Metastatic Pattern at Autopsy in non-resectable Adenocarcinoma of the Lung

A Study From a Cohort of 259 Consecutive Patients Treated with Chemotherapy

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A cohort of 259 consecutive patients with non-resectable adenocarcinoma of the lung (ACL) received chemotherapy and were followed until death with 124 cases examined by autopsy (autopsy rate 48%). Metastatic sites were identified and the following localisations were affected in 40% or more of patients post mortem: lungs, mediastinal lymph nodes, liver, pleura, adrenals, brain, and bones. Significant more metastatic sites were observed in patients who responded to the chemotherapy compared with non-responders ($p = 0.04$), in patients aged below the median of 58 years compared with older patients ($p = 0.002$), and, as expected, in patients with initial extensive disease compared with limited disease ($p = 0.03$). In contrast, no differences in metastatic pattern at autopsy could be detected with regard to other variables, such as initial TNM-stages, degree of histological differentiation, histologic subtypes, performance status, or LDH.

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The management of adenocarcinoma of the lung (ACL), as well as in other types of non-small-cell lung cancer (NSCLC), strongly depends on the stage of the disease. The clinical course in non-resectable cases can be predicted from several established prognostic parameters including performance status, LDH, gender, age, histologic subtype, histologic degree of differentiation and extent of disease (1).

Many patients are presenting with either local or metastatic disease beyond the possibility of curative resection (2) and no standard curative treatment exists in this situation. Chemotherapy or palliative radiotherapy are the major options in this serious and frequent situation, depending on stage and symptoms (3). It has previously been showed that the metastatic pattern in another type of lung cancer, small-cell lung cancer (SCLC), were influenced by clinical response to the treatment and by several pretreatment variables such as residual primary tumor, regional lymph node involvement, and bone and renal metastases (4).

A detailed description of the metastatic spread discovered at autopsy in a homogenous, consecutive patient population with NSCLC receiving homogeneous treatment has not previously been published. The tendency of decreasing autopsy rates observed in the past few years (5–7) severely hampers autopsy studies, because such studies often lack sufficient number of patients to allow firm conclusions.

Earlier autopsy studies in lung cancer patients include patient populations with major inhomogenities with respect to factors such as histologic types, including patients with both NSCLC and SCLC histology, or treatment, including heterogenously treated patient populations who had received surgery, irradiation, or chemotherapy in various fractions (8–16). Most previous studies have either retrospectively analysed autopsy findings in cases from a defined geographic region over a certain time period or were retrospective analysed by departments of pathology, emphasising the need for data from a homogeneuos cohort of patients in a prospective study in order to obtain a more firm evaluation of the metastatic potential.

Accordingly, the purpose of the present study was to describe the metastatic pattern at autopsy in patients with non-resectable ACL. Another purpose was to elucidate a possible relation between various pretreatment variables such as histolocic subtypes and degree of differentiation of ACL and the metastatic pattern in a large prospective

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collected patient population in order to achieve information about the course of the disease with possible implications on the clinical management.

MATERIAL AND METHODS

From February 1981 through July 1985, 259 consecutive patients with inoperable ACL were treated within a randomized study comparing vindesine single agent treatment with a combination of either CCNU, methotrexate and cyclophosphamide, or a combination of all 4 drugs (17). Inclusion criterias were: histologically or cytologically confirmed non-resectable ACL, no previous chemo-or radiotherapy, no other previous or concurrent malignant disease, normal organ function, age ≤ 70 years, and a Karnofsky performance status ≥ 50. All patients had regular 4-week follow-up visits for recording of response, and no patients were lost to follow-up. Pretreatment evaluation included: complete history and physical examination, complete blood cell count, liver enzymes, bilirubin, serum electrolytes, ECG, chest roentgenogram and bone marrow biopsy. Staging was performed based on these clinical results (18). Histologic subtyping and degree of differentiation were performed according to WHO-classification by the pulmonary pathologist at the respective admitting hospital and revised by one of the authors (JEO, pathologist), (19). Treatment outcome evaluation was also performed in accordance with WHO-criteria (20). No differences in response rate or survival were observed between the three treatment arms in the randomized phase III study (17).

