Prognostic Factors in Patients with Brain Metastases from Non-Small Cell Lung Carcinoma

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A retrospective study of 53 patients suffering from non-small cell carcinoma of lung with brain metastases is presented. They were treated in the Department of Therapeutic Radiology of Kyung Hee University Hospital from 1983 to 1990. There were 37 male and 16 female patients. The age range was 39 to 85 years (median=59). The most common histologic cell type of tumor was adenocarcinoma (50.9%), followed by squamous cell carcinoma and large cell carcinoma. All patients were treated with whole-brain photon irradiation (WBI) using lateral opposing fields.

The overall median survival time was 5 months. Age, sex, histologic type, and initial performance status were not prognostically important. The most important prognostic factors were the response to radiotherapy and the presence of brain metastases alone. Increasing the dose of radiotherapy to the main bulk of tumor may improve the symptom-free survival or overall survival in patients who present with brain metastases as the sole site of extrathoracic disease.

Key Words: Non-small cell lung cancer, Brain metastases, Radiotherapy

INTRODUCTION

Brain metastasis is a major problem for bronchogenic carcinoma, its incidence varys from 18% to 57%[1~4]. Large cell carcinoma and adenocarcinoma among non-small cell lung carcinomas spread to the brain as frequently as small cell carcinoma. Regardless of the primary tumor site, patients frequently develop severe neurologic dysfunction and may ultimately die of a direct consequence of metastatic cerebral deposits despite adequate control of the primary cancer site[5,6]. Due to the short median survival following diagnosis, patients with brain metastases have routinely been treated with palliative intent. Palliative therapy consists of corticosteroids and cranial irradiation. While palliative therapy can often alleviate the neurologic deficit, the overall results are variable. The median survival of patients following such palliative therapy is 3~6 months, with a few patients (20%) living beyond a year[6].

The value of whole brain irradiation has been well established for relief of specific symptoms and improvement of neurologic function with minimum morbidity and has become the preferred mode of treatment for brain metastases[5,7~9]. Order et al[9] demonstrated the superiority of radiation over surgery for most patients, in particular those with primary sites originating in the lung. They evaluated the functional improvement accomplished by radiation and showed that a higher palliative index was achieved by radiotherapy of brain metastases. This suggest that supplemental irradiation to a small volume containing gross disease might be needed in patients with a longer survival probability. However, survival benefit from such palliative treatment has proved to be relatively limited, with median values following treatment ranging between 3~6 months[5,7,9~11].

The aim of this study was to identify the prognostic factors that may influence the survival in patients with brain metastases of non-small cell lung cancer. A number of factors may influence the degree and duration of response to irradiation. These factors include: Extent of metastases, status of the primary site, neurological status, general functional status and whether corticosteroids are used. Difficulties for evaluation of these factors arise not only from the varying site and extension of brain metastases but also from differences in natural history and aggressiveness of the primary tumor. In addition, the clinical course may depend on the general condition of the patient, treatment modality, and presence or absence of other distant metastass.

MATERIALS AND METHODS

1. Selection of Patients

A retrospective study of 53 patients suffering from carcinoma of the lung with brain metastases has been undertaken. They were treated from 1983 to 1990 at the Department of Therapeutic Radiol-

ogy, Kyung Hee University Hospital. There were 37 male and 16 female patients with median age of 59 years (Range, 33~85).

Fifty-three of these patients had histological or cytological confirmation of the primary tumor. The percentage distribution by histology was: 50.9% (27/53) adenocarcinoma, 39.7%(21/53)squamous cell carcinoma, and 9.4% (5/53) large cell anaplastic cell carcinoma. All of the 53 patients were performed CT scan of brain with single lesion of 21 patients (39.6%) and multiple foci of 32 (60.4%) cases.

Two patients were considered ineligible for evaluation of the effects of radiotherapy. Brain metastases were presented at diagnosis in 35 patients, and developed subsequently in an additional 18. Clinical characteristics of all patients are listed in Table 1.

