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WHOLE BRAIN IRRADIATION FOR METASTASES FROM LUNG CARCINOMA

A clinical investigation

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Abstract

Sixty-nine consecutive patients with brain metastases from lung carcinoma were randomly allocated to one of two radiation therapy schedules: 30 Gy/10 fractions/2 weeks or 50 Gy/20 fractions/4 weeks. The improvement rate for neurologic function was similar in the two groups. The median survival times for patients receiving the short course and the long course were 4 months and 3 months, respectively. The half-year survival rate was 42 per cent after the short course and 14 per cent after the long course ($p<0.05$). Performance status and lactate dehydrogenase were other factors which significantly influenced the half-year survival rate.

Radiation therapy is an effective means of palliation for patients with brain metastases from lung carcinoma. In numerous publications, however, different opinions have been expressed concerning the value of this treatment (5). Difficulties for evaluation arise not only from the varying site and extension of the brain metastases but also from the differences in natural history and aggressiveness of the primary tumor. In addition, the clinical course may depend on the general condition of the patient and the presence or absence of other distant metastases. In September 1980, a prospective randomized trial was started at this Center in order to compare two fractionation models and to study a number of prognostic factors.

Material and Methods

From September 1980 to October 1983, 69 consecutive patients with brain metastases from lung carcinoma were treated at this institution. The diagnosis was established by clinical symptoms and by computed tomography. The patients were randomly allocated (4) to one of two treatment schedules (Table 1). Those in group A were treated with 4 MV roentgen rays from a linear accelerator using two parallel opposed fields which included the entire brain. The midline tumor dose administered was 30 Gy in 10 fractions over a 2-week period. One field was treated every treatment day. The patients in group B were treated with the same technical modalities but with 50 Gy in 20 fractions over a 4-week period. All patients received steroids (prednisone or betamethasone) during the radiation therapy.

Survival rates were calculated by the KAPLAN & MEIER method (1). The half-year (180 days) survival rate was used in order to study the influence of different factors. The significance of differences at that time was estimated by the chi-square test (Tables 2, 3). The influence of different factors on the half-year survival rate was also studied by multivariate analysis; Hayashi's method of quantification II (6).

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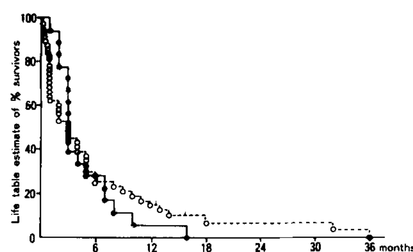

Fig. 1. Survival curves according to neurologic improvement. Not improved, (○), n=51. Improved, (●), n=18. Log rank test: Not improved versus improved, χ^2=0.047(d.f.=1, NS).

Results

The minimum follow-up time after the start of radiation therapy was 6 months. At the completion of the treatment, 25 per cent of the patients in group A and 27 per cent in group B showed definite improvement of the neurologic symptoms, while in 6 per cent in each group a deterioration in the clinical manifestations was noted. Thus, no significant difference between the two groups was noted regarding the frequency of improvement. The response rates in the different histologic groups were respectively 5 of 27 (19%) for small cell carcinoma, 2 of 6 for squamous cell carcinoma, and 10 of 32 (31%) for adenocarcinoma. The survival rates in the patients with improvement of neurologic symptoms during radiation therapy are shown in Fig. 1. There was no statistically significant difference in survival rates between the group with neurologic improvement and the unimproved group (χ^2=0.047).

The median survival time for patients in group A was 4 months and in group B 3 months. The survival curve in group B showed a rapid fall-off up to 180 days and thereafter a slower decline. In group A, the survival curve showed a slower decline during the first 180 days (Fig. 2), and the half-year survival rates in groups A and B were 42 and 14 per cent, respectively ($p<0.05$).

For the analysis, the following variables were selected: treatment modality, age, sex, histology, interval from diagnosis of primary tumor to brain metastases, multiplicity of brain metastases, other distant metastases, interval from onset of symptoms to brain irradiation, performance status, neurologic function (2), prior brain surgery, and lactate dehydrogenase (LDH). Patients with adenocarcinoma showed a somewhat better half-year survival rate than patients with small cell carcinoma but the difference was not statistically significant (Table 2). For the further analysis, adenocarcinoma was grouped with squamous cell carcinoma and small cell carcinoma with large and giant cell carcinoma. At 180 days after treatment 49 patients were dead and 20 alive.