If death occurred in a hospital and autopsy was performed, the autopsy report was requested and the organs with malignant involvement were recorded. The number of metastases to the specific organs were not recorded, but the particular organ system involved (e.g. liver) regarded as one site. The frequency of intrathoracic (local) and extrathoracic (distant) malignant involvement was also determined.

Non-parametric statistical methods were employed. Mann-Whitney U-test was applied for comparison of distributions and χ^2-test for comparison of ratios. A two-sided p-value less than 0.05 was considered statistical significant.

"Limited" disesase was defined as disease confined to one hemithorax, including mediastinal and supraclavicular lymph nodes, whereas all the other cases were regarded as "extensive", including those with malignant pleural effusion.

RESULTS

Among all 259 patients treated with chemotherapy the response rate was 24% and the median survival was 203 days (range 1–1685). There were no significant differences in response rate or survival between the three treatment regimens (17). A total of 124 autopsies were performed, corresponding to an autopsy rate of 48%.

Patient characteristics did not differ significantly between patients who had an autopsy performed compared with those who were not autopsied (Table 1). Median age for patients with autopsy was 58 years (range 31–70) and median survival was 5.7 months (172 days; range 1–1189).

The frequencies of organs with malignant involvement are shown in Table 2. The most commonly involved sites were the following: Primary lung (97% of cases), mediastinal lymph nodes (85%), liver (54%), pleura (46%), adrenals (43%), brain (41%), bones (41%), and contralateral lung (40%). Frequencies of metastases to abdominal organs other than liver and adrenals were: abdominal lymph nodes (17%), kidneys (17%), spleen (9%), and pancreas (3%).

Eight out of 87 examined patients had meningeal involvement (9%), six of them with concurrent parenchymal brain metastases whereas 2 of these cases were without brain metastases at autopsy.

The median number of tumour-involved organs were 5 (range 0–15), while the median number of intrathoracic (local) sites were 3 (range 0–7), and of extrathoracic (distant) sites 2 (range 0–9).

The impact of various pretreatment clinical and histological characteristics on the frequency and distribution of metastatic sites at autopsy are shown in Table 3. A higher number of metastatic sites were observed in patients below the median age of 58 years compared with patients aged above the median. This difference was observed both for all metastatic sites ($p = 0.002$) and for the extrathoracic metastases ($p = 0.0012$). However, no difference was observed between the oldest and the youngest patient group with respect to the frequency of intrathoracic organ involvement ($p = 0.26$).

With respect to the impact of response to chemotherapy, significantly more extrathoracic metastases were observed at autopsy in the 25 patients responding to chemotherapy (median 3, range 0–9) compared with the 99 non-responding patients (median 2, range 0–7) ($p = 0.012$). Also the total number of metastatic sites were significantly higher among the responding patients (median 6, range 2–15), compared with the non-responding patients (median 5, range 0–12) ($p = 0.04$), but no difference was observed with respect to the intrathoracic number of sites ($p = 0.30$).

When comparing the study populations with limited versus extensive disease, significantly more extrathoracic metastatic sites were observed also post mortem in 63 patients with extensive disease (median 2, range 0–9) compared with 61 patients with limited disease (median 2, range 0–6) ($p = 0.03$). A similar difference was not observed with respect to neither the number of intrathoracic sites ($p = 0.41$) nor the total number of metastatic sites ($p = 0.30$).

