Metastatic Pattern in Non-resectable Non-small Cell Lung Cancer

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This study describes the metastatic pattern at autopsy in patients with non-resectable non-small cell lung cancer (NSCLC) and evaluates the impact of various pretreatment variables and treatment outcomes on the metastatic spread. In eight phase II chemotherapy trials from 1985 through 1993, 337 patients were treated and 51 autopsies were performed (autopsy rate 15%). The male/female ratio was 31/20, median age 56 years (range 36–71), response rate to chemotherapy 8%, and median survival 88 days (range 3–899). Histologic types included adenocarcinoma, 31 cases (60%), squamous cell carcinoma, 9 cases (18%), large cell carcinoma, 9 cases (18%), and unclassified NSCLC, 2 cases (4%). Patients who were autopsied had a shorter median survival than patients without autopsy ($p = 0.002$, log-rank test). Most commonly involved metastatic sites found at autopsy were mediastinal lymph nodes (84%), pleura (51%), liver (47%), bone (34%), brain (32%), pericardium (29%), adrenals (29%) The median number of involved organs was 5 (range 1–16), with a median of 3 intrathoracic sites (range 1–8) and 2 extrathoracic sites (range 0–11). Patients who initially had metastatic NSCLC also had significantly more metastatic sites at autopsy both extrathoracic ($p = 0.004$) and totally ($p = 0.03$) compared to patients with locally advanced disease. No other relation to pretreatment variables was found.

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Non-small cell lung cancer (NSCLC) is one of the leading causes of death world-wide. Surgery is the treatment of choice, but almost 75% of the patients present with non-resectable disease (1). In most cases, the treatment options therefore include chemotherapy and/or radiotherapy (2, 3). Systemic treatment is associated with a statistically significant, though modest, improvement in survival (4).

Previous autopsy studies in patients with small-cell lung cancer (SCLC) (5) and resectable adenocarcinoma of the lung (6) have shown correlations between various clinical prognostic parameters and the metastatic spread as discovered post-mortem by autopsy. In these studies a number of pretreatment variables have significant impact on the metastatic potential in both resectable (6) and non-resectable adenocarcinoma of the lung (7): with higher pretreatment disease stage, the number of metastases increases post mortem ($p = 0.03$) (7), patients with stage I adenocarcinoma of the lung have better local control postoperatively than stage II ($p = 0.01$) (6), and poorly or moderately differentiated tumors have higher metastatic potential, i.e. more extrathoracic metastatic sites post-mortem than highly differentiated tumors ($p = 0.01$) (6). Furthermore, patients with non-resectable NSCLC with response to chemotherapy have significantly more metastatic sites at autopsy than non-responders ($p = 0.04$) (7).

In our study the aim was to describe the metastatic pattern as detected at autopsy in patients with non-resectable NSCLC who received experimental cytotoxic treatment and also to relate pretreatment prognostic variables (8) and treatment outcome (response and survival) and evaluate a possible impact of these on the metastatic potential. In patients with non-resectable NSCLC treated with experimental chemotherapy, the relation between pretreatment prognostic variables and the metastatic potential has not previously been described. Furthermore, the declining autopsy rates attributable to changes in the legal basis and the general attitude in the population severely hamper autopsy studies now and are likely to do so in the future (9–11), making it interesting to describe such data while this is still possible. Previous large autopsy series are mostly collected from geographic regions, but unfortunately, without pretreatment or uniform clinical characteristics (12). Discrepancies between clinical diagnosis or even death certificates are still common in up to 20% of patients presented for autopsy (13, 14). Accordingly, we found it of interest to collect autopsy data from patients included in eight consecutive phase II trials including all histologic

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types of NSCLC (15), thereby providing an opportunity to compare potential differences in metastatic pattern between, for example, squamous cell carcinoma and the other major histologic types (adenocarcinoma, large cell carcinoma) in NSCLC with standardized inclusion criteria, response evaluation, and treatment.

