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Original Article

Efficacy and Toxicity of Short Course and Ultra-Short Course Radiotherapy in Metastatic Brain Cancer

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Abstract

Background: *The occurrence of brain metastasis represents a critical event in the progression of malignant disease. Whole brain radiotherapy (WBRT) with 20 Gray administered in 5 fractions (short course) is a commonly employed treatment protocol for metastatic brain cancer. Given the limited survival associated with brain metastasis, a shorter WBRT regimen of 12 Gray in 2 fractions (ultra-short course) has been proposed as an alternative.*

Aim of the study: *This study aimed to compare the efficacy, including response rates and toxicities, of ultra-short-course versus short-course whole-brain radiotherapy in patients with brain metastasis.*

Method: *This quasi-experimental study included 118 patients who met the inclusion and exclusion criteria between January 2018 and June 2019. Participants were enrolled using convenience and purposive sampling and were allocated equally into two groups (n=59 each). Group A received ultra-short-course, and Group B received short-course WBRT. Follow-up assessments were conducted at one, two, four, and eight weeks after completion of radiotherapy. Each follow-up included clinical examination and relevant laboratory investigations. Data were compiled and analyzed using SPSS (Version 24.0) employing the chi-square test and Fisher's exact test.*

Results: *The most common symptoms associated with brain metastases were headache, nausea, vomiting, convulsions, and cognitive dysfunction. For Grade 3 headache, response rates were 76.19% in the ultra-short-course group and 75.00% in the short course group (p-value <0.05). For Grade 2 nausea, response rates were 54.55% in Arm A and 56.25% in Arm B (p-value <0.05). Therapeutic response rates for vomiting, convulsions, and cognitive dysfunction were similar between both groups. Fatigue, skin reactions, and alopecia were identified as common acute toxicities of whole brain radiotherapy, with comparable frequencies in both arms. These toxicities were manageable with appropriate supportive measures.*

Conclusion: *Ultra-short-course whole brain radiotherapy demonstrates comparable effectiveness to short course radiotherapy for palliation of symptoms in metastatic brain cancer. This approach may facilitate treatment of a greater number of patients using existing resources, with manageable toxicities.*

Keywords: *Brain metastases, Whole-brain radiotherapy, Hypofractionation, Palliative radiotherapy, Acute toxicity.*

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Introduction

Brain metastases are the most frequent neurological complications of systemic malignancy and remain a major cause of cancer-related morbidity and mortality worldwide.1 Historically, prognosis was extremely poor due to delayed diagnosis, limited local treatment options, and the relative ineffectiveness of systemic therapies within the central nervous system.[1,2] Over the past two decades, however, substantial advances in neuroimaging, neurosurgery, radiotherapy techniques, systemic treatments, and supportive

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care have transformed clinical management, allowing earlier detection, better symptom relief, and meaningful survival gains in selected patients.[2,3] Despite these advances, brain metastases represent a highly heterogeneous clinical entity, with outcomes influenced by primary tumor biology, the number and volume of intracranial lesions, the extent of extracranial disease, and patient performance status, making treatment selection increasingly individualized and complex.[2,3]

The true incidence of brain metastases is challenging to ascertain, as many cases are not systematically recorded in cancer registries. However, available data indicate that up to 30% of adult cancer patients develop brain metastases during their illness, representing a significant population-level burden.[1,4,5] Brain metastases may be diagnosed concurrently with the primary malignancy or may arise later as metachronous disease. Approximately one third of patients present with a solitary lesion in specific clinical contexts.[2] The risk of brain metastases varies substantially by primary tumor type, with cumulative incidences of approximately 50% in lung cancer, 15–20% in breast cancer, 7–10% in renal cell carcinoma, about 7% in melanoma, and less than 2% in colorectal cancer.[4]

