

Therapeutic effects of 20 Gray Radiotherapy over a week in the management of brain metastases

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Abstract

Objective: To determine the therapeutic effects of 20 Gy over a week in the management of multiple brain metastases. Secondly to determine the toxicity profile and survival at 6th month in patients treated with the above-mentioned protocol.

Methods: This was a single arm interventional study, conducted at Nuclear Medicine, Oncology and Radiotherapy Institute (NORI), Islamabad from May 8, 2006 to May 31, 2007. Thirty patients with multiple brain metastases were inducted in this study. Mean age was 52±11 years. Fifty Four percent were females and 46% males. After initial workup, all were planned for whole brain radiotherapy. 20 Gy was given to whole brain by two parallel opposed, equally weighted lateral fields in five consecutive daily fractions. Dose per fraction was four Gy. All were followed up for six months for survival. Treatment response was categorized in four different categories i.e., >50%, ~50%, <50% and no response.

Results: It revealed that there was significant effect of treatment with 20 Gy radiotherapy as 76% of the patients during and 80% on the last day of therapy showed >50% response (p<0.05). Secondly, median survival of the patients after radiotherapy was two months (p<0.05). No serious toxicity was noted during this therapy.

Conclusion: Twenty Gy over a week is highly effective in palliation of symptoms due to multiple brain metastases. In comparison with other studies, this protocol had no significant difference in overall survival and acute toxicity (JPMA 59:278; 2009).

Introduction

Metastatic brain disease is one of the common complications in cancer patients. It is 5 to 10 times more common than primary brain tumours and occurs after the spread of tumour cells originating outside the nervous system into the brain.¹ Its incidence in adults and children suffering from malignancy is 10% to 30% and 6% to 10% respectively.² The most common primary malignant tumour leading to brain metastases in adults is lung (50%) followed by breast (15%-20%), unknown (10%-15%), melanoma (10%), and colon (5%) while in children; it is sarcomas, neuroblastoma, and germ cell tumours.³

Patients with brain metastasis usually present with headache, nausea, vomiting, seizures or any focal neurological dysfunction i.e., hemiparesis, visual impairment or cognitive disorders. Median survival of untreated patients is just one month. Treatment with corticosteroids alone prolongs survival up to two months while addition of whole brain radiotherapy along with steroids further prolongs it up to 3 to 6 months.^{4,5} It is therefore necessary to palliate these patients with radiotherapy. Cure is not possible at this stage.

There are many ways of palliation including corticosteroids, anticonvulsants, surgery, radiotherapy, stereotactic radiosurgery or interstitial brachytherapy. Most often opted therapy in multiple brain metastases is

corticosteroids along with radiotherapy as it is non-invasive, cheap and easily available. In radiotherapy, there are further different protocols like 40 Gray (Gy) in 3 to 4 weeks, 30 Gy in 2 to 3 weeks or 20 Gy in one week. International data reveal that results of all above-mentioned protocols are almost equivalent and no significant difference has been noted in median survival.^{6,7} Protocols of higher fractions like 20 Gy over a week showed early response and palliated the symptoms in 75% to 80% of the patients but overall survival was not different.⁸

The purpose of this study was to determine the therapeutic effects of 20 Gy over a week in the management of multiple brain metastases in our setup. Secondly, to determine the toxicity profile and survival at sixth month among patients treated with the above-mentioned protocol.

Patients and Methods

This study was conducted at Nuclear Medicine, Oncology and Radiotherapy Institute (NORI), Islamabad and was approved by the ethical committee of the institute. Total duration of this study was one year. Research work was started on May 8, 2006 and completed on May 31, 2007.

Thirty patients were inducted in this study and all were diagnosed cases of multiple brain metastases irrespective of their primary. Informed written consent was taken from all

patients before the start of procedure. Non-probability and purposive sampling technique was used. Any patient having single space occupying lesion (SOL) in brain, undergone cranial irradiation or having history of surgery in the past for these metastases was excluded from this study. No patient with diabetes mellitus, hypertension or having any other co-morbid condition was included as this could affect the survival of the patient. Visceral metastases like liver and lungs were the confounding variables in this study. It was difficult to exclude them as most of the patients presented with brain metastases after the appearance of extra-cranial metastases.

It was a single arm interventional study. Intervention designed in this study was radiation given in five consecutive fractions. Total dose delivered was 20 Gy. Two equally weighted parallel opposed lateral fields were planned for this treatment. All patients underwent baseline investigations including complete blood examination, blood urea nitrogen, creatinine, liver function tests, urine complete examination, chest X-ray, ultrasonography abdomen and pelvis and CT Scan or MRI Brain. Related investigations according to primary were also performed before starting the treatment.