PATIENTS AND METHODS

From November 1985 to June 1993, 337 patients entered 8 consecutive phase II trials at the Departments of Oncology at Finsen Center, National University Hospital, and at Herlev Hospital, Denmark (15–23). Standardized inclusion criteria were used during the whole period and consisted of histologically confirmed non-resectable NSCLC, no previous chemo- or radiotherapy treatment, no other previous or concurrent malignant disease, normal organ function, age = 70 years, and a WHO performance status = 2. All patients had regular 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 count, liver enzymes, bilirubin, serum electrolytes, ECG, and chest roentgenograms. Staging was performed based on clinical results according to the new international staging system for lung cancer (24). Histologic classification was in accordance with the WHO classification and performed by the pulmonary pathologist at the respective admitting hospitals (25).

The applied chemotherapy and the treatment results are outlined and a résumé presented in Table 1. Treatment outcome evaluation also followed the WHO criteria and were unchanged during the period of data collection to ensure that results were comparable (26). Major clinical endpoints are shown in Table 1. The characteristics of patients submitted for autopsy are compared with those of all patients included in the phase II trials (see Table 2). All cases were classified as non-small cell lung cancer and none of the cases with any change in histology to NSCLC from pretreatment small cell lung cancer (SCLC) were included (27).

If an autopsy was allowed, the autopsy report was recorded and the organs with malignant involvement were noted. The number of metastases to the specific organs was not recorded, but the particular organ system involved (e.g. liver) was regarded as one site. The frequency of intrathoracic and extrathoracic 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 comparisons of ratios. A two-sided p-value of less than 0.05 was considered statistically significant.

RESULTS

All 333 patients have expired and 51 autopsies were performed (autopsy rate 15%).

Characteristics of patients presented for autopsy are compared with those of all the patients treated in the 8 phase II trials summarized in Table 2. The median survival for patients with autopsy performed was short: 88 days (range 3–899), emphasizing the aggressive behaviour of inoperable NSCLC, even though 33 out of 51 patients had initial stage IIIa or IIIb disease. This survival rate was significantly shorter than that for cases without autopsy ($p = 0.0002$, log-rank test). The proportion of patients of poor performance status (2 vs. 0 or 1) was significantly higher ($p = 0.001$, Mann-Whitney test) in the 51 patients with an autopsy compared with the 282 patients without autopsy (Table 2).

Frequencies of organs with malignant involvement at autopsy are presented in Table 3. The most commonly involved organs were: primary lung 96%, mediastinal lymph nodes 84%, pleura 51%, liver 47%, bone 34%, brain 32%, adrenals 29% and pericardium 29%, kidneys 22%, spleen 12%, and pancreas 8% of cases. The central nervous system was examined in 34 patients (67%) at autopsy; 3 patients (9%) had meningeal involvement, but none of these patients had this manifestation without concomitant parenchymal brain metastases.

Table 1

Treatment outcome in 333 patients with NSCLC from eight Phase II trials

Treatment	No. of patients	Median survival (days)	Response rate CR + PR (%)	Reference (no.)
TCNU (single dose)	58	139	14	23
TCNU (split dose)	39	168	10	24
TCNU + Vindesine	47	149	13	25
Iododoxorubicin	43	146	2	26
Teniposide	23	119	8	29
Gemcitabine (weekly)	32	166	16	27
Gemcitabine (twice weekly)	58	163	16	28
Gemcitabine + Vindesine	33	140	32	30
Cumulated	333	150	14*	15

*95% Confidence Interval: 11–18%.
Adapted from Larsen et al. 1995 (15).

Table 2

Comparison of pretreatment characteristics and treatment outcome in 51 NSCLC patients with and 282 patients without autopsy after experimental chemotherapy

	Patients with autopsy (n = 51). No. of patients (%)	Patients without autopsy (n = 282). No. of pts. (%)
Female/Male	20/31 (39/61)	144/138 (51/49)
Stage		
I+II	0 (0)	11 (3)
IIIa	12 (24)	73 (26)
IIIb	21 (41)	73 (28)
IV	18 (35)	125 (43)
LDH (U/L), median (range)	400 (224–1 790)	388 (87–3 120)
Histology		
Squamous cell carcinoma	9 (18)	45 (16)
Adenocarcinoma	31 (60)	200 (71)
Large cell carcinoma	9 (18)	29 (10)
Adeno-squamous carcinoma	0 (0)	5 (2)
Unclassified carcinoma	2 (4)	3 (1)
Prior surgery		
Resection	6 (12)	48 (17)
No resection	45 (88)	234 (83)
Performance Status (WHO)		
0	7 (14)	61 (22)
1	25 (49)	172 (61)
2	19 (37)*	49 (17)*
Best response		
CR+PR	4 (8)	43 (15)
NC+PD	47 (92)	239 (85)
Survival (days), median (range)	88 (3–899)**	150 (0–1619)**

*p = .001, Mann-Whitney test.
**p = .0002, log-rank test.
Abbrevations: CR = complete response; PR = partial response; NC = no change; PD = progressive disease (WHO criteria).
All patients reported have expired.

