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Incidence of hospitalization in patients receiving short course palliative cranial radiotherapy on outpatient basis in a limited resource setting – Experience from a regional cancer center in India

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ABSTRACT

Aim: To investigate incidence of toxicity and related hospitalization among patients treated at our institute by a short course of palliative cranial radiotherapy against a longer, widely established schedule.

Background: Shorter schedule palliative cranial radiotherapy is more convenient for patients and reduce waiting times. Although many studies have established safety of short schedules, the need for hospitalization due to acute treatment toxicity remains under-explored. Hospital admissions are an economic burden both for the patient and healthcare system in a limited resource setting. Delivery of treatment on an outpatient basis and within shorter times is preferred by patients, caregivers and healthcare staff.

Materials and methods: This was a prospective study on 68 patients treated with palliative whole brain radiotherapy between November 2010 and October 2012. One group received 20 Gy in 5 fractions over 1 week and the other group, 30 Gy in 10 fractions over 2 weeks. Treatment toxicity due to cranial radiotherapy was assessed as per RTOG acute and late toxicity criteria. Need for hospitalization owing to acute toxicity was also noted. Significant differences in the study parameters between the two groups were calculated by Fisher's t-test.

Results: Requirement for hospital stay due to acute toxicity was not significantly different between the two groups. Patients in both groups experienced similar toxicity both during and after treatment.

Conclusions: The shorter course entailed no significant increase in toxicity related admissions, suitable for limited resource settings where patient transport is difficult, there are financial constraints, and the healthcare system is overburdened.

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1. Background

During the course of treatment for cancer, many patients develop metastases to various organs, including the central nervous system (CNS). CNS metastases are not an uncommon initial presentation in many cancer patients and, indeed, accounts for the majority of CNS tumors.[1,2] In India, due to limited resources, a major proportion of the population, especially rural, do not have adequate access to healthcare services. Residing in remote areas with transport being difficult, treatment duration attains importance. Arranging transport or accommodation near the treatment center becomes a considerable economic burden. Under these circumstances, a short treatment schedule is preferred by most patients and their families. However, hospitals in our setting sometimes find it challenging to deliver short course treatment with larger dose per fraction on an outpatient basis, owing to a perception that larger dose per fraction delivered to the brain may cause greater acute radiation toxicity that may require hospitalization to manage. In such an event, with an overwhelming burden on indoor facilities, this would increase pressure on the department workflow and also be detrimental to patient safety if admission is not urgently possible. Additionally, the expenditure for supportive care is a financial burden on the patients' family as well.

Additionally, most patients usually present with large or multiple lesions. These are not amenable to treatment by methods other than whole brain radiotherapy (WBRT). Most rural patients who could benefit from surgery or alternative techniques, such as stereotactic radiotherapy, do not have access to those services. In the absence of alternative management, it is sometimes compelling to treat these patients with WBRT, too.

The safety of short schedule palliative WBRT has been established by clinical studies.[3,4] A review of literature reveals evidence suggesting similar progression and survival between short schedules of palliative WBRT, as opposed to the widely established 30 Gy in 10 fractions over 2weeks schedule.[5,6] Delivery of palliative radiotherapy for brain metastases in as few as 2 fractions has also been documented in certain situations, with comparable results.[7]

Cranial radiotherapy may lead to treatment-related toxicities that may be stressful to the patient and their caregivers. The toxicity-related hospital admission may put economic pressures on the healthcare system, on the patient and their families. A comprehensive search of Pubmed does not reveal studies that compare acute toxicity due to short fractionation schedules with that of prolonged schedules.

2. Aim

We compared the toxicity and the related need for hospitalization among patients treated with a 20 Gy in 5 fractions over 1 week schedule with 30 Gy in 10 fractions over 2 weeks. Primary endpoints were the incidence of acute toxicity and toxicity-related need for hospitalization. The secondary objective was the incidence of late toxicity.

