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ORIGINAL ARTICLE

Results of hypofractionated whole brain radiotherapy (2×8 Gy) for patients with brain metastases from lung cancer

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Summary

Purpose: *To evaluate the clinical and radiologic response rates, toxicity and tolerability of 2×8 Gy whole brain radiotherapy (WBRT) in lung cancer patients with brain metastases (BM).*

Methods: *WBRT was delivered to 126 lung cancer patients with BM during 2002-2006. External beam RT was delivered with a fraction dose of 8 Gy on the same day of each consecutive week. Tumor and symptom response and toxicity were recorded at every follow-up. Recursive partitioning analysis (RPA) and the new Graded Prognostic Assessment (GPA) were used for analysis of overall survival (OS).*

Results: *Twenty-three patients had small cell (SCLC) and 103 had non small cell lung cancer. Pretreatment median Karnofsky performance score (KPS) was 70 (range 20-90). Clinical response rates were as follows: complete 31%; good partial 30.2%; partial 21.4%; stable 7.9%; and progressive 5.6%. Median palliation and survival duration was 57 and 80 days, respectively. Two- and 6-month survival rates (SR) were 59.5% and 25.4%, respectively.*

According to recursive partitioning analysis (RPA) 6-month SR for groups 1, 2 and 3 were 61.5, 41.6 and 33.9%, respectively (p=0.002). Six-month SR for the new Graded Prognostic Assessment (GPA) were: GPA 0-1, 7%; GPA 1.5-2.5, 34.2%; GPA 3, 25%; and GPA 3.5-4.0, 66.6% (p=0.0003).

Conclusion: *2×8 Gy WBRT was found to be feasible. However, the late morbidity of this schedule is unknown so its use could be restricted to patients with poor performance status, with a short life expectancy and/or social problems, unlikely to tolerate more protracted radiotherapy regimens.*

Key words: brain metastases, 2×8 Gy, non small cell lung cancer, palliative radiotherapy, small cell lung cancer

Introduction

Lung cancer is the most frequent primary malignancy among patients with BM who are treated with steroids or WBRT and with more aggressive methods like surgery or radiosurgery [1,2]. Patients with BM from lung cancer are a heterogeneous group, and many of them have very limited life expectancy. The appropriate therapeutic approach for a patient with BM depends on the patient's clinical status, the extent of disease, and the patient's wishes [3]. Although WBRT has remained a mainstay of the therapeutic strategy for BM, the results are disappointing with median survival of 2-6 months [1,3-6]. The addition of surgery or radiosurgery for the treatment of BM improves overall survival compared with WBRT alone, but this treatment could be used only in selected patients [7-9].

WBRT has long been used with palliative intent in patients with BM. WBRT has unquestioned value in the palliation of symptoms [1-14]. For WBRT, standard dose fractionation schedules are 30 Gy in 10 fractions or 20 Gy in 5 fractions [2,7]. However, short median survival durations have prompted clinicians to try different treatment schedules and alternate fractionation schedules to improve these results. The Radiation Therapy Oncology Group (RTOG) published results for two small groups of patients treated with hypofractionated regimens (10 Gy in a single fraction or 12 Gy in 2 fractions). In a non-randomized comparison, the speed of response and response rates of the two regimens were similar to the more prolonged arms and showed no obvious increase in toxicity. The duration of improvement and time to progression of the neurologic status was significantly shorter in the ultra rapid dose schedules, but the

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median survivals of patients were comparable to those of patients receiving more protracted dose schedules [12].

The Royal College of Radiologists` trial had randomized elderly and poor performance status patients to receive WBRT of 12 Gy in 2 fractions or 30 Gy in 10 fractions. In that study, the median overall survival was improved by 7 days (84 vs. 77 days) in the 10-fraction arm. Although the improvement of median survival was significant, that came at the expense of 8 extra days of treatment [13,14].

Based on the results of these previous studies, we used 16 Gy WBRT (2×8 Gy) on consecutive weeks to treat patients who also had low performance status, short life expectancy and/or social problems, like having no place to stay during treatment, problems of transportation to hospital, etc.

The primary endpoint of this trial was to evaluate the symptomatic and radiological response rates of treatment. The second and third endpoints were to assess prognostic factors and RPA related with outcome and side effects of treatment.