The influence of 12 factors on the 180-day survival rate is shown in Table 3. Except for treatment method, LDH, performance status, and prior brain

Table 1

Patient characteristics

Characteristic	No. of patients		Chi-square
	Group A	Group B	
Age (years)			
≤60	17	12	1.248
60<	18	22	(d.f.=1, NS)
Sex			
Male	27	28	0.290
Female	8	6	(d.f.=1, NS)
Histology			
Large, giant and small cell carcinoma	16	16	0.013
Squamous cell carcinoma and adenocarcinoma	19	18	(d.f.=1, NS)
Primary to brain metastases interval (days)			
<180	18	17	0.014
180≤	17	17	(d.f.=1, NS)
Brain metastases			
Single	13	10	0.464
Multiple	22	24	(d.f.=1, NS)
Other than brain metastases			
Present	26	25	0.005
Absent	9	9	(d.f.=1, NS)
Onset to brain irradiation interval (days)			
<30	21	24	0.852
30≤	14	10	(d.f=1, NS)
Performance status			
1, 2	12	11	0.136
3	17	16	(d.f.=2, NS)
4	6	7	
Neurologic function (2)			
1, 2	8	8	0.502
3	21	18	(d.f.=2, NS)
4	6	8	
Prior brain surgery			
Yes	3	1	1.001
No	32	33	(d.f.=1, NS)
LDH (U/l)			
≤250	21	22	0.163
250<	14	12	(d.f.=1, NS)

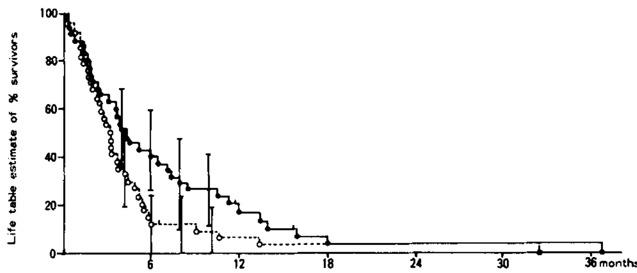

Fig. 2. Survival curves. 30 Gy/10 fractions/2 weeks (●), n=35. 50 Gy/20 fractions/4 weeks (○), n=34. Vertical bars indicate 95% confidence limits.

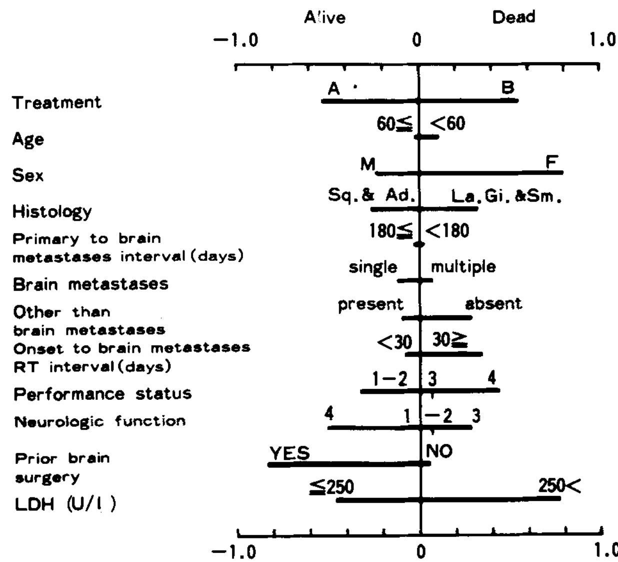

Fig. 3. Category scores for half-year survivors.

Table 2

Half-year survival rates after radiation therapy according to histology

Histologic type	Survival
Large cell carcinoma	2/3
Giant cell carcinoma	0/1
Squamous cell carcinoma	2/6
Small cell carcinoma	5/27 $>\chi^2$=1 219 (d.f.=1, NS)
Adenocarcinoma	11/32
Total	20/69

