SURVIVAL AND PROGNOSTIC FACTOR ANALYSIS IN WHOLE BRAIN IRRADIATION OF PATIENTS WITH BRAIN METASTASES

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ABSTRACT

Objective: The aim of the study was to analyse the survival results in patients with brain metastases treated by whole brain external radiotherapy and determine the prognostic factors affecting survival.

Methods: Eighty-three patients with brain metastases were treated by external radiotherapy. Before irradiation 21 had metastatectomy, 4 had stereotactic radiosurgery and 4 had stereotactic biopsy for diagnosis. The primary tumor was controlled in 39 patients (47%), 30 (36%) had metastases other than brain. Whole cranial irradiation was performed on all patients by a linear accelerator with 6 MV energy.

Results: Median follow-up for all patients was 14 weeks (1-143 weeks). Median overall survival and 1 year survival for the whole group was 14 weeks and 25%, respectively. Cranial progression free survival was median 40 weeks. In multivariate analysis Karnofsky Performance Scale score, gender and metastatectomy / radiosurgery were found to be independent prognostic factors.

Conclusion: External radiotherapy is an efficient treatment modality for palliation and stabilizing cranial progression in patients with brain metastases. Better survival results are obtained in younger, solitary metastatic patients with good performance status and controlled systemic disease when metastatectomy or radiosurgery added.

Key Words: Brain metastases, Radiotherapy, Prognostic factors.

INTRODUCTION

Brain metastases occur in approximately 30% of cancer patients and represent the most common type of intracranial tumors (1). They exert a profound effect on the quality and length of life and directly cause death in 1/3 to 1/2 of the patients (2). Lung (especially small cell, adeno types), breast, melanoma and colorectal cancers have a propensity to metastasize in the brain more frequenlty though it may happen in any type of cancer (3). About half of the patients present with single lesion (4). Although these patients have poor prognosis for long-term survival, treatment is mandatory for immediate palliation of cranial symptoms and durable symptom-free remission. Median survival of symptomatic patients with brain metastases is 1 month without any treatment, 2 months with steroid treatment (5). Whole brain irradiation prolongs survival to 3-5 months and achieves palliation of symptoms for a longer period with moderate doses like 30 Gy/10 fractions (2, 6). Occasionally in patients

(Accepted 20 September, 2000) *Marmara Medical Journal 2001;14(1):7-11*

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with single cerebellar or large cavitating cerebral lesions who need urgent palliation surgical removal is a favourite option prior to radiation treatment (7). Recent literature supports radiosurgery as an alternative treatment to surgery in selected patients (8).

In order to compute survival results with whole brain irradiation and to identify prognostic factors affecting survival, we performed a retrospective analysis.

MATERIALS AND METHODS

Eighty-three patients with diagnosis of brain metastases who applied to our department for palliative radiotherapy were evaluated retrospectively. Characteristics of the patients are seen on Table I. Before radiotherapy 19 cases had a metastatectomy operation, 2 had gammaknife radiosurgery and 4 had a stereotactic biopsy for diagnosis. Furthermore, two patients had both metastatectomy and radiosurgery.

Table I. Characteristics of the patients.

	number (%)
Male	59 (71.1%)
Female	24 (28.9%)
Age	median 57 (35-82 range)
≥ 57	46 (55.4%)
< 57	37 (44.6%)
Primary origin	
Lung	40 (48.2%)
Breast	11 (13.3%)
Primary unknown	22 (26.5%)
Others	10 (12.0%)
Solitary metastases	19 (22.9%)
Multiple metastases	64 (77.1%)
Karnofsky Performance Scale score	
80-100	57 (68.7%)
50-70	23 (27.7%)
30-40	3 (3.6%)

The primary tumor was controlled in 39 (47%) of the patients after diagnosis of brain metastases. Thirty patients (36%) had distant metastases other than brain.

