Factors Influencing the Distribution of Metastases and Survival in Extensive Disease Small Cell Lung Cancer

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This study was conducted to investigate the distribution of metastatic lesions and their influence on survival, as well as other prognostic factors previously shown to have an impact on the outcome of patients with extensive small cell lung cancer (SCLC). Of the 207 patients were included and retrospectively analyzed; 124 patients had extended disease at initial presentation and the remaining 83 developed metastatic disease during follow-up. Patients who relapsed presented most frequently with distant metastases. The brain was the most frequent organ targeted for metastatic disease following the completion of chemotherapy ($p < 0.05$). Serum LDH levels correlated significantly with the presence of liver metastasis ($p < 0.001$). The site of involvement did not seem to have an impact on survival. Nevertheless, patients with multiple metastatic sites had a significantly poor survival rate ($p = 0.001$). Weight loss, performance status, gender, clinical stage, serum LDH and albumin levels were all shown to correlate with survival ($p < 0.05$). Response to chemotherapy was determined to be the most important prognostic factor.

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Small cell lung cancer (SCLC), which constitutes 25% of all lung tumors, is a fatal disease with a rapid systemic dissemination. About two-thirds of patients present with distant metastasis and the remainder who present with limited stage initially eventually develop metastatic disease as a consequence of resistance to chemotherapy. Although almost all organs can be involved, the most frequent target sites are the liver, bone and the brain. Despite recent advances in the understanding of oncogenic mechanisms and therapeutic interventions, the mean survival in patients with metastatic disease does not go beyond 8–11 months; whereas patients with limited stage can live for 14–18 months.

The most important prognostic factor for patients with SCLC is the clinical stage. Increased tumor bulk and relative resistance to chemotherapy are the main factors associated with the decreased overall survival rate in patients with extensive disease. High complete response rates can be achieved in limited stage. However, the failure to achieve a high complete remission rate is thought to play an important role in the decreased overall survival in patients with extensive disease. Performance status, gender, serum LDH, ALP (alkaline phosphatase), and Na levels are other prognostic factors shown to play relevant roles in the outcome of SCLC. Bias exists in the potential role of serum albumin and Hb levels as prognostic factors.

The relevance of the site and extent of metastatic involvement in the outcome of extensive stage SCLC is well documented. Overall survival of patients with one organ, especially with soft tissue and bone involvement, is almost equivalent to those with limited disease. Conversely, in patients with liver and brain metastasis, a grave outcome is more likely.

In this retrospective study, we analyzed the metastatic pattern and survival as well as the influence of prognostic factors in patients with extensive stage SCLC.

MATERIAL AND METHODS

Two hundred and seven histologically confirmed patients with SCLC, treated in our clinic with metastatic disease from 1991 to 1997 were evaluated retrospectively; 124 patients presented initially with metastatic disease, while 83 patients with limited stage developed metastasis during treatment or follow-up.

All patients were evaluated and staged at the first visit by history, physical examination, CBC, serum biochemistry analysis, chest x-ray and CT imaging, cranial CT or MRI, whole-body scan and abdominal CT or USG (ultrasonography). After initial evaluation all patients were

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given combination chemotherapy. Response to treatment was assessed after 2 or 3 cycles and graded as standard response criteria. Treatment was continued in responded patients, while those who responded received a median of 6 cycles of therapy (1–12 cycles). Combinations included various cytotoxic agents, such as cisplatin, doxorubicine, etoposide (IV or oral), cyclophosphamide, ifosfamide, methotrexate, vincristine, and carmustine.

Overall survival was determined as the time elapsed between the time of histologic diagnosis and the date of death or the last follow-up visit. The period from the date of relapse to death or last follow-up day was referred to as the post-recurrence survival.

χ^2 tests were performed to test differences of frequencies. Overall and post-recurrence survival values were analyzed by the Kaplan–Meier method. Endpoints for survival analyses were death caused by cancer or other causes. Univariate and multivariate analyses were performed by the log-rank and Cox's proportional hazard model tests, respectively.