Pretreatment variables such as gender, performance status, and LDH did not predict the number of metastatic sites neither with respect to total number, nor number of intrathoracic metastases or number of extrathoracic metastases. When comparing the impact of survival on

Table 1

Comparison of pretreatment characteristics and treatment outcome in 124 patients with autopsy and 135 patients without

	Patients with autopsy ($n = 124$)	Patients without autopsy ($n = 135$).
	No. of pts. (%)	No. of pts. (%)
Male/Female	69/55 (56/44)	70/65 (52/48)
Stage		
IIIa	23 (18)	42 (31)
IIIb	43 (35)	28 (21)
IV	58 (47)	65 (48)
Disease extent*		
Limited	61 (49)	46 (34)
Extensive	63 (51)	89 (66)
Histologic subtypes of ACL		
Acinar adenocarc.	62 (50)	68 (50)
Papillary adenocarc.	12 (10)	11 (8)
Bronchiolo-alveolar carc.	5 (4)	8 (6)
Solid carcinoma with mucus formation	16 (13)	16 (12)
Unclassified**	29 (23)	32 (24)
Degree of differentiation		
High	7 (6)	10 (7)
Moderate	17 (14)	18 (13)
Poor	71 (57)	75 (56)
Unclassified**	29 (23)	32 (24)
Performance status (Karnofsky)		
100–90	30 (24)	58 (43)
80–70	64 (52)	51 (38)
60–50	30 (24)	26 (19)
LDH (U/L) median (range)	418 (220–4465)	386 (223–3850)
Best response ***		
CR + PR	25 (20)	28 (21)
NC + PD	99 (80)	107 (79)

* Limited disease, confined to one hemithorax including mediastinal and supraclavicular lymph nodes; extensive disease, all other cases.
** Unclassified: Subtype and degree of differentiation can not be established due to presence of cytologic material only.
*** Abbreviations: CR: complete response, PR: partial response, NC: no change, PD: progressive disease (WHO criterias)

metastatic pattern, the analyzed groups were divided below and above the median survival. No impact on the number of total, intrathoracic or extrathoracic metastatic sites were observed (Table 3).

No difference in metastatic pattern could be detected when dividing the patients according to the New International Staging system (18) into pretreatment stage IIIa, IIIb, and IV (Table 3).

Also the degree of histologic differentiation (Table 3) or the histologic subtype (Table 3) were unable to predict the metastatic potential discovered post mortem.

DISCUSSION

Large variations in frequencies of organ involvement were reported in previous autopsy studies (10, 11, 13, 14, 21–24). None of these studies include consecutively selected patients with homogeneus treatment. Data about stage, histologic subtyping, degree of differentiation and other pretreatment variables are not available, nor concerning treatment outcome results, such as response and survival. The organs with malignant involvement in over 40% of the cases post mortem in the present study were: lungs, mediastinum, liver, pleura, adrenals, brain, and bones. Comparison of these data to previous studies are given in Table 4. Large variations are observed in frequencies of both intrathoracic and extrathoracic metastases post mortem, and an exact definition of the study population is of paramount importance in order to be able to interpret the data. Based on these findings the metastatic pattern in ACL was not conclusively different from that in small-cell lung cancer (SCLC) (4, 23).

ACL is reported to have a high incidence of parenchymal brain metastases, with 10% of the patients presenting with this manifestation at the time of diagnosis (24). During the course of the disease this risk steadily increases, estimated to be 30% for patients surviving 1 year and 40% for patients surviving 2 years (25, 26). The condition is associated with a poor prognosis, as the median survival after brain metastases is only 2.4 months (26). As the risk of this manifestation increases with increased survival brain metastases had a trend to occur more often in patients with response to chemotherapy, though not significant (26). The incidence of brain metastases of 41% in the current study confirms the magnitude of this troublesome metastatic event.

Differences in frequencies of metastatic involvement between studies might be due to selection of study populations, including differences in stage of NSCLC, differences in treatment, variation in the histologic types of NSCLC included or they may represent stocastic variation. The 0.7–10% autopsy rates in the studies in Table 4 were considerally lower than the 48% autopsy rate in the present study, raising question about how representative these previous data sets are for the entire population of patients with NSCLC.