Clinical manifestations are determined by lesion size, location, associated edema, and hemorrhage. Common symptoms include headache, focal neurological deficit, seizure, nausea, vomiting, altered mental status, ataxia, speech disturbance, and impaired coordination.[2] Neurocognitive dysfunction is frequently observed prior to treatment, reflecting both tumor-related injury and peritumoral edema.[5] Imaging is central to diagnosis and management. Computed tomography can detect larger lesions or acute hemorrhage, but contrast-enhanced magnetic resonance imaging is preferred due to its superior sensitivity for identifying lesion number, size, location, posterior fossa involvement and leptomeningeal disease.[2] Brain metastases typically present as well-circumscribed enhancing lesions, often multiple and located at the gray-white matter junction, with a predilection for the cerebral hemispheres, followed by the cerebellum and less commonly, the brainstem.[2] Certain histologies, such as melanoma, renal cell carcinoma, choriocarcinoma, thyroid carcinoma, and some germ cell tumors, are more likely to result in hemorrhagic metastases. Important differential diagnoses include abscesses, demyelinating lesions, vascular abnormalities, and primary brain tumors.[2]

The prognosis for patients with symptomatic brain metastases remains poor. Without treatment, median survival is approximately one month, and corticosteroids alone extend survival to about two months, providing symptomatic relief without durable tumor control.[6] Survival is determined by several clinical variables, including performance status, age, response to steroids, control of the primary tumor, extracranial disease burden, and the number of brain metastases.[2,3] Prognostic classification systems, such as the Recursive Partitioning Analysis developed by the Radiation Therapy Oncology Group and the Graded Prognostic Assessment, offer structured frameworks for patient stratification and survival estimation. Median overall survival ranges from approximately 2.6 to 11 months across prognostic groups.[7,8]

Accurate assessment of intracranial disease burden using MRI, along with evaluation of primary tumor histology and systemic disease status, is critical for effective treatment planning.[2,3] Treatment options include surgical resection, stereotactic radiosurgery, whole brain radiotherapy (WBRT), or combinations of these modalities. Surgery followed by adjuvant WBRT has historically improved intracranial control and reduced neurologic mortality in selected patients with solitary, surgically accessible lesions.[9] For patients with a limited number of brain metastases, randomized trials have demonstrated superior intracranial control with the addition of WBRT to stereotactic radiosurgery. However, this benefit is counterbalanced by an increased risk of neurocognitive decline, leading to a greater focus on focal therapies and neuroprotective strategies in suitable patients.[5,10] Pharmacologic interventions, such as memantine, have been shown to delay onset and reduce the severity of cognitive decline in patients receiving WBRT.[11]

In resource-limited settings such as Bangladesh, whole-brain radiotherapy (WBRT) remains a primary management strategy for patients with inoperable or multiple brain metastases. Commonly used fractionation schedules include 30 Gy in 10 fractions, 20 Gy in 5 fractions, and ultra-short regimens such as 12 Gy in 2 fractions, primarily targeting symptom palliation and intracranial disease control. Acute toxicities may include transient worsening of cerebral edema, headache, nausea, vomiting, alopecia, and scalp skin reactions, with occasional otologic effects depending on dose distribution and individual susceptibility.[3] Given the need to balance symptom relief, treatment duration, and toxicity in patients with limited life expectancy, this study compares the treatment response and toxicity profiles of WBRTwith short-course (20 Gy in 5 fractions) versus ultra-short-course (12 Gy in 2 fractions) in patients with inoperable brain metastases.

Methodology & materials

This quasi-experimental study was conducted from January 2018 to June 2019 in the Department of Oncology, Bangladesh Medical University (BMU), and the Department of Radiation Oncology, National Institute of Cancer Research and Hospital (NICR&H), Dhaka. A total of 118 patients with brain metastases were enrolled using convenient and purposive sampling and were allocated equally into two treatment arms (n=59 per group). Patients received whole-brain radiotherapy (WBRT);

- **Group A (n=59):** Patients received 12 Gy in 2 fractions on two consecutive days.[12]
- **Group B (n=59):** Patients received 20 Gy in 5 fractions delivered over one week

Eligible participants were adults aged 18–70 years with histopathologically or cytopathologically confirmed malignancy and radiologically evident brain metastases, with no prior history of cranial irradiation. Patients were excluded if they had Karnofsky Performance Status (KPS) <70, were pregnant or lactating, or had serious concomitant medical illnesses, including clinically significant cardiovascular disease, uncontrolled diabetes mellitus or hypertension, or uncontrolled infection.