RESULTS

The median age of our patients was 59 years (range, 32–82) and there was a predominance of males, 92% of subjects were men. Patient characteristics are summarized in Table 1. One hundred and twenty four patients presented initially with extensive disease, while 83 developed metastatic disease during follow-up for limited stage. The distribution of metastatic involvement is shown in Table 2.

The median period from the end of chemotherapy to the first evidence of metastasis was 4 months (range, 0–19).

Table 1

Patient characteristics

Variables	n	%
Gender		
Male	190	91.8
Female	17	8.2
Performance status		
<2	81	64.8
≥ 2	44	35.2
Weight loss (%10)		
Present	94	58.4
Not present	67	41.6
Clinical stage		
Limited	83	40.1
Extensive	124	59.9
Hemoglobin (12g/dl)		
Low	61	30.3
Normal	140	69.7
Albumin (3.5 g/dl)		
Low	29	17.9
Normal	133	82.1
LDH (470 U/L)		
Normal	110	64.0
High	62	36.0

Table 2

Metastatic patterns of cases

Distribution	Metastasis at presentation	Metastasis during follow-up
No. of patients	124	110
Site of involvement		
Brain	27	51
Liver	52	15
Others*	70	23
Locally	–	34
Number of involvement		
Single	101	99
Multiple	23	11

*Bone, soft tissue, adrenal gland, bilateral lung involvement, malignant pleural effusion.

Patients who developed metastatic disease presented more frequently with cerebral involvement ($p < 0.05$). In the group with initial limited stage presentation, relapse occurred mostly in the form of distant metastasis when compared to local recurrence ($p < 0.05$) (Table 2). There was no difference in metastatic event presentation, either initially or during follow-up, with respect to the number of organ sites involved ($p = 0.11$) (Table 2).

Liver metastasis was associated with elevated serum LDH levels ($p < 0.001$) (Table 3). There was no correlation between the site of metastasis compared with other variables in patient characteristics ($p > 0.05$).

Overall survival rates of metastatic patients are presented in Table 4. Median and 1-year survival rates of initially metastatic patients were determined as 9 months and 34.5%, respectively. The median survival of those who developed metastatic disease during follow-up was 3 months. The overall survival in the same group was 14.5% (Figs. 1 and 2). There was no correlation with the site of metastatic involvement with respect to survival in either group ($p > 0.05$). Overall survival was found to be significantly lower in extensive disease with multiple organ involvement than disese with one metastatic site; 7 and 10 months, respectively ($p = 0.0013$).

All patients received systemic chemotherapy. One hundred and seventeen patients were eligible for response assessment after treatment. Overall survival rates were significantly different between responsive (complete and partial response) and non-responsive (stable and progressive response) patients ($p < 0.001$) (Table 5, Fig. 3). Sur-

Table 3

Serum LDH levels with respect to metastatic site involvement

Metastatic site	Normal LDH n	High LDH n
Brain	17	2
Liver	7	25
Others	23	12

Table 4

Survival data with respect to metastatic pattern

Parameter	Initial metastatic presentation					Metastatic development during follow-up				
	n	Median (mo)	Mean (mo)	±SD	1-year survival (%)	n	Median (mo)	Mean (mo)	±SD	1-year survival (%)
Overall survival[a]	124	9	10.8	0.8	34.5	110	3	5.5	0.7	14.5
Involvement site[b]										
Brain	22	9	14.4	2.6	40.9	45	3	5.0	0.7	12.6[c]
Liver	38	10	10.6	1.2	37.3	10	1	5.1	2.6	10.0[c]
Other	41	10	10.5	1.0	39.0	16	3	6.1	1.7	20.5[c]
Locally						28	4	4.3	0.8	5.5[c]
Chemotherapy										
Yes	124	9	10.8	0.8	34.5	30	6	9.9	1.8	26.0
No	–	–	–	–	–	80	2	4.1	0.5	10.3

[a]All metastatic cases.
[b]Cases with multiple organ involvement are not included in survival analysis.
[c]No. of patients who lived more than 1 year is <5.

vival after relapse was significantly higher in patients who received second-line chemotherapy (30 patients), compared with those in the group supplied with supportive care (80 patients); median values were 6 and 2 months, respectively. One-year survival rates in the same groups were 26 and 10%, respectively ($p = 0.001$).