All patients were irradiated by a linear accelerator with 6 MV energy. Radiation was given with two parallel opposed beams covering the whole brain. Median total dose to whole brain was 30 Gy (5-33 Gy). Seven of them were boosted to a smaller volume with median 6 Gy (6-15 Gy). Overall and progression free survival curves were drawn by Kaplan-Meier estimates (9). Overall survival was calculated from the start of radiotherapy to death of any reason and cranial progression for symptomatic or radiological progression in the cranium. Univariate analysis was performed for age, gender, primary tumor type, Karnofsky Performance Scale (KPS) score, multiplicity, presence of other distant metastases and presence of metastatectomy/radiosurgery (M/RS) by log-rank test. Independent prognostic factors were identified by Cox regression analysis using the significant factors in univariate analysis (10).

RESULTS

Median follow-up for all patients was 14 weeks (1-143 weeks). At the time of analysis 59 out of 83 patients were dead related to their disease while 2 patients had died because of intercurrent events. Median overall survival and 1 year survival for the whole group was 14 weeks and 25%, respectively (Fig. 1). Progression free survival median was 40 weeks (Fig. 2).

In 23 patients with M/RS median survival was 65 weeks while in 60 patients with only radiotherapy it was 12 weeks ($p<0.001$) (Fig. 3). Patients with solitary and multiple metastatic lesions had a median survival of 62 weeks and 12 weeks, respectively ($p=0.006$) (Fig. 4).

Other prognostic factors found to be significant for survival in univariate analysis were KPS score, distant metastases other than brain and age (Figs. 5, 6, 7). Male gender showed a trend for worse prognosis (Fig. 8). Primary tumor type did not influence outcome ($p>0.05$). Statistically significant prognostic factors in univariate analysis were entered in multivariate analysis. In multivariate Cox regression analysis KPS score,

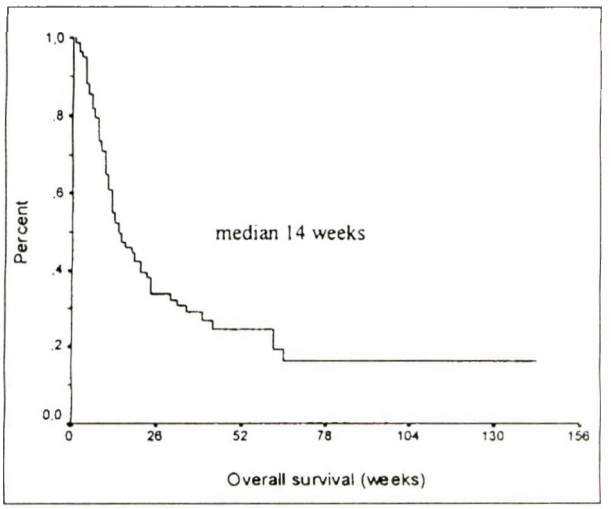

Fig.1.: Overall survival rate of all patients.

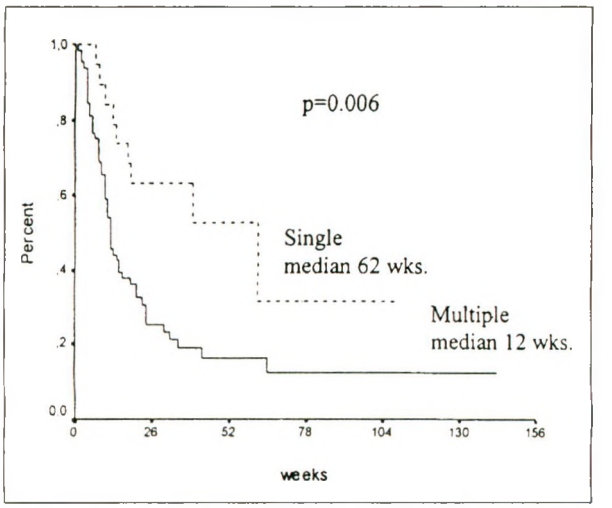

Fig.4.: Comparison of survival rates for patients with single and multiple metastases.