Methods

Patients

We reviewed the data that we collected prospectively between October 2002 and May 2006, from 126 patients with BM who were treated with palliative intent at the Ege University Medical School, Department of Radiation Oncology. Inclusion criteria for the study entry were histologically confirmed diagnosis of lung cancer, BM detectable by imaging methods and no previous cranial radiotherapy (RT). Patients with single metastasis, with high performance status and without extracranial metastases were evaluated for brain surgery. Patients not amenable for surgery, those with uncontrolled primary tumor, and/or with extracranial metastases were included in our study.

Our initial evaluation included detailed neurological and physical examination, chest radiography, magnetic resonance imaging (MRI) of the brain, complete blood count, and serum biochemistry panel. Each patient was evaluated for KPS and neurological status using the Medical Research Council-Neurological Performance Status scale (MRC-NPS) [4]. Patients who had received no treatment for their primary tumor during the 6 months preceding the diagnosis of BM were classified as having a "controlled primary tumor". BM presenting at the time of primary lung cancer diagnosis or within 6 months after the initial diagnosis were defined as synchronous metastases; BM developing more than 6 months after the initial diagnosis were defined as metachronous metastases. We determined RTOG RPA classes of the patients with BM in accordance with the methods described by Gaspar and colleagues [15]. Also, the new GPA index was used for the analysis of overall survival of our patients [16].

Treatment

WBRT comprised parallel opposed lateral fields and was prescribed to the midline. All patients were immobilized during treatment and treated with either 6 MV photons (Elekta) or Cobalt-60 (Theratron 780-c). External beam RT was delivered with a fraction dose of 8 Gy on the same day of each consecutive week. At the beginning of treatment, anticonvulsants were given to patients with a history of epilepsy. The dexamethasone dose was standardized at 16-20 mg/day during RT and was gradually decreased over 3 weeks.

Response evaluation

Patients were followed every 3-6 months with brain MRI or computed tomography (CT) and with physical examination. All symptoms were recorded at every follow-up visit. Neurological status and intellectual functions were also assessed. Tumor response to RT was evaluated by CT or MRI one month after the last day of RT. Tumor and symptom response were recorded as follows: complete response: complete disappearance of all known disease or symptoms for at least 4 weeks after treatment; good partial response: response between 80-99%; partial response: response between 50-80%; stable disease: response < 50%; and progressive disease: 25% or more increase of tumor dimension or development of new lesion(s) or symptoms. If dexamethasone was started before RT, the patient's response to RT was assessed by comparing the symptoms just before the beginning of RT. Toxicity was assessed using by the RTOG-European Organization for Research and Treatment of Cancer (EORTC) radiation morbidity criteria [17].

Statistical analysis

All statistical analyses were performed using SPSS 10.0 software (SPSS Inc., Chicago, IL). Survival was calculated according to the actuarial method of Kaplan-Meier [18]. Overall survival (OS) was defined as the time from the first day of RT to death or last follow-up. Duration of palliation was measured from the last day of RT to the first need of dexamethasone therapy. Log-rank test was employed to test for statistically significant differences. Risk of failure was determined

using the Cox proportional hazards regression model. Patient age, gender, interval from the initial diagnosis of lung cancer to the diagnosis of BM, control of primary tumor, pretreatment hemoglobin level, response to treatment, lactic dehydrogenase level (LDH), number of brain lesions, performance status and RPA class were the factors used to analyze OS. Statistical significance was set at < 0.05.

Results

Patients

The median age of the 126 patients was 58 years (range 36-78); 114 were male and 12 female. The median pretreatment KPS score was 70 (range 20-90) and the median hemoglobin level 13 g/dL (range 7.9-16.7). The vast majority of the patients (n=103) had NSCLC. The most common symptoms due to BM were headache (38.2%), loss of neurological (e.g. paresis, paresthesia etc; 16.2%), and seizures (15.4%). Metastases were multiple in 53.2% of the patients and bilateral in 64.3%. The median number of metastatic lesions was 3 (range 1-8). Patient characteristics are shown in Table 1. Sixty-two patients (49.2%) were diagnosed with lung cancer and brain metastases at the same time. In the remaining 64 the time to development of brain metastases was 6 months (range 1-25). RPA class distribution was as follows: class 1, 25.4% (n=32); class 2, 27.8% (n=35); and class 3, 46.8% (n=59).