Sixty-nine percent of patients (57 patients) who presented initially with limited stage disease were given additional treatment with radiotherapy. There was no difference in response to chemotherapy between radiation-treated or untreated groups. Radiation treatment did not offer a survival advantage ($p = 0.8$). Moreover, the sequence of radiotherapy administered either after 3 cycles (24 patients) or after completion of chemotherapy (29 patients) did not create a survival difference ($p = 0.1$).

Uni and multivariate analyses of prognostic factors having an impact on survival are summarized in Table 6. Response to treatment was the most important prognostic factor; while clinical stage, weight loss, performance status, gender and serum LDH and albumin levels were other relevant parameters in predicting the outcome of patients with SCLC ($p < 0.05$).

DISCUSSION

Distant metastasis is almost always encountered in the natural history of SCLC. Autopsies performed on patients who died of advanced disease have shown disease confined to the thorax in only 4% of patients (1). Initial staging evaluations have determined that 60–70% of patients present with metastatic disease. The most common sites of extrathoracic metastatic organ involvement encountered in pretreatment evaluations are the bone (19–38%), liver (17–34%), bone marrow (17–23%), lymph node (7–25%), and soft tissue (3–11%) (2–4). We have seen the same pattern of metastatic involvement in our patients. Despite the fact that patients with limited disease have a more favorable outcome than those with metastatic disease, survival of extensive stage patients with isolated unifocal brain (5–7), bone involvement (8) or malignant pleural effusion (9, 10) seems to be equivalent to those with limited disease. Generally, it has been well documented that abdominal involvement compared to supradiaphragmatic disease; multiple organ when compared to one site involvement, and presence of brain or liver metastasis are less favorable with respect to survival (3, 11). In our study overall survival of patients with multiple organ metastasis was found to be lower than survival of those with one-site involvement. However, site of involvement did not have an impact on overall survival.

Serum LDH is known to play an important role in metastatic evolution and is a relevant enzyme in the prediction of the metastatic pattern. High serum levels of LDH have been shown in patients with liver and bone

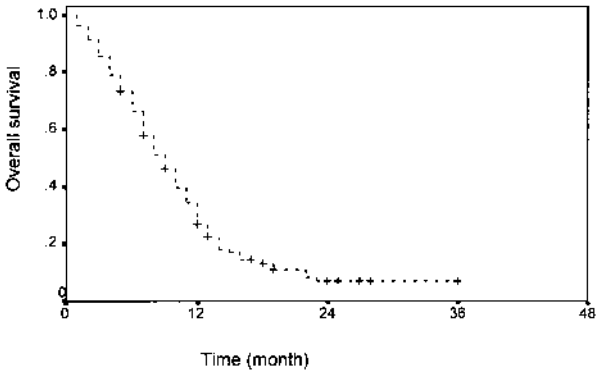

Fig. 1. Overall survival analysis of patients with metastatic presentation (median survival 9 months; 1-year survival 34.5%).

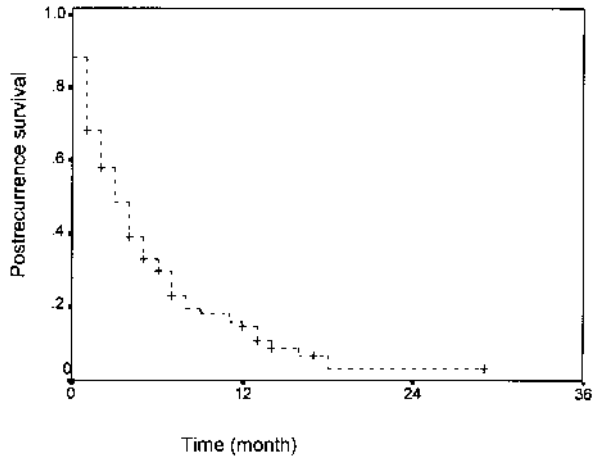

Fig. 2. Survival analysis of patients after recurrence (median survival 3 months; 1-year survival 14.5%).

marrow involvement (12, 13). We have confirmed the association between liver metastasis and high LDH levels.