3. Materials and methods

3.1. Patients

The study included 68 patients with brain metastases treated with palliative cranial radiotherapy at our institute between November 2010 and October 2012. Thirty-eight had received 30 Gy in 10 fractions over 2 weeks, whereas 30 patients had been treated with 20 Gy in 5 fractions over 1 week. Majority of the patients had breast or lung cancer. The patients who had received 30 Gy in 10 fractions over 2 weeks ($n = 38$) had similar characteristics as the group that received short course treatment ($n = 30$) (Table 1).

Five patients had brain metastases at initial diagnosis of cancer. Nineteen patients (63.33%) from the short course group and 30 patients (78.94%) from the group that received longer course of radiotherapy had only brain metastases at the time of cranial radiotherapy. Seven patients (23.33%) from the short course group and 5 patients (13.15%) from the other group had metastases to a single site apart from the brain at the time of receiving palliative cranial radiotherapy. Four patients (13.33%) from the short course group and 3 patients (7.89%) from the longer course group had metastases to more than one non-CNS site at the time of receiving cranial radiotherapy and these patients had a Karnofsky Performance Score of <40 at the time of cranial radiotherapy (Table 2).

3.2. Treatment

3.2.1. Radiation therapy

All patients received radiation to the whole brain once daily, five days per week.

Patients were treated in a supine position. Parallel opposed lateral fields were used with the gantry at 90° and 270°. The field borders were 2 cm beyond the skull in the superior, anterior, and posterior margin, and the lower border of C2 vertebra in the inferior margin. All patients were treated by telecobalt.

As per institutional protocol, all patients received dexamethasone 2 mg orally twice daily during the period of cranial radiotherapy.

3.2.2. Follow-up

Patients were assessed daily during radiotherapy by the physician for any symptoms of treatment-related acute toxicity. On completion of WBRT, they were seen after 1 week at the radiation oncology department to be assessed for any problems related to daily activities, self care and any worsening of symptoms since the completion of treatment. Also, it is necessary to address the caregivers concerns in view of the absence of social support services in our setting. After that, patients were followed up at medical or radiation oncology at 1 month, followed by 3 monthly for as long as the patient remained alive or attended hospital. Toxicity was graded using the RTOG acute and late toxicity criteria.

3.3. Statistical analysis

Data of patients who received 20 Gy in 5 fractions over 1 week ($n = 30$) was compared to that of the group treated by 30 Gy

Table 1 – Patient characteristics.

Patient demographic data in both groups	Patients who received 20 Gy/5#/1 week $n = 30$	Patients who received 30 Gy/10#/2 weeks $n = 38$
Gender		
Male	21	27
Female	19	11
Age	Median: 48 year (range 38–55 year)	Median: 52 year (range 40–73 year)
Primary site		
Breast	10	14
Lung	8	10
Prostate	2	3
Bladder	1	0
Rectum	1	0
Anal canal	1	0
PNET	2	2
Renal cell carcinoma	2	4
Vulva	1	0
Unknown primary	2	5
Performance status at diagnosis		
KPS >70	13	18
KPS 50–70	10	15
KPS <50	7	5
RPA class		
Class 1	11	13
Class 2	2	5
Class 3	17	20
Number of brain metastases		
Single	11	21
Multiple	19	17

in 10 fractions over 2 weeks ($n = 38$). Acute toxicity needs for hospital stay due to treatment toxicity, as well as late toxicity were noted. Patients who died during the course of follow up were excluded for late toxicity but included for acute toxicity analysis.

Fisher's *t*-test was used to assess the endpoints.

Statistical analysis was done using the GraphPad QuickCalcs Web site: http://www.graphpad.com/quickcalcs/contingency1 (accessed November 2012).