Table 1. Characteristics of Patients with Brain Metastases

Characteristics		No.
Number of patients irradiated		55
Excluded patients*		2
Evaluated patients		53
Sex		
	Male	37
	Female	16
Age		
	Median	59 yr
	Range	33–85 yr
Histology		
	Adenocarcinoma	27
	Squamous-cell	21
	Large-cell	5
Time of diagnosis		
	Synchronous	35
	Metachronous	18
Metastatic lesion of brain		
	Single	21
	Multiple	32
Extent of extrathoracic disease		
	Sole extrathoracic site	28
	Multiple extrathoracic site	25
Radiation dose		
	less 30 Gy	14
	30–40 Gy	29
	over 40 Gy	10

* 2 irradiated after surgical resection

2. Treatment

Systemic corticosteroids were administered to all patients receiving therapeutic cranial irradiation. Radiation dose and fractionation schedules were variable (180~200 cGy/20~25 fractions to 300 cGy/10~14 ractions) depending upon the patient's performace and disease status. All patients were treated with whole-brain irradiation using bilateral opposing fields by Co-60 gamma rays. The dose was prescribed at the central plane. Complete response to brain irradiation was defined as disappearance of signs and symptoms of brain metastases and/or normalization of previously abnormal brain CT scans. Partial response represented improvement of signs and symptoms of brain metastases and/or brain CT scan evidence of 50% reduction in size of tumor. All other patients were considered non-responders, except that no attempt was made to assess response in patients dying within 4 weeks of the beginning of radiotherapy. This latter group was designated as having early death.

3. Follow-up Studies

Detailed examinations of the patients were performed at the completion of irradiation and every month for the first six months after treatment, and every two or three months thereafter. Each patient was required to have an interval history, physical examination with assessment of performace status, chest films, neurological assessment to detect any evidence of intracranial metastasis, and CT scans as indicated.

4. Statistical Analysis

Survival was determined from the initiation of brain radiotherapy. Survival data were calculated using the Kaplan-Meier product limit method. Differences between subgroups were analyzed statistically by means of the log-rank test. Factors evaluated for prognostic significance included the time onset of the brain metastases after initial diagnosis of lung cancer (synchronous versus metachronous), histological cell types, extent of extrathoraicic disease, response to irradiation and number of metastatic brain lesion.

RESULTS

1. Response Rate

Response rates to irradiation according to time of presentation of brain metastases are given in

Table 2. Response to Cranial Irradiation

Time of brain metastases	No. of patients	Complete response (%)	Partial response (%)	No. response (%)	Early death (%)
Synchronous	35	13 (37.1)	11 (31.4)	6 (17.1)	5 (14.3)
Metachronous	18	6 (33.3)	4 (22.2)	4 (22.2)	4 (22.2)
All patients	53	19 (35.8)	15 (28.3)	10 (18.9)	9 (17.0)

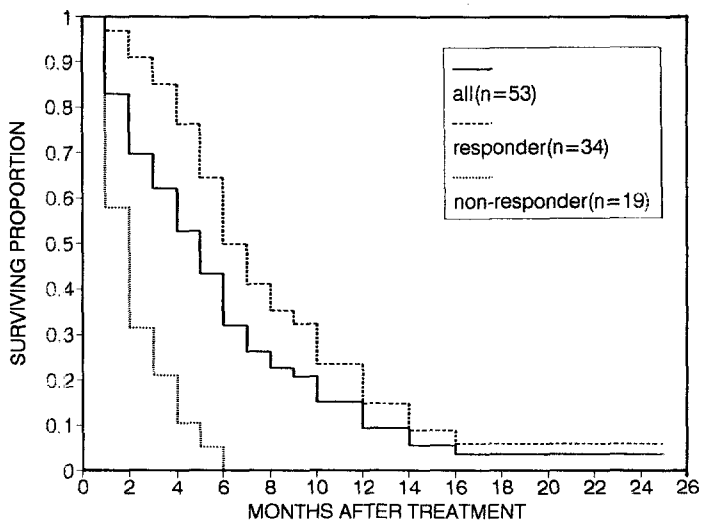

Fig. 1. Period of survival by response to craial irradiation. Non-responder was associated with significant poor survival ($p<0.001$).

Table 2. Thirty-four patients (64.1%) achieved an objective response to radiation, including 35.9% with a complete response, with response rates 68. 6% and 55.5% in patients treated for synchronous brain metastases and metachronous metastases, respectively (Table 2). Of the 36 patients available for follow-up with CT scans, the objective response rate to dexamethasone and radiotherapy was 77. 8% (28/36). The reamining 8 patients (22.2%) had no response to dexamethasone and radiotherapy, although neurologic symptoms improved in many of these patients.