Table 2

Organs with malignant involvement at autopsy among 124 patients treated with chemotherapy for inoperable adenocarcinoma of the lung

Organs	No. positive/No. of patients examined	(%)
Primary lung	120/124	(97)
Mediastinal lymph nodes	104/123	(85)
Liver	67/124	(54)
Pleura	57/123	(46)
Adrenals	53/124	(43)
Brain	36/87	(41)
Bones	43/106	(41)
Contralateral lung	49/124	(40)
Pericardium	29/124	(23)
Skin	7/31	(23)
Kidney	22/124	(18)
Abdominal lymph nodes	21/122	(17)
Oesophagus, stomach	12/124	(10)
Meninges	8/87	(9)
Spleen	11/124	(9)
Trachea	9/123	(7)
Thyreoid gland	7/117	(6)
Heart	7/122	(6)
Ovary	2/55	(4)
Pancreas	4/123	(3)
Aorta	3/124	(2)
Pulmonal artery	3/124	(2)
Urinary bladder	2/124	(2)
Testes	0/69	(0)
Spinal cord	0/16	(0)

The variations in pulmonary involvement at autopsy range from 14% to 97% (Table 4) which may be due to variations in treatment or stage of the included patients as no differences in the autopsy procedure or description were reported.

In the present study, 4 patients were without any sign of local recurrence at autopsy. One of these patients died more than 3 years after systemic treatment due to a cardiac event with malignant arrythmias, while three other patients died with widespread haematogenous metastases. One of these patients had a non-complete pulmonary resection before protocol enrollment but had extensive intraabdominal involvement at death, and two patients had a partial response of the evaluable tumour at chest roentgenograms but developed progressive bone-marrow involvement.

The significantly higher number of metastatic sites, both total and extrathoracic, in the study population aged below the median age point to a more aggressive course of the disease with a higher metastatic potential in younger patients.

None of the previous studies evaluated metastatic pattern at autopsy in relation to age or other pretreatment variables. Thus, no comparison with the literature was possible with regard to these topics. However, selection of patients could have an impact on such correlations. The risk of concurrent diseases increases with age and an aggressive course of ACL could possibly detoriate an older patient earlier than a younger patient. If the performance status becomes substantially affected, it may lead to exclusion from the experimental treatment, causing a potential bias in the recruitement of patients to the examined cohort.

The significantly higher number of metastatic sites, both total and extrathoracic among responding patients when compared with non-responders may be due to a prolongation of survival for the responding patients (3, 17), even though being short and not statistically significant, thereby increasing the 'risk time' for development of metastases. Such a difference for responders compared with non-responders was observed with regard to the extrathoracic sites but not for the frequencies of intrathoracic metastases.

However, no difference in metastatic pattern or frequency of different organ involvements could be detected with regard to length of survival. This may suggest that the systemic treatment may delay the development, but not basicly change the course of non-resectable ACL. If an effective systemic treatment could be defined, it would be of great value to reduce the observed high risk of distant metastases. Another possibility is that these observations were chance findings due to mass-significance because of the multiple statistical testing performed. Thus, the findings should be further investigated in subsequent studies

Table 3

Autopsy findings in 124 inoperable ACL patients related to pretreatment characteristics and treatment outcome