Table 3

Influence of 12 factors on the half-year survival rate. Single-factor analysis

Characteristic	Survival	Chi-square
Treatment		
A	15/35	6.640
B	5/34	(d.f.=1, p<0.01)
Age (years)		
≤60	10/29	0.734
60<	10/40	(d.f.=1, NS)
Sex		
Male	18/55	2.506
Female	2/14	(d.f.=1, NS)
Histology		
Large, giant and small cell carcinoma	7/32	1.466
Squamous cell carcinoma and adenocarcinoma	13/37	(d.f.=1, NS)
Primary to brain metastases interval (days)		
<180	10/35	0.006
180≤	10/34	(d.f.=1, NS)
Brain metastases		
Single	9/23	1.725
Multiple	11/46	(d.f.=1, NS)
Other than brain metastases		
Present	16/51	0.541
Absent	4/18	(d.f.=1, NS)
Onset to brain irradiation interval (days)		
<30	10/45	2.875
30≤	10/24	(d.f.=1, NS)
Performance status		
1, 2	11/23	7.191
3	8/33	(d.f.=2, p<0.05)
4	1/13	
Neurologic function (2)		
1, 2	8/16	5.114
3	10/39	(d.f.=2, NS)
4	2/14	
Prior brain surgery		
Yes	3/4	4.368
No	17/65	(d.f.=1, p<0.05)
LDH (U/l)		
≤250	18/43	9.190
250<	2/26	(d.f.=1, p≤0.01)

surgery no statistically significant differences were found.

The result of the multivariate analysis is illustrated in Fig. 3. Treatment method, sex, and LDH showed an extremely wide range of category scores. Histology, general performance status, neurologic function, and prior brain surgery showed a moderately wide range, while age, interval from primary to brain metastases, multiplicity of brain metastases and interval from onset of symptoms to brain irra-

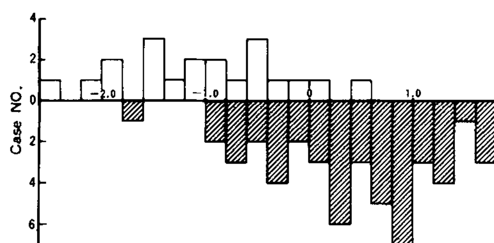

Fig. 4. Distribution of sample scores according to patient status 180 days after radiation treatment. Alive (□), n=20. Dead (■), n=49.

diation and other metastases than brain metastases had a narrow range of category score. Distribution of sample scores by patient status 180 days after treatment is shown in Fig. 4. According to this analysis, 77 per cent of all cases were discriminated by 12 factors.

Repeat irradiation was given to 6 patients because of recurrent neurologic symptoms. Computed tomography of the brain was performed in all cases and demonstrated solitary or muliple foci of metastatic disease. All 6 patients had received 30 Gy in 10 fractions over 2 weeks (group A) as an initial course of irradiation. As re-irradiation, 5 patients received 30 Gy in 10 fractions over 2 weeks and survived for more than 180 days after the start of the initial irradiation. In one patient the retreatment was interrupted after 18 Gy in 6 fractions because of general deterioration. He died 109 days after the start of the initial irradiation.

Discussion

Since estimation of the duration of response or the length of remission was difficult in this series as in others (7), the response rate was evaluated from the status at the completion of the treatment. This may be one reason for the rather poor improvement rate and the absence of significant difference in the present series. Prospective studies by KURTZ et coll. (2) did not demonstrate any difference between 30 Gy in 2 weeks (short course) and 50 Gy in 4 weeks (long course), with respect to palliation of symptoms, improvement rate, median time to progression, or median survival, except for cases with class II neurologic function. Patients with evidence of extracranial metastases, progressive uncontrolled primaries, or class IV neurologic function were excluded in their analysis.

In the present trial, prognostic factors were investigated with a method of multivariate analysis (6). According to this analysis, treatment modality, sex and LDH were factors which essentially influenced the half-year survival rate. Of these three factors, however, sex did not show a statistically significant influence according to the single-factor analysis, probably due to the small number of females included in the series. LDH showed a statistically significant influence also in the single-factor analysis. This result suggests that LDH reflects an increased aggressiveness of the tumor. It may be an important factor for deciding whether a second course of radiation therapy should be given. Histology, general performance status, neurologic function, and prior brain surgery showed a moderately wide range of category scores. Of these four factors, only performance status and prior brain surgery showed a significant influence on the half-year survival rate ($p<0.05$), in the single-factor analysis. The influence of prior brain surgery seems rather uncertain, however, due to the small number of cases, while performance status may be an important prognostic factor.

Re-irradiation was in this series effective for palliation of recurrent neurologic symptoms. KURUP et coll. (3) expressed the opinion that patients who initially responded well had a better chance of responding to a second course of radiation therapy. In order to improve the quality of life, re-irradiation of brain metastases may be of value in selected patients.

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