All were started on corticosteroids if not taking previously and having no medical contraindication for its use. Loading dose was 10 mg/day followed by 16 mg/day in divided doses as advised.⁹ Dose was tapered by 25% every third day after the completion of radiation. Patients were examined on alternate days during radiotherapy and then on the last day of treatment. After completion of radiotherapy, all were followed on 6th, 12th and 24th week to determine their treatment response and survival.

Treatment response was determined both clinically and radiologically. Clinical response was determined in the form of symptomatic improvement i.e., how much time did it take for improvement of symptoms and what was the level of improvement. Similarly, radiological response was determined by comparing pre-radiotherapy CT/MRI scan with that of post-radiotherapy done on 12th week after the completion of radiation.

Data were analyzed using Statistical Package for Social Sciences (SPSS). Chi-square test was used to analyze this ordinal and paired data while one sample t- test was used for survival analysis.

Results

Most of the patients had presented with headache, nausea and vomiting (Figure 1). Results showed that there was significant effect of treatment with 20 Gy radiotherapy as 76% of the patients during radiotherapy and 80% on the last day of therapy showed greater than 50% symptomatic response ($p < 0.05$). Secondly, mean survival of the patient after radiotherapy was 2.62 ± 1.73 months ($p < 0.05$) while median

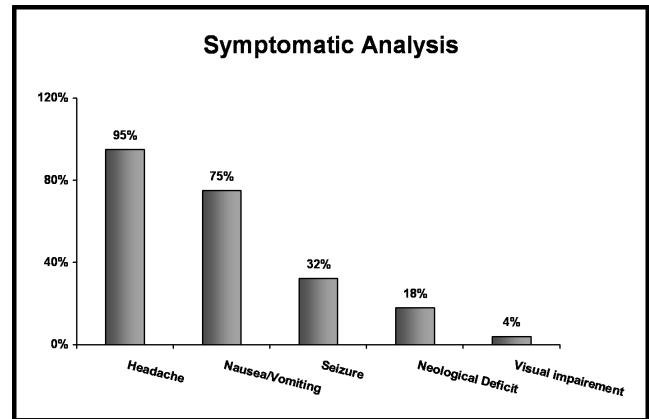


Figure 1: Frequency distribution of symptoms observed in this study.

survival was two months ($p < 0.05$). Carcinoma lung was the most common cancer that presented with brain metastases in this study (43%). Second most common malignancy was breast (30%) while unknown primaries were 16%.

Age distribution revealed that most of the patients were between 40 to 60 years of age. Range was 38-85 years with mean age of 52 ± 11 years. Fifty four percent were female while 46% were male. Average Karnofsky Performance Scale (KPS) was 65 ± 10 with a range of 40-80. Time for development of brain metastases after primary diagnosis was one to 36 months with a mean of 11 ± 10 months. Minimum duration for patient's death after radiotherapy was 6 days while maximum was 6 months with a mean of 2.62 ± 1.73 months. Three patients were alive even after six months of radiotherapy (Table 1). Most of the patients did not have any other site of metastases (66%).

Table 1: Data representing the average values of different variables.

	N	Min.	Max.	Mean	Median	SD
Age (in Years)	30	38	85	52	50	11
Duration from primary diagnosis to brain metastases (in months)	30	1	36	11	9	10
Karnofsky Performance Scale (KPS %)	30	40	80	65	70	10
Time to death after Radiotherapy (in days)	27	6	180	78	70	52

N: Number of Patients, Min: Minimum, Max: Maximum, SD: Standard Deviation.

However, 16% had lung metastases and 6% bone metastases. Ten percent of the patients had multiple organ metastases. Treatment response had to be evaluated both clinically and radiologically, but most of the patients did not come for follow-up or had expired. Radiological response could thus not be evaluated in all the cases.

Clinical evaluation showed 76% patients to have greater than 50% response while 20% had approximately 50% response during radiotherapy. Only one patient had less than

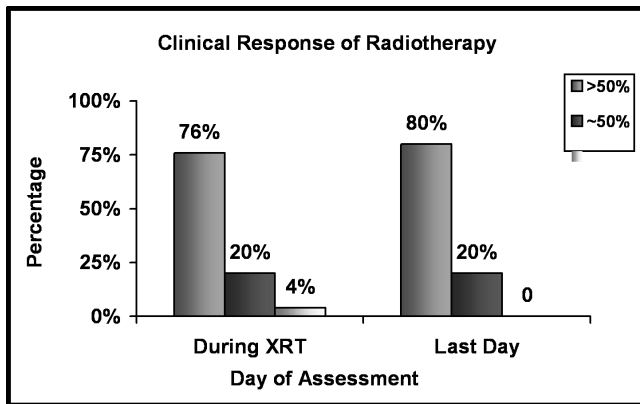


Figure 2: Clinical response of radiotherapy (p<0.05).