In order to define possible predisposed sites for metastases in squamous cell carcinoma, we compared the frequencies of organ-involvement in the nine cases with squamous cell carcinoma to the remaining patients with other histologic types of NSCLC (Table 3).

Among the 51 patients submitted for autopsy, the total number of organs with metastases was in median 5 (range 1–16). The median number of intrathoracic malignant sites was 3 (range 1–8), and the median number of extrathoracic metastatic sites was 2 (range 0–11).

Patients' ages at the start of chemotherapy did not predict the number of metastatic sites discovered postmortem (Table 4). Pretreatment stage had a significant impact on the metastatic autopsy pattern, as patients with initial stage IIIa disease had fewer metastatic sites both totally ($p = 0.03$) and extrathoracic ($p = 0.05$), compared with patients with initial stages IIIb and IV (Table 4). Furthermore, patients with initial metastatic disease (stage IV) had more metastatic sites totally ($p = 0.03$) and extrathoracic sites (distant) ($p = 0.004$) than patients with initial stages IIIa and IIIb (Table 4). In contrast, no differences between initial stages IIIa and IIIb could be detected.

Other pretreatment variables such as gender, performance status, histology, and LDH did not predict the number or distribution of metastatic sites at autopsy, either with respect to number of intrathoracic metastases or extrathoracic metastases. Similarly, no differences were observed between patients responding to chemotherapy and non-responders.

When comparing the impact of survival on metastatic pattern, the patients were divided in one group below and one above the median survival. Analyses for the lowest and the highest quartile of survival and correlation analyses (Spearman test) were performed with the same variables as well. No impact of the total number of intrathoracic or extrathoracic metastatic sites was detected (Table 4).

DISCUSSION

Studies of the metastatic pattern in NSCLC reveal large variations in frequencies of involvement of various organ systems (7). The most frequently involved intrathoracic sites are: lungs (24–97%), mediastinal lymph nodes (46–85%), and pleura (14–46%). The most frequently extrathoracic sites are: liver (38–58%), brain (14–45%), adrenals (36–64%), and bone (21–41%). The data from our study are within the same range. The variations observed may be due to inhomogeneity in patient selection, especially with regard to stage, but differences in primary treatment and in palliative measures could also have an impact on the findings.

Previous studies suggest that there are differences in both local recurrence rate (28–31) and distant metastatic involvement (28–30) between the major histologic types, though this was not a uniform observation, especially in later studies on resectable patients (32–34). These investigations in primarily resected patients describe the failure pattern as depending on pretreatment variables and treatment outcome. Immerman et al. (34) found that nodal involvement in patients with resectable NSCLC significantly increased the risk of first, local recurrence by 40% compared to cases without nodal involvement, in whom the highest risk was distant treatment failure ($p = 0.025$). Smaller non-significant differences between histologic types were also described with a decreased risk of overall recurrence in squamous cell carcinoma. Matthews et al. (28) reported a non-significant difference in metastatic

Table 3

Organs with most frequent involvement at autopsy among 51 patients after experimental chemotherapy for non-resectable NSCLC

Organs	Squamous cell carcinoma		Other NSCLC histologies		Totally (95% confidence intervals)	
	No. positive/no. of patients examined	(%)	No. positive/no. of patients examined	(%)	No. positive/ no. of patientsexamined	(95%–CI)
Primary lung	8/9	89	41/42	98	49/51	87–100
Mediastinal lymph nodes	6/9	67	37/42	88	43/51	71–93
Pleura	5/9	56	21/42	50	26/51	37–65
Liver	4/9	44	20/42	48	24/51	33–62
Bones	1/8	13	16/42	38	17/51	21–48
Brain	0/6	0	11/28	39	11/34	17–51
Pericardium	2/9	22	13/42	31	15/51	18–44
Adrenals	2/9	22	13/42	31	15/51	18–44