Table 1. Patient characteristics

Characteristics	*Patients n (%)*
Gender	
Women	12 (9.5)
Men	114 (90.5)
Median age, years (range)	58 (36-78)
Median KPS (range)	70 (20-90)
Median hemoglobin level, g/dL (range)	13 (7.9-16.7)
Histopathology	
NSCLC	103 (81.7)
SCLC	23 (18.3)
Symptoms	
Headache	47 (38.2)
Seizure	19 (15.4)
Motor deficit	20 (16.3)
Ataxia	14 (11.4)
Dizziness	10 (7.9)
Vomiting	5 (4)
Others	11 (8.8)
MRC-NPS	
1	2 (1.7)
2	38 (32.8)
3	32 (27.6)
4	33 (28.4)
5	11 (9.5)
Distribution	
Frontal lobe	17 (13.5)
Parietal lobe	17 (13.5)
Occipital lobe	7 (5.6)
Temporal lobe	4 (3.2)
Cerebellum	7 (5.6)
Brain stem	7 (5.6)
Multiple lobes	67 (53.2)
Localization	
Bilateral	81 (64.8)
One side	19 (35.2)
Control of primary tumor	
Yes	74 (58.7)
No	52 (41.3)

KPS: Karnofsky performance status, NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer, MRC-NPS: Medical Research Council-Neurological Performance Status scale

Treatment

We treated 126 patients with two fractions of 8 Gy on the same days of two consecutive weeks. Nine patients died in a median of 3 days after the first fraction. The median KPS score of those patients was 30 (range 20-50) and the MRC-NPS score 5 (range 4-5). After WBRT, 27 patients received different types of chemotherapy in varying doses from 1-6 cycles.

Treatment results

Median follow-up was 90 days (range 10-727). At the end of WBRT, the median KPS score was 80 (range 20-100). Symptomatic response to WBRT was evaluated in 117 patients, with the following distribution: complete response 33.5% (n=39), good partial response 32.5% (n=38), partial response 23% (n=27), stable disease 8.5% (n=10) and progressive disease 2.5% (n=3). Three months after RT, MRI or CT of the brain were carried out in 54 patients. Radiological response rates were as follows: complete response 7.4% (n=4), good partial response 5.6% (n=3), partial response 35.2% (n=19), stable disease 44.4% (n=24) and progressive disease 7.4% (n=4). All of the patients with complete radiological response had SCLC histology.

At the time of analysis, 117 patients had died, 8 were lost to follow-up, and only one patient was alive at the 12-month follow-up, and was receiving WBRT re-irradiation (2.5 Gy/ fraction in 10 fractions) due to neurological and radiological progression. OS and palliation duration were 80 days (range 1-727) and 57 days (range 0-727), respectively. The 2- and 6-month OS rates for all patients were 59.5% and 25.4%, respectively (Figure 1).

WBRT re-irradiation was performed to 11 pa-

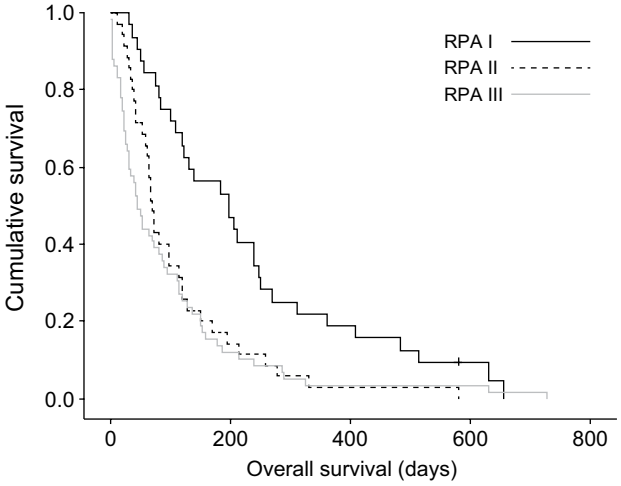

Figure 1. Comparison of RPA class I, II, III regarding survival after whole brain radiotherapy (p=0.024).

tients. Median time to neurological and/or radiological progression was 5 months (range 4-12). The median OS of these patients from the time of initial diagnosis of BM was 10.1 months (range 3.8-21).