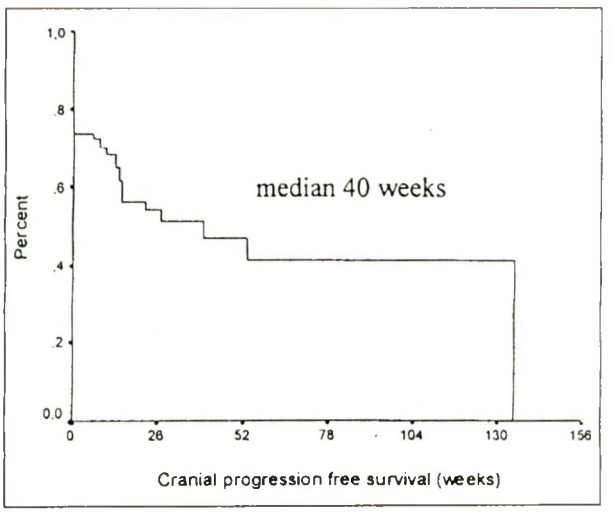

Fig.2.: Cranial progression free survival rate.

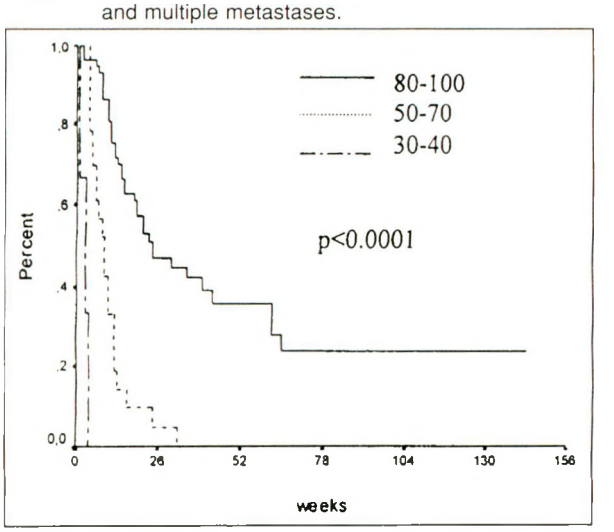

Fig.5.: Comparison of survival rates due to Karnofsky Performance Scale scores.

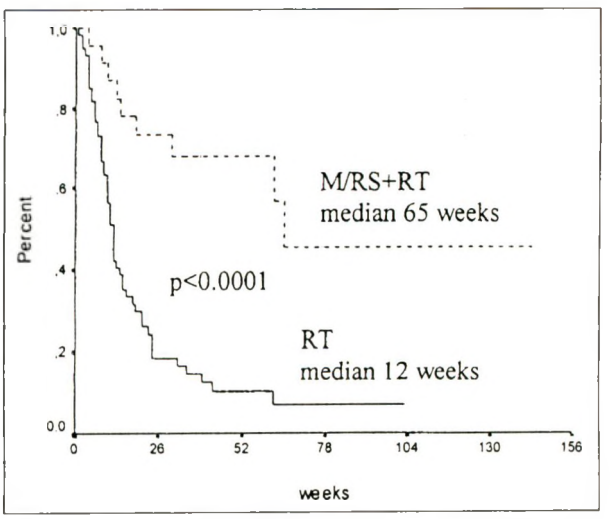

Fig.3.: Comparison of overall survival rates for metastatectomy/radiosurgery + radiotherapy (M/S+RT) and radiotherapy alone (RT) groups.

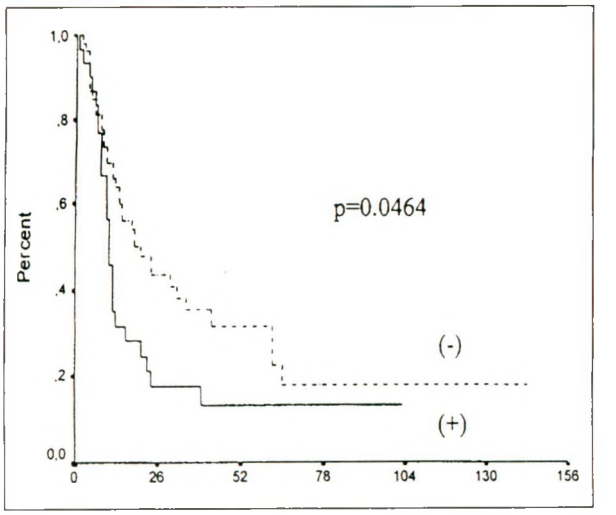

Fig.6.: Survival rate curves due to absence (-) or presence (+) of distant metastases other than brain.