2. Survival

The median survival of all 53 patients was 5 months, including 7 months for the 34 patients who showed an objective response to radiotherapy and 2 months for the 19 patients who showed no response to treatment (Fig. 1). These differences are highly statistically significant ($p<0.001$). The median survival of the 28 patients with brain metastases only was 6 months and 3 months for the 25 patients with brain and other visceral sites of multiple metastases (Table 3).

This difference is highly statistically significant ($p<0.05$), showed in Fig. 2. The actuarial survival for the three groups of patients with different histologic subtypes were also compared (Fig. 3) and there was no significant difference in overall survival ($p>0.5$). Similarly, performace status at the time of presentation was noted not prognostically important. Median survival of 21 patients with single brain lesion and of 32 patients with multiple brain metatses were 6 months and 4 months, resprectively, but there was not statistically significant difference (Fig. 4).

DISCUSSION

Carcinoma of the lung is the most common source of brain metastases (60%), while the breast is second most common (17%)[12]. More than 70% of patients improved in the performance status with whole brain irradiation, regardless of the fractionation scheme. Those receiving the large fraction sizes and shorter courses demonstrated more

Table 3. Survival from Initiation of Brain Irradiation

	Synchronous brain metastases		Metachronous brain metastases	
	No. patients	Survival Mo.	No. patients	Survival Mo.
All patients	35	6 (1–25)*	18	3 (1–16)
Response to treatment				
Responders	22	7 (1–25)	12	7 (1–20)
Non-responders	13	2 (1– 6)	6	1 (1– 3)
Brain lesion				
Single	15	7 (1–25)	6	4 (1–20)
Multiple	20	5 (1–16)	12	2 (1–10)
Extent of metastases				
Brain only	23	7 (1–25)	5	4 (1–16)
Multiple sites	12	4 (1–20)	13	2 (1–14)

* Median survival (range of survival).

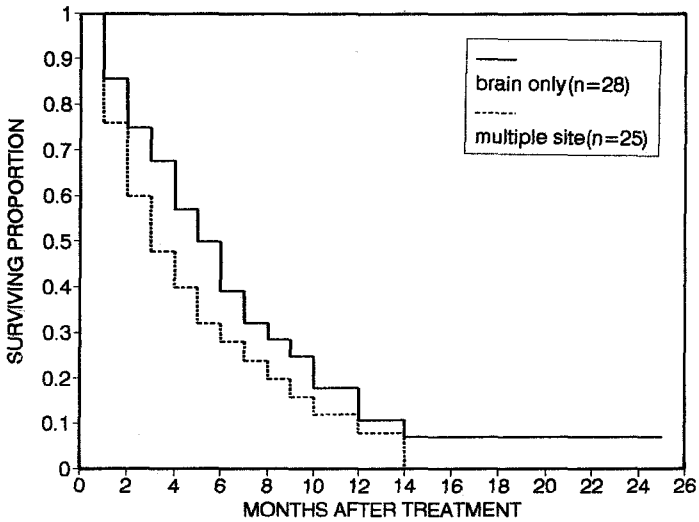

Fig. 2. Period of suvival by extent of the extrathoracic disease. The patients with multiple extrathoracic diseases were associated with poor prognosis ($p<0.05$).

prompt improvement. The development of brain metastases in non-small cell lung carcinoma heralds short-term survival. Hence, the treatment has been palliative in nature, usually consisting of whole brain radiation combined with corticosteroid administration[13]. The median survival with such forms of therapy have ranged between 4 to 6 months[5,7,14].

The detection of multiple metastatic deposits plays a critical role in the choice of therapy because most authors restrict surgery to single metasasis. Multiple deposits are present in 53% of patients, although autopsy studies suggest that smaller (<3 mm) metastases are undetected, and the frequency of multiple tumors is higher[12]. Brain metastases may present in three temporal patterns precocious (occult primary), synchronous (simultaneous primary), and metachronous (antecedent primary). Most patients (81%) present in a metachronous manner; the median interval from diagnosis of primary tumor to the discovery of cerebral metastasis in a recent series was 17 months. The mode of presentation is influenced by the primary tumor; lung, melanoma, and renal tumors tend to have short intervals from the time of initial diagnosis to evolution of a brain metastasis, whereas