50% response during radiotherapy. Similarly, 80% patients had greater than 50% response while 20% had approximately 50% response on the last day of the treatment (Figure 2). Separate response evaluation with steroids and radiotherapy was not performed as steroids were started along with radiation to get maximum treatment benefit. Seventy percent of patients were alive while 30% expired within six weeks of radiotherapy. Similarly, 47% were alive and 53% expired after 12 weeks of radiation. Week 24 i.e., 6th month evaluation revealed that only 10% of the patients were living while 90% had expired (p<0.05). (Figure 3) All the patients were

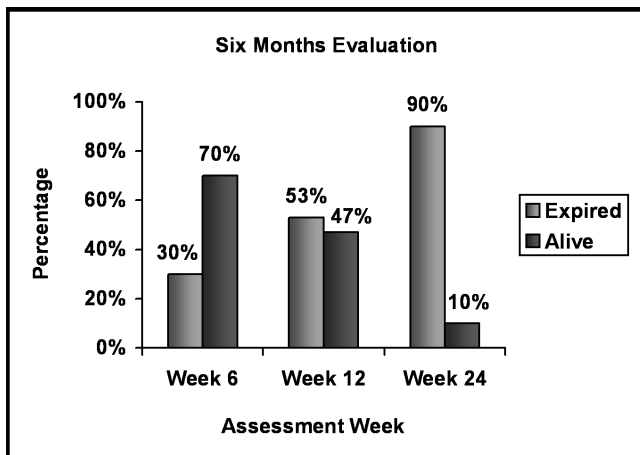


Figure 3: Six months evaluation after radiotherapy.

monitored regularly for the development of new symptoms during their treatment and most (76%) remained symptom free. However, 16% developed headache and 8% vomiting during radiotherapy. These patients were managed with symptomatic therapy. No serious toxicity was observed in the survivors of this study till the end of six months (Table 2).

Statistical analysis revealed that there was a significant response of radiotherapy in palliating the symptoms and this

Table 2: Toxicity profile in the survivors of in this study.

	No. of patients	No Toxicity	Headache	Vomiting
Third day of XRT	30	60%	28%	12%
Last day of XRT	30	76%	16%	8%
At 6th week after XRT	21	90%	10%	-
At 12th week of XRT	14	92%	8%	-
At 24th week of XRT	7	92%	8%	-

response was significant both during and on the last day of treatment (Table 3). Survival analysis was performed using one sample t-test. This test was also significant at 95% confidence interval (p<0.05).

Table 3: Statistical analysis.

N	During Radiotherapy		Last day of Radiotherapy	
	Observed N	Expected N	Observed N	Expected
>50%	23	10	24	15
~50%	6	10	6	15
<50%	1	10	0	-
Total	30	-	30	-
χ^2 Value	26.6		10.8	
p-value	<0.05		<0.05	

Discussion

Metastasis to the brain is the most feared complication of systemic cancer and the most common intracranial tumour in adults. The frequency of metastasis is rising with improved survival. Treatment of brain metastases depends upon the site, size and number of lesions. It also depends upon the clinical presentation of the patient and availability of facility for such treatment. Small sized single focus is best managed with surgery or stereotactic radiosurgery. However, multiple lesions involving most parts of brain and also poor general condition of patient discourages big surgery. In such a scenario, palliative procedures as whole brain radiotherapy is significant.

Tsao MN and colleagues¹⁰ compared the altered fractionation protocol with standard protocol of 30 Gy in 10 fractions. They found that there was no significant difference in overall survival, neurologic function or symptomatic control of the patients treated with either protocol.

Similarly, another study done by Yaneva MP¹¹ found no significant difference in the survival of patients whether treated with 20 Gy or 30 Gy. In this study, 39 patients were treated either with 20 Gy or 30 Gy. All patients were of carcinoma lung having brain metastases. It was found that whole brain radiotherapy was significantly effective in palliation of symptoms but no significant difference in the survival could be noted. Their mean survival time was 6.6 months while in our study it was 2.62 months. Reason may be those 45% patients who were having solitary brain metastasis