Patterns of failure

According to univariate analysis, the prognostic factors influencing OS were KPS score above 70 (p=0.004), age under 65 years (p=0.033), hemoglobin level above 12 g/dL (p=0.037), brain metastases diagnosed metachronously (p=0.034), metastases located in one lobe (p=0.05), primary tumor under control (p=0.045), no other organ metastases (p=0.034), good response to dexamethasone therapy (p=0.000), symptomatic complete or partial response (p=0.0044), administration of chemotherapy after RT (p=0.001), normal LDH (p=0.026) and RPA class 1 (p=0.0024) (Table 2). In multivariate analysis significant factors were KPS score, chemotherapy, response to dexamethasone therapy, hemoglobin level and RPA classification. The results of the univariate and multivariate analysis are shown in Table 2.

According to the RPA classes, the median OS for groups 1, 2, and 3 were 6.5, 2.5, and 1.5 months, respectively. The 6-month OS was as follows: group 1, 61.5%; group 2, 41.6%; and group 3, 33.9% (p=0.0024) (Table 3). Using the GPA prognostic assessment index, the 6-month OS rates were: GPA 0-1, 7%; GPA 1.5-2.5, 34.2%; GPA 3, 25%; and GPA 3.5-4.0, 66.6% (p=0.0003). There were 8 patients in GPA 3 and 4 patients in GPA 3.5-4 group. When we compared GPA 0-1 and GPA 1.5-2.5 classes, the level of significance was p=0.000.

Side effects

WBRT was generally well tolerated and relatively easy to deliver. No grade 3 or 4 late side effects were encountered. The most frequently observed acute side effects related with WBRT were hair loss (n=116), and headache and mental confusion (n=19). Grade 2 mucositis was observed in one patient. Only 2 patients experienced side effects due to dexamethasone: one patient had stomach bleeding and another one developed Steven-Johnson syndrome.

Discussion

The management of BM is a significant health care problem. For many years this management has been confined to treating patients with high dose steroids, combined with WBRT, with only a small percentage of patients eligible for surgical resection of a single BM. Besides the aim of controlling these metastases, outcomes of interest include quality of life, symptom control, and neurological functions [5]. In the present study, we treated 126 patients with BM from lung cancer with 16 Gy (in 2 fractions on the same days of 2 consecutive weeks). Most of our patients had low performance status, short life expectancy and/or social problems like having no place to stay during treatment, problems of transportation to hospital, etc. The overall partial and complete response rate of the 2×8 Gy WBRT was 89%.

For over 4 decades, the mainstay of treatment for BM has been palliative WBRT. Palliative WBRT was first used in 1977 by Harwood et al. and 10 Gy were used in a single fraction compared with 30 Gy in 10 fractions. Median survival was 4.4 and 4 months, respectively [19]. The Royal College of Radiologists trial randomized 533 poor performance status patients to receive either 12 Gy in 2 fractions or 30 Gy in 10 fractions. Although the 2-week schedule improved median OS survival time, it was only by 7 days (84 vs. 77 days), and came at the expense of 8 extra days of treatment [13]. The median OS of patients in our series was 2.6 months which is in agreement with the results of Harwood and the Royal College of Radiologists. The proportion of patients with multiple BM and a short life expectancy was remarkably high in our study. In a review of the RTOG database, Gaspar et al. revealed that as many as 40% of high-risk patients do not survive more than 2 months [15]. Data from the Royal College of Radiologists study showed that one-third of the patients died within a month from starting treatment for BM [13].