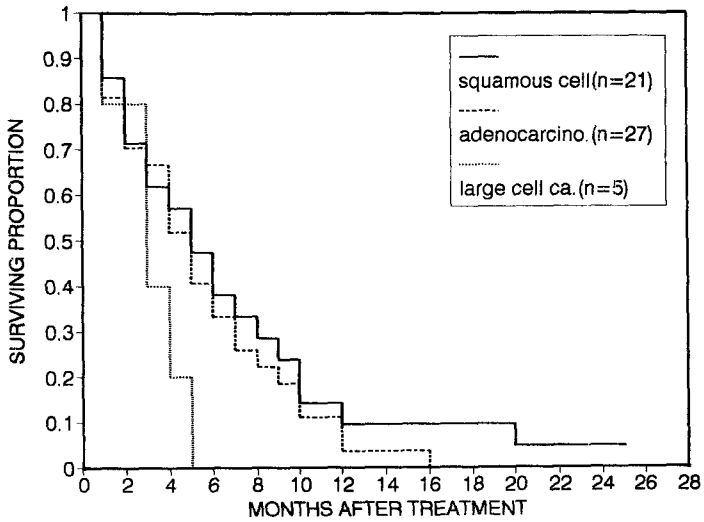

Fig. 3. Period of survival by histologic cell types. The difference between the survival curves was not statistically significant ($p>0.5$).

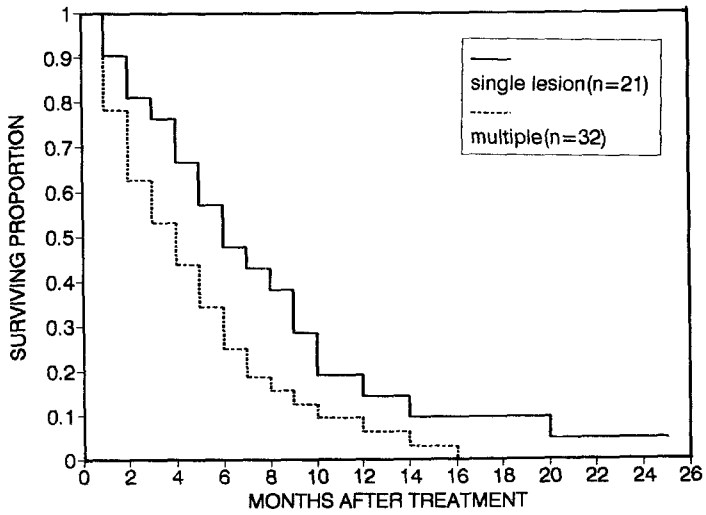

Fig. 4. Period of survival by the number of brain metastatic lesions. The difference was not statistically significant ($p>0.5$)

breast, colon, and sarcomas have long intervals[15]. Neurologic performance at the time of brain metastasis is correlated with the prognosis and favorable group tends to undergo surgery[16].

The author undertook the present analysis to identify the prognostic factors that may influence the outcome of therapy and survival. Knowledge of these potential prognostic factors may be useful in identifying patients who may respond well to treatment and in stratifying patients for future clinical trials.

The value of whole brain irradiation using conventional fractionation in patients with brain metastases in impriving the performance status is well proven[5,7,8,12~14,17,18]. The survival of this group of patients is however short, especially when the primary is in the lung and a significant proportion of survival time is occupied by the treatment. There are reports that there is no time-dose response effect and rapid fractionated WBI may be as effective as conventional treatment[8,10]. Borgelt et al[10] suggested that ambulatory patients with brain as

the only site of metastases may benefit from higher dose of cranial irradiation. Order et al[9] reported that with increased duration of survival, the proportion of patients with controlled CNS symptoms decreases. Sham et al[19] reported that a large proportion of patients (80.4%) had progression of neurological symptoms before death. It is suggested that some patients may benefit from a boost irradiation to the gross brain tumor, thus prolonging the symptom-free or overall survival. Prospective studies by Kurtz et al[20] did not demonstrated 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. In Chatani's trial[21], the median survival time for patients receiving the short course and the long course were 4 months and 3 months, respectively. The 6 month survival was 42% after the short course and 14% after the long course ($p<0.05$). Histology, general performance status, neurologic function, and prior brain surgery were studied for the prognostic factors, but performance status and prior brain surgery showed a significant influence on the half-year survival rate ($p<0.05$), in the single-factor analysis. Robin et al[22] reported that the most important factors were response to therapy (corticosteroids, radiotherapy, and chemotherapy) and the presence of brain metastases alone. Diener-West et al[23] reported that favorable prognostic characteristics were KPS 70~100, an absent or controlled primary tumor, age<60 years and metastases limited to the brain, and the patients with the highest predicted probability of surviving 200 days or more (52%) possessed all four favorable characteristics.