4. Results

Median age of patients in the short course group was 48 years (range 38–55 years) and 52 years (range 40–68 years) in those receiving long course radiotherapy. 75% of patients had initially presented with locally advanced tumors; 11 of 30 patients (36.66%) from the short course group and 8 of 38 patients (21.05%) from the longer course group had non-CNS systemic metastases at the time of diagnosis of brain metastases. 36.66% patients from the short course group and 36.84% patients from the longer course group had multiple brain metastases. Patients having solitary brain metastases had either large lesions or were not amenable for surgery due to medical reasons. These patients comprised 26.66% of the shorter schedule group and 42.10% of the group that received a longer course of radiotherapy.

Overall, patients had a median follow-up of 6 months (range 2–16 months). Median follow up for the short course group was 7 months and that for the longer course group was 5 months. Thirteen patients (43.33%) who received the short course and 17 patients (44.73%) who received long course radiotherapy continued follow up beyond 6 months. 93.33% of these patients were of RPA class 1 and 2. One patient

Table 2 – Distribution of metastases at time of cranial radiotherapy.

Metastases at initiation of cranial radiotherapy		Patients receiving 20 Gy/5 fractions/1 week ($n = 30$)	Patients receiving 30 Gy/10 fractions/2 weeks ($n = 38$)
CNS metastases only	Solitary	8	16
	Multiple	11	14
Simultaneous non-CNS metastases present at time of cranial radiotherapy	Patients with single metastasis (non-CNS) at start of cranial radiotherapy	7	5
	Patients with more than 2 metastatic sites (non-CNS)	4	3

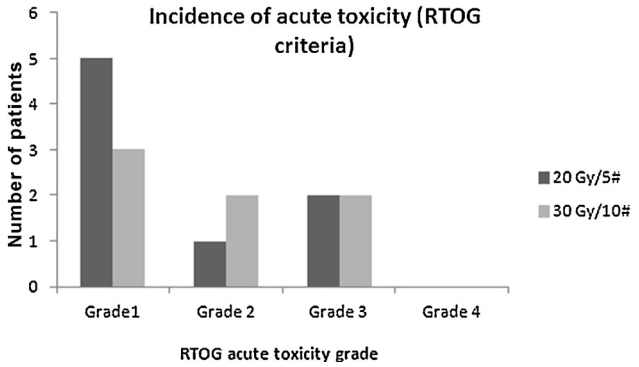

Fig. 1 – Incidence of acute toxicity.

who had received 20 Gy/5 fractions/1 week, died one month after the completion of treatment due to widespread visceral metastases, however his pre-treatment performance status was KPS 20. Two patients from the longer course died within 3 weeks of the completion of treatment, one at 10 days due to thromboembolism, and the other patient at 3 weeks due to widespread metastatic disease. Pre-treatment performance status of this patient was KPS 30. These patients were excluded from late toxicity analysis but included for acute toxicity analysis.

4.1. *Acute toxicity (Fig. 1)*

Incidence of acute RTOG toxicity was not significantly different between the two groups (two-tailed P value = 0.5574). No treatment interruption was required due to toxicity.

4.2. *Need for hospital admission during treatment*

During the course of treatment, 2 patients from the short course arm and 4 patients from the 30 Gy/10 fractions arm needed hospital stay due to sudden onset of limb weakness in one patient, repeated seizure episodes in 3 patients and difficulty in feeding orally in 2 patients. None of these patients had these problems prior to the start of cranial radiotherapy. Hospital stay due to acute CNS toxicity was also not significantly different between the two groups (two tailed $P = 0.6871$).

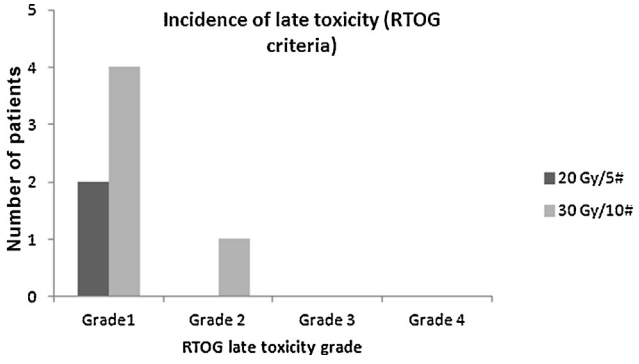

Fig. 2 – Incidence of late toxicity.

