma of the lung: a multivariate regression analysis of 137 consecutive patients. J THORAC CARDIOVASC SURG 1990;99:218-26.
17. World Health Organization. Histological typing of lung tumors. 2nd ed. Geneva: World Health Organization, 1981:1-41.
18. Sørensen JB, Olsen JE. Prognostic implications of histopathologic subtyping in patients with surgically treated stage I or II adenocarcinoma of the lung. J THORAC CARDIOVASC SURG 1984;97:245-51.
19. Pantel K, Izbicki JR, Angstwurm M, et al. Immunocytological detection of bone marrow micrometastasis in operable non–small cell lung cancer. Cancer Res 1993;53:1027-31.
20. Feld R, Rubinstein LV, Weisenbergeeer TH, and the Lung Cancer Study Group. Sites of recurrence in resected stage I non–small cell lung cancer: a guide for future studies. J Clin Oncol 1984;12:1352-8.
21. Notter M, Schwegler N. Metastaseninzidenz und verteilungsmunster beim bronchuskarzinom. Dtsch Med Wochenscr 1989;114:343-9. [German]
22. Oehler W, Eichhorn HJ. Autopsy and clinical findings in case of metastases of the bronchial carcinoma: study about 649 intensively irradiated patients. Strahlenther Onkol 1983;159:669-75. [German]
23. Matthews MJ, Kanhouwa S, Pickren J, Robinette D. Frequency of residual and metastatic tumor in patients undergoing curative surgical resection for lung cancer. Cancer Chemother Rep 1973;4 Pt 3:63-7.
24. Martini N, Burt ME, Bains MS, McCormack PM, Rusch VW, Ginsberg RJ. Survival after resection of stage II non–small cell lung cancer. Ann Thorac Surg 1992;54:460-6.
25. Pairolero PC, Williams DE, Bergstrahl EJ, Piehler JM, Bernatz PE. Postsurgical stage I bronchogenic carcinoma: morbid implications of recurrent disease. Ann Thorac Surg 1984;38:331-8.
26. Mountain CF. Staging and surgical treatment of lung cancer. Adv Oncol 1993;9:10-4.
27. Holmes EC. Management of early lung cancer. Adv Oncol 1993;9:15-21.