Various prospective and retrospective studies that have shown improved quality of life and survival

Table 2. Univariate and multivariate analysis of patients with brain metastases from lung cancer

Analyzed factors	*Number of patients*	*Median survival (days)*	*3-month survival*	*6-month survival*	*12-month survival*	*Univariate analysis p-value*	*Multivariate analysis p-value*
Gender							
Men	114	80	47.0	26.5	7.6		
Women	12	40	33.3	11.1	0	0.18	
KPS							
<70	67	45	33.9	13.6	3.4		
≥70	59	115	56.7	35.8	10.4	0.004	0.028
Age (years)							
≥65	91	107	51.4	29.2	8.7		
<65	35	44	31.4	14.2	2.8	0.0033	0.778
Interval from diagnosis of the primary to development of brain metastases							
Metachronous (>6 months)	45	68	33.3	17.7	2.2		
Synchronous (<6 months)	80	98	52.2	30.0	10.0	0.034	0.346
Localization							
One lobe	59	115	55.9	32.2	10.2		
Multiple lobes	67	68	37.3	19.4	0.4	0.05	0.09
Control of the primary tumor							
Yes	73	115	53.4	34.2	9.5		
No	52	64	36.5	13.4	3.8	0.04	0.270
Symptomatic palliation							
Complete or partial	101	107	54.4	29.7	7.9		
Stable or progression	20	21	15.0	10.0	5.0	0.0044	0.988
Presence of extracranial metastases							
Yes	45	65	35.0	15.0	2.2		
No	77	112	54.4	32.0	10.0	0.034	0.071
Chemotherapy after RT							
Yes	27	117	92.5	59.2	18.5		
No	99	59	33.3	16.1	4	0.0001	0.028
Response to dexamethasone							
Yes	92	115	59.7	33.7	8.7	0.000	0.015
No	8	44	0	0	0		
Hemoglobin level (g/dL)							
≤12	52	64	36.5	19.2	3.8		
>12	56	115	58.9	32.1	10.7	0.0037	0.0037
LDH level							
Normal	52	120	63.4	30.0	13.0		
Elevated	36	56	33.0	19.0	2.7	0.026	0.115
Number of metastatic lesions							
1	28	115	60.1	35.7	3.5		
2-3	37	72	40.5	18.9	10.8	0.7	
>4	40	71	40.0	25.0	5.0		
RPA							
1	26	197	80.7	61.5	15.3		
2	41	75	41.4	19.5	7.3		
3	59	45	33.9	13.5	3.3	0.0024	0.013
MRC-NPS							
1	40	98	55.0	32.5	2.5		
2	31	115	58.1	25.8	0.9		
3	45	49	31.1	17.8	0.8	0.403	

KPS: Karnofsky performance status, RT: radiotherapy, RPA: recursive partitioning analysis, MRC-NPS: Medical Research Council-Neurological Performance Status scale, LDH: lactic dehydrogenase

Table 3. Response evaluation after whole brain radiation treatment

Symptoms	*Patients, n*	*Complete response n (%)*	*Good partial response n (%)*	*Partial response n (%)*	*Stable or progressive disease n (%)*
Headache	70	35 (50.0)	18 (25.7)	11 (15.7)	6 (8.6)
Dizziness	59	26 (44.1)	19 (32.2)	11 (18.6)	3 (5.1)
Ataxia	58	21 (36.2)	16 (27.6)	14 (24.1)	7 (12.1)
Seizure	21	16 (76.2)	2 (9.6)	2 (9.6)	1 (4.8)
Tinnitus	22	9 (40.9)	5 (22.7)	5 (22.7)	3 (13.6)
Disorientation	32	21 (65.5)	4 (12.5)	2 (6.2)	5 (15.6)
Visual symptoms	22	10 (45.5)	3 (13.6)	7 (31.8)	2 (9.1)
Motor deficit	33	11 (33.3)	8 (24.3)	9 (27.2)	5 (15.2)