This study indicates that the response to radiation therapy and the absence of any metastatic deposits outside the brain are the most important two prognostic factors in patients with lung carcinoma and brain metastasis. The author found that age, sex, histologic cell type, and initial performance status were not prognosticaly important in patients with NSCLC and brain metastases. Knowledge of these potential prognostic factors may be useful in identifying patients who may respond well to treatment and in stratifying patients who enter future clinical trials.

Surgical resection has been employed in the management of brain metastases[3,15,19~22,24~27], and its superiority over conventional WBI has not been demostrated. However the patients with no extracranial disease and single brain metastases treated with surgical resection and radiation, showed encouraging results and, more specifically, in those patients with a primary lung non-small cell carcinoma[3,24~27]. Direct comparision between surgical results and historic results of conventional radiation is difficult due to variable factors involved, such as patients selection, individual institutional policy, and technique over varied time periods. Mandell et al[14] reported that, with surgical resection and radiation, the overall subjective and objective responses were 80% and 87%, respectively, and with radiation therapy alone, 83% and 72%, respectively. But their survival analysis showed a significant advantage of surgical resection and radiation over radiotherapy alone with median survival of 16 months versus 4 months ($p<0.0001$). They recommanded the absolute and relative indication for surgery including a solitary lesion with minimal neurologic impairment, limited extra-CNS disease, a long interval from the diangosis of a primary cancer to brain metastasis, and precocious presentation or occult disease. But only small proportion of patients with brain metastasis may benefit from surgical approach.

In previously irradiated patients with progressive CNS disease, retreatment with further radiation therapy is reported to be beneficial. Kurup et al[28] expressed the opinion that patients who initially responsed 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[18]. Shehata et al[29], in a series of 35 patients, reported the improvement in neurological function and duration of survival with re-irradiation. Kurup and associates[28] reported improved quality of survival in 56 patients re-treated with two or more courses of irradiation. It was a 75% response rate to the second course of irradiation and 43% to the third course. However, Hazuka[30] reported that median survival following retreatment was only 8 weeks, that is similar to the median survival reported in patients treated with steroid alone.

The present study suggests that it may be appropriate to treat the gross tumor with radiation doses of more than 40 Gy in patients with brain metastasesas as the sole site of distant metastatic disease, and timely and effective therapy for cerebral metastases can restore function or prevent the neurologic complications of cancer. Future diagnostic and therapeutic advances will hopefully offer more effective means of prevenitng and treating the neurologic complications of metastatic dis-

ease.

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= 국문초록 =

비소세포성 폐암에 의한 뇌전이 환자의 예후인자

경희대학교 의과대학 치료방사선과학교실

홍 성 언

비소세포성 폐암의 뇌전이 환자에서 방사선 치료후 예후인자를 분석하기 위하여 경희대학 부속병원 치료방사선과에서 치료받은 53예의 방사선치료 결과를 분석하였다. 전체 53예중 남자가 37명 여자가 16예이고, 연령분포는 39세부터 85세까지로 평균 59세 였다. 조직학적 소견은 선암이 27예(50.9%)로 가장 많았으며 편평세포암(21예), 대세포암(5예) 순이었다. 모든 환자에서 스테로이드투여와 함께 전뇌조사를 시행하였다. 전체 환자의 중간생존 기간은 5개월이었고, 나이, 성별, 조직형태, 초기 수행상태는 예후에 영향을 미치지 않았다. 가장 중요한 예후인자는 방사선치료후 반응여부와 뇌이외 부위의 다발성 전이 유무 였다. 따라서 뇌전이 단독소견을 가진 비소세포성 폐암 환자에서 적정한 방사선 치료선량으로 적극적인 치료로써 생존기간을 연장시키고 quality of life를 향상시킬 수 있을 것으로 기대한다.