4.3. *Late toxicity (Fig. 2)*

Two patients receiving the short course schedule developed RTOG grade 1 late toxicity. Among these patients, one had developed grade 2 acute toxicity during treatment. No grade 2, 3 or 4 late toxicities were noted. The two-tailed P value was 0.4472.

5. Conclusions

The most widely used fractionation schedule for palliative cranial radiotherapy is usually 30 Gy/10 fractions/2 weeks. Various studies on altered fractionation in palliative radiotherapy for brain metastases have established the safety of alternative schedules. Some studies have used doses lower than 300 cGy per fraction while other employed higher fraction sizes with shorter overall treatment time.

It has been demonstrated that lower doses per fraction up to a higher total dose have not necessarily translated to improved survival outcomes or lower treatment toxicity. In the study by Murray et al., no advantage in terms of grade 3 and 4 toxicity were noted in the patient group treated by accelerated hyperfractionation at 1.6 Gy per fraction twice daily up to a total dose of 54.4 Gy.[5] Survival at one year was 19% among patients who received the hyperfractionated schedule as opposed to 16% in the hypofractionated treatment group who received 30 Gy/10 fractions/2 weeks. As described by Borgelt et al., various shorter fractionation schedules that were analyzed in terms of response and survival showed comparable results, favoring no particular schedule.[6]

Development of acute radiation toxicity is stressful for patients and their families. It may be particularly difficult for caregivers who have to deal with this additional crisis in an already stressful scenario.[8] The occurrence of acute radiation toxicity may also necessitate hospital admission. Unfortunately, hospital admission has a significant impact on the healthcare system in this setting of limited resources. This makes decision making especially challenging for physicians and healthcare staff.

Under these circumstances, it was compelling to study the incidence of radiation toxicity among these patients who require a shorter treatment time causing least inconvenience, and comparable toxicity to a more widely used albeit longer schedule.

Studies in literature comparing results of shorter fractionation schedules for palliative cranial radiotherapy found no significant increase in radiotherapy toxicity among patients treated by shorter schedules. In the study by Priestman et al.,[3] radiation related side effects, other than alopecia, were seen in 12% of patients receiving two fractions and 8% of those given 10 fractions.

In our study, acute toxicity between the two radiation schedules was comparable. The shorter schedule of treatment did not seem to increase the need for hospital stay, which was an advantage for the patients. Also, the secondary endpoint, late toxicity during the follow up did not significantly differ between the groups.

Studies in literature point out a worsening of the quality of life in patients who receive radiotherapy for brain

metastases.[9] Whether quality of life depends on fractionation schedules, and whether different fractionation produces varying effects on the quality of life and neurocognitive decline, is still underexplored.

Owing to the short duration of follow up and the limited number of patients that could be studied, generalization of these results is limited, further studies are needed in this regard. Also, survival data for our patient group is not available for the entire cohort owing to considerable drop out from follow up, which is not uncommon among patients in our scenario. Communicating with patients who are lost to follow up is not feasible in most cases because of remote areas of residence and lack of infrastructure. As a consequence, these results are not being published.

Despite these limitations, our study shows that a shorter duration of treatment did not affect the hospital admission rate in our patients. Palliation and treatment toxicity were comparable. Patients found the shorter duration of therapy more acceptable, the burden on hospitalization did not significantly differ, both of which are essential in this setting.

Delivering larger doses per fraction on an outpatient basis was found to be safe and feasible with similar outcomes in our patients. The shorter course of palliative cranial radiotherapy was not associated with more toxicity and did not significantly alter hospitalization rates during treatment. It was convenient and more acceptable for patients as well as their caregivers; additionally, it helped reduce patient waiting times in the radiation oncology department.

Conflict of interest

None declared.

Financial disclosure

None declared.

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