Table 4

Autopsy findings in 51 non-resectable NSCLC patients related to pretreatment characteristics and treatment outcome

Variable		No. of metastatic sites			
		No. of patients	Totally median (range)	Intrathoracic median (range)	Extrathoracic median (range)
Stage	IIIa	12	4 (1–8)*	3 (1–4)	1 (0–5)**
	IIIb + IV	39	6 (1–16)	3 (1–5)	3 (0–11)
Stage	IIIa + IIIb	33	4 (1–15)*	3 (1–8)	1 (0–7)***
	IV	18	6 (3–10)	3 (2–6)	3 (0–11)
Histology	Squamous cell carcinoma	9	5 (1–9)	3 (1–5)	2 (0–4)
	All other NSCLC	42	5 (1–16)	3 (1–8)	2 (0–11)
Performance status	0 + 1	32	5 (1–15)	3 (1–8)	2 (0–8)
WHO	2	19	5 (2–16)	4 (2–6)	3 (0–11)
Survival (median 88 days)	Below	26	5 (2–16)	3 (2–5)	2 (0–11)
	Above	25	5 (1–15)	3 (1–8)	2 (0–7)

For abbrevations, see Table 2.
*$p = 0.03$.
**$p = 0.05$.
***$p = 0.004$.

pattern after curative resection for NSCLC between the histologic types, with a higher tendency towards local recurrence in epidermoid carcinoma, whereas adenocarcinoma had a higher risk of distant metastases.

Similarly, Pairolero et al. (33) observed an increased risk of treatment failure with increased disease extension (T1 vs. T2, $p = 0.012$), especially when nodal involvement was present ($p = 0.001$). No significant differences between histologic types were found.

A lower risk of recurrence has been observed in squamous cell carcinoma when compared to other histologic types of NSCLC (24, 27), though no differences in failure pattern were detected. Feld et al. (32) found a significantly shorter time to recurrence in non-squamous histology of NSCLC after resection ($p = 0.001$). No differences in failure pattern according to TNM classification were, however, reported, though it was confirmed that time to failure was significantly shorter in T2- than in T1-disease ($p = 0.002$). Furthermore, Martini et al. (29) reported an impact of histologic type on the pattern of recurrence with a somewhat greater risk of recurrence ($p = 0.06$) and a greater frequency of distant metastases ($p = 0.001$) in other histologic types of NSCLC compared to squamous cell carcinoma, but no differences in local failures were observed.

We could not confirm these trends in the present study, probably because of lack of statistical power with 9 out of 51 autopsies in patients with squamous cell carcinoma. Another explanation for the findings may be that even in cases with variations in the clinical course between the different histologic types, these variations could be wiped out in the terminal-stages of the disease. Accordingly, in the present study we observed no such variation and it seems that different histologic types of NSCLC have simi-

lar metastatic potential at autopsy, suggesting that all histologic types of non-resectable NSCLC should be treated as one entity.

In a previous autopsy study of patients with resected adenocarcinomas (6), there were significantly more metastases after resection for stage II disease, both totally and intrathoracic (both p-values = 0.01), in patients with a survival of less than one year (p = 0.01), and in patients with less differentiated tumors (p = 0.01). In the present study we observed a significantly higher number of distant (extrathoracic) and total number of metastatic sites with increasing stages (p = 0.004 and 0.05, respectively), (Table 4). Despite increasing use of sophisticated non-invasive methods for staging, diagnostic inaccuracy still occurs in up to 20% of patients compared to autopsy findings (12, 14).

Remarkably, the group of patients who had an autopsy performed had a significantly shorter survival, than the those without autopsy. They also had a significantly poorer pretreatment performance status, compared with patients without autopsy. The poorer performance status at the start of treatment may increase the risks of toxicity and hospitalization, thereby selecting a group of patients for autopsy in contrast to patients who died outside the hospital.

Increased knowledge on what determines the metastatic potential in NSCLC could be used to enable selection of the appropriate treatment. Clinical and histologic variables are not sufficient to explain fully any differences in metastatic potential and subsequently progression, and, accordingly, increased knowledge on the biologic characteristics of the tumors is needed.

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