The relative high frequency of cerebral metastasis in patients treated previously has been linked with the fact that most cytotoxic agents cannot pass the blood-brain barrier readily. Metastatic progression during or following chemotherapy has been associated with a lower median survival of about 8 weeks (14). Our patients who had progressive disease lived for a median of 3 months. When compared to initially metastatic patients, this value is profoundly lower. Chemotherapy offers a significant survival advantage not only as a primary treatment, but also on a second-line basis for relapsed patients. Response to treatment for initially metastatic disease persists as the most important prognostic factor on overall survival.

Many independent factors have been implicated and documented to have an impact on prognosis in patients treated with chemotherapy (9, 15–18). Parallel to literature data, we have shown that besides response to treatment as the most valuable predictive factor (3, 19); serum LDH levels (15, 20–23), performance status (3, 21), gender

Table 5

Survival data with respect to chemotherapy response status

Response	n	Median survival (mo)	1-year survival (%)
Complete response	12	22	66.7 ± 16
Partial response	44	12	46.7 ± 7
Stable response	31	8	22.6 ± 7
Progressive response	30	3	0.0*

*Maximum survival was 7 months.

Table 6

Uni- and multivariate analysis of various prognostic factors implicated to have an impact on survival

Prognostic factor	Univariate analysis (p)	Multivariate analysis (p)
Age (< > median)	0.77	0.83
Gender (male/female)	0.10	0.01
Performance status (<2/≥2)	0.001	0.005
Weight loss (yes/no)	0.003	0.02
Clinical stage (limited/extensive)	<0.001	0.04
Hemoglobin (low/normal)	0.06	0.14
Albumin (low/normal)	<0.001	0.03
LDH (normal/high)	<0.001	0.003
Response to chemotherapy (yes/no)	<0.001	<0.001

(15, 17, 22–25), weight loss (3, 21, 23), serum albumin levels (20, 25, 26), and clinical stage (21, 23, 26, 27) are strong prognostic factors for SCLC. Age and hemoglobin levels were insignificant variables in both uni- and multivariate analysis.

Although many factors have been associated with survival, response to chemotherapy is determined to be the most important prognostic factor in patients with SCLC. Despite recent advances in molecular mechanisms and

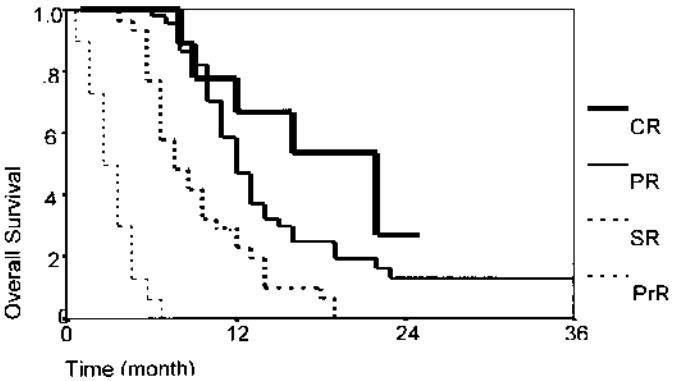

Fig. 3. Overall survival analysis of initially metastatic patients with respect to response to treatment ($p < 0.001$). CR = complet response; PR = partial response; SR = stable response; PrR = progressive response.

development of modern therapeutic approaches, maximum achieved survival advantage can be expressed only in months. Further studies are required to obtain a better understanding of the mechanisms responsible for the pathology of SCLC and to develop new insights for more effective therapeutic schemes.

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