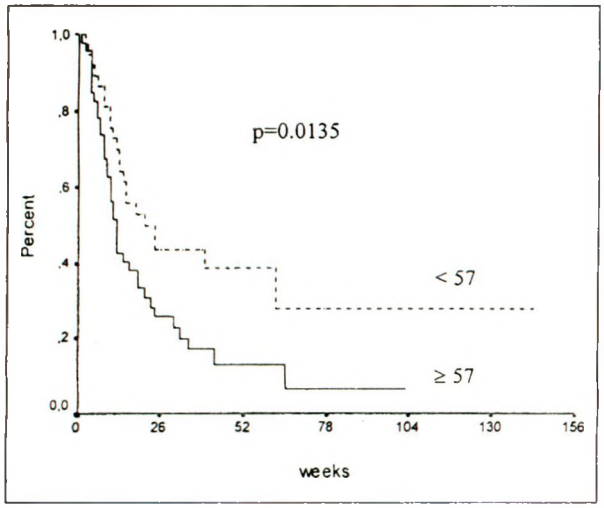

Fig.7.: Survival rate curves due to age distribution of <57 vs. ≥57.

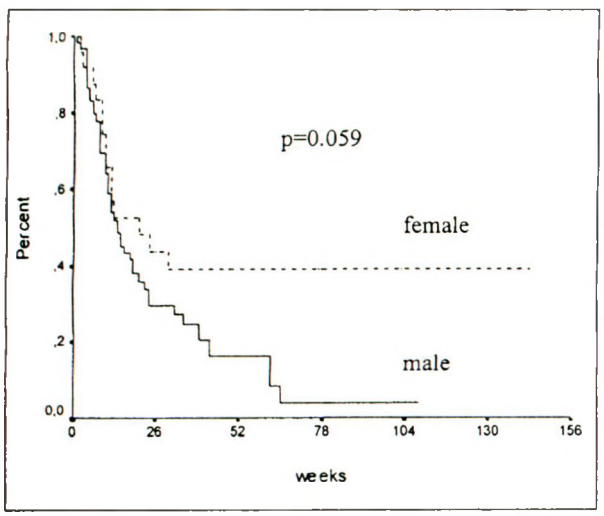

Fig.8.: Comparison of survival rates due to gender.

Table II. Prognostic factors analysed in multivariate analysis (KPS: Karnofsky Performance Scale) (Statistically significant factors in bold).

	p value
KPS score	**0.0001**
Gender	**0.0328**
Metastatectomy / Radiosurgery	**0.0392**
Age	0.3336
Solitary or multiple	0.3432
Other distant metastases	0.3788

gender and M/RS were found to be independent prognostic factors for overall survival (Table II).

DISCUSSION

Patients with brain metastases is a very poor prognostic group of cancer patients. Our survival results coincide with published results of world series which show 3-6 months of median survival and 15% 1-year survival (6, 11, 12). The most important patient and disease related good prognostic factors such as younger age, higher performance status, single lesion, indisseminated disease other than brain found to be significant in univariate analysis are similar to findings in larger series (12, 13). Age and performance status remains significant in multivariate analysis.

The significance of M/RS in univariate analysis continues to be significant in multivariate analysis, furthermore terminating the significance of single or multiple lesions. In two randomized trials comparing surgery and radiotherapy to radiotherapy alone for patients with solitary brain metastases and inactive extra-cranial disease adding surgery significantly prolonged median survival (3.5vs. 9 months and 6 vs. 10 months) (1, 14). In our study group when a subgroup analysis is performed for solitary or multiple metastases, M/RS is still a prognostic factor. In the group with multiple metastases median and 1 year survival results are 11 weeks and 9,6% for only radiotherapy patients, 65 weeks and 58,3% for M/RS + radiotherapy patients (p=0.01). Recent publications assessing the role of radiosurgery in the treatment of multiple brain metastases support our results (15, 16). In Chang et al.'s report it is concluded that radiosurgery for up to four brain metastases can be used with a 91% rate of response and 9.6 months median survival (15).

In conclusion, external radiotherapy is an efficient treatment modality for palliation and stabilizing cranial progression in patients with brain metastases. Adding metastatectomy or radiosurgery to radiotherapy in young patients with good performance, less than four lesions and controlled systemic disease may reveal longer survival and cranial symptom control.

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