in patients with surgical resection or radiosurgery have led to some confusion regarding the appropriate selection of patients for aggressive treatment of BM. In order to create homogeneous patient groups and to evaluate new treatment techniques, RTOG evaluated 1200 patients from 3 RTOG studies in 1997. Based on their statistical analysis, they generated a RPA classification and grouped the patients according to the presence of 3 prognostic factors: performance status, presence of extracranial metastases, and age [15]. In the RTOG study, the median OS for RPA groups 1, 2, and 3 were 7.1, 4.2 and 2.3 months, respectively [15]. The RPA was not integrated with the number of BM. Also, no standardized type and timing of the diagnostic images were defined to assess the control of systemic disease, so there could be inconsistency between the evaluations of the systemic disease. Because of these limitations, the new GPA was developed by Sperduto et al. [16]. Using the GPA classification for our patients, the 6-month OS was found lower than in the study by Sperduto et al. [16]. A likely reason for that was that, in contrast to our study, 90% of their patients KPS score was ≥ 70. They also analyzed the patients' data from 5 RTOG randomized trials. In the validation study of this index, Nieder et al. evaluated 223 patients with BM treated outside of randomized clinical trials, and the 6-month OS for each group was as follows: GPA 0-1, 10%; GPA 1.5-2.5, 38%; GPA 3, 50%; and GPA 3.5-4.0, 65% [20]. These results were similar with our series (Table 3). As our study is a retrospective analysis, the numbers of patients in the groups were not balanced. Comparing only GPA 0-1 and GPA 1.5-2.5 group (which comprised 90.4% of our patient population), a significant difference was found between the two GPA groups.

There are no widely accepted parameters for the evaluation of symptomatic response [21]. Zimm et al. evaluated quality of response depending on the symptoms and concluded that patients with headache, seizure, ataxia, dizziness and syncope responded quite well to WBRT. However, patients who had a motor deficit or disorientation, aphasia, lethargy, coma or a sensory deficit did not have a high rate of response [22]. In our study, the highest palliation rates were seen in patients with headache, disorientation and seizures (Table 4).

In view of the poor survival rates of patients with BM and their low performance status, post-treatment radiological response evaluation is difficult. Even if we followed these patients prospectively we could have obtained follow-up imaging in 42.8% of them. There is a limited number of studies dealing with the evaluation of the radiological response of patients treated for BM. Bergqvist et al. defined the tumor response of 94 patients by using CT scans (47%) or autopsy (53%); regressions occurred in 26% of the cases, and 9% of the patients were tumor-free. Also, with respect to histology, 7 of 8 patients who showed complete response had SCLC [6]. SCLC and adenocarcinoma are known to be more sensitive than other histological types [23]. In our study, radiological complete response was seen in 4 patients. Of these patients 2 had SCLC.

Disseminated metastases are usually seen in lung cancer, resulting in decreased survival. Various studies have shown that the presence of extracranial metastases varies from 57-81% [21,24]. In our study, 46 patients

Table 4. Comparison of median overall survival according to RPA classes

Study	*RPA I (months)*	*RPA II (months)*	*RPA III (months)*
RTOG [20]	7.1	4.2	2.3
Rodrigus [5]	4.8	3.3	2.0
EUTF (current study)	6.5	2.5	1.5

RPA: recursive partitioning analysis, RTOG: Radiation Therapy Oncology Group, EUTF: Ege University Faculty of Medicine

(36.1%) had extracranial metastases when BM were first detected.

The relatively low percentage of extracranial metastases in our patients could be due to their low KPS scores and social problems which created obstacles in carrying out full metastatic investigation.

Performance status has been shown by several authors to be a major determinant of survival [15,16, 21,24,25]. We saw similar improvement in our series; the patients with KPS score <70 or > 70 had median survival 2 and 3.6 months, respectively.

Serum LDH level has been established as an important indicator for tumor burden and progressive disease [26]. Elevation of LDH proved to be an independent significant unfavorable prognostic factor for patients with BM [14,25,26]. Lagerward et al. investigated the impact of serum LDH on median survival. Survival for patients with elevated LDH was lower (2.3 months) compared with patients with normal LDH levels (4 months) [25]. In our study, median survival of patients with elevated LDH was decreased from 4 months to 1.8 months.

Conclusion

WBRT is still the most effective means of treating patients with BM with symptom relief occurring in 70-90% of the cases. The results of our retrospective study clearly showed that 16 Gy hypofractionated WBRT (8 Gy/fraction and 2 fractions on consecutive weeks) is a feasible treatment for patients with BM from lung cancer. Our results also indicated that this approach has acceptable early side effects. Long term side effects were not known. The prognostic factors such as performance status, age, status of the primary tumor, response to steroid treatment, presence of other metastases, and serum LDH level were also consistent with the literature. However, the late morbidity of this schedule is unknown at the moment and the conclusions were based on a retrospective study, so their use should be restricted to patients with poor performance status, short life expectancy, and social problems, as seen commonly in patients with lung cancer in daily practice.

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