Variable	No. of pts	Number of metastatic sites		
		Totally median (range)	Intrathoracic median (range)	Extrathoracic median (range)
Age (years) (median 58 years)				
Below	62	6 (1-15)*	3 (1-6)	3 (0-9)**
Above	62	5 (0-10)	3 (0-7)	2 (0-7)
Disease extention				
Limited	61	5 (0-10)	3 (0-7)	2 (0-6)****
Extensive	63	6 (0-15)	3 (0-6)	2 (0-9)
Stage				
IIIa	23	6 (0-9)	3 (0-5)	2 (0-6)
IIIb	43	5 (0-15)	3 (0-7)	2 (0-9)
IV	58	6 (1-10)	3 (0-6)	2 (0-7)
Histologic degree of differentiation				
High	7	4 (2-9)	3 (0-5)	2 (0-4)
Moderately	17	5 (3-9)	3 (2-5)	2 (0-5)
Poor	71	6 (0-12)	3 (0-7)	2 (0-7)
Histologic subtyping				
Acinar	62	5 (1-2)	3 (0-7)	2 (0-7)
Papillary	12	5 (0-10)	3 (0-5)	2 (0-7)
Bronchio-alveolar	5	4 (2-9)	2 (0-5)	2 (0-4)
Solid carcinoma	16	7 (1-10)	3 (1-6)	2 (0-6)
Response				
CR + PR	25	6 (2-15)	4 (0-7)	3 (0-9)***
NC + PD	99	5 (0-12)	3 (0-6)	2 (0-7)
Survival (median 5.7 months)				
Below	62	5 (1-10)	3 (0-6)	2 (0-7)
Above	62	5 (0-15)	3 (0-7)	2 (0-9)

For abbreviations, see Table 1. * $p = 0.02$; ** $p = 0.0012$; *** $p = 0.012$; **** $p = 0.03$

for refusement as chance findings or verification as true predictors of the metastatic potential in ACL.

When analysing the metastatic pattern for patients with stage IIIa, IIIb, and IV disease no significant difference in the number and localization of metastatic sites was observed, suggesting that, when inoperability has been established, the disease will spread according to the same pattern in all stages. This emphasizes the fact that local control in stage IIIa and IIIb may not prevent distant metastatic spread, calling for more effective systemic treatment also in these cases of NSCLC.

In conclusion, the metastatic pattern in this prospective study of inoperable patients with ACL treated with chemotherapy was mostly in accordance with previously reported autopsy findings from studies including patients with other types of NSCLC as well as with respect to organs outside the primary affected lung and pleura. However, in the present study a more aggressive course, with more extrathoracic metastatic sites, was found in younger patients with age below the median of 58 years and also patients responding to chemotherapy had significantly more metastatic sites, both totally and extrathoracic, compared with non-responders. Molecular biologic markers will possibly add new knowledge about the metastatic potential and prognosis in ACL (27), but at present no marker is universally agreed upon selecting patients for systemic treatment.

The metastatic pattern was not dependent on the initial TNM-stage, but patients with initial extensive disease had significantly more organs affected also post mortem than patients with limited disease. No impact from histologic subtype or degree of differentiation was observed, possibly due to lack of statistical power as 23% of the patients were unclassified for this variable due to the presence of cytological material only.

The current findings suggest that younger patients suffer from a higher metastatic potential than older patients, and are thus candidates to be treated more aggressively in order to improve outcome of the disease.

Table 4

Previous autopsy studies in lung cancer

	Author (% organ involvement)							
	Guillan et al., 1967	Koletsky, 1938	Strauss et al., 1957	Abrams et al., 1950	Engelman et al., 1954	Onuigbo, 1963	Present study	Range
Pts. with ACL/total no. cases (%)	24/24 (100)	22/100 (22)	106/296 (36)	160/160 (100)	21/234 (9)	701/2000 (35)	124/124 (100)	22–701 (9–100)
Autopsy rate (%)	1.5	1.3	0.7*	NR	NR	10.0	48	0.7–48
Organs								
Lung (total)	17	55	68	47	24	NR	97	24–97
Med. glds	46	NR	81	83	48	NR	85	46–85
Liver	58	50	38	40	43	40	54	38–58
Pleura	25	NR	NR	28	14	NR	46	14–46
Adr. glds	58	64	43	36	52	41	43	36–64
Brain	25	NR	45	43	14	24	41	14–45
Bones	21	32	38	33	29	NR	41	21–41
Kidney	13	36	25	23	44	21	18	13–44
Spleen	17	23	12	9	5	4	9	4–23
Pancreas	17	18	11	10	0	9	3	0–18
Heart	33	23	17	8	0	NR	6	0–33

* Over a 60-year period. NR: not reported

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