All patients underwent standardized pretreatment evaluation comprising complete history, performance status assessment, general physical examination, systemic and neurological examinations, and assessment of the primary malignancy and metastatic disease status. Neuroimaging included a CT scan and or an MRI of the brain. Laboratory investigations included complete blood count, renal function tests (serum creatinine, serum electrolytes, and creatinine clearance when indicated), liver function tests (serum bilirubin, SGPT, SGOT), ECG, and histopathology or cytopathology confirmation of the primary disease. Additional imaging included chest radiograph (P/A view) and ultrasonogram of whole abdomen.

During the radiotherapy, patients were positioned supine using a thermoplastic immobilization shell and neck rest in a neutral, comfortable position. Lateral opposing fields were planned to encompass the whole skull from the vertex to Reid's baseline, defined by a line joining the external auditory meatus and outer canthus; where skull base involvement was suspected, the inferior border was extended 1–2 cm below this line. Treatment was delivered using a Cobalt-60 teletherapy machine with simple opposing lateral beam arrangements, with wedge filters used when required to improve dose homogeneity. Supportive medications, including steroids, anticonvulsants, antiemetics, and antibiotics, were prescribed as clinically indicated.

Patients were assessed daily during radiotherapy. Post-treatment follow-up was conducted weekly for two weeks, then at week 4 and week 8, including symptom review and neurological examination. Cognitive dysfunction was assessed clinically by history and orientation to time, place, and person; laboratory and imaging tests were performed when required. Acute toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Data were recorded in a structured case record form, coded, and analyzed using SPSS for Windows version 24.0. Categorical comparisons of symptomatic response and acute toxicity between fractionation schedules were performed using chi-square and or Fisher's exact tests as appropriate, with a two-tailed p-value <0.05 considered statistically significant. Ethical approval was obtained from the Institutional Review Board of BMU and the NICR&H ethical committee, written informed consent was obtained from all participants, and confidentiality was maintained throughout.

Results

At baseline, both groups were dominated by older patients, particularly those aged 60–70 years. This was more prominent in Group A than Group B, 35 (59.32%) vs 27 (45.76%). Group B had a noticeably higher male predominance, 51 (86.44%), compared with 38 (64.41%) in Group A. Most participants were middle class in both arms, 33 (55.93%) in Group A and 35 (59.32%) in Group B, with smaller proportions in poor and rich categories.

Table 1. Baseline sociodemographic characteristics by study group (n = 59 per group)

Variables	Group A (n=59) n (%)	Group B (n=59) n (%)
Age group (in years)		
18-29	0 (0.00)	4 (6.78)
30-39	5 (8.47)	4 (6.78)
40-49	5 (8.47)	8 (13.56)
50-59	14 (23.73)	16 (27.12)
60-70	35 (59.32)	27 (45.76)
Sex		
Male	38 (64.41)	51 (86.44)
Female	21 (35.59)	8 (13.56)
Economic Status		
Poor(< 12,260 Taka/Month)	10 (16.95)	12 (20.34)
Middle class(12,260-31,640 Taka/Month)	33 (55.93)	35 (59.32)
Rich(> 31,640 Taka/Month)	16 (27.12)	12 (20.34)

Lung cancer was the predominant primary in both groups, more frequent in Group A than Group B, 46 (77.97%) vs 35 (59.32%). Group A also included CUP and esophageal primaries, each 5 (8.47%), which were absent in Group B. In contrast, Group B had a more diverse non-lung distribution, with head and neck and breast each 8 (13.56%), colon 5 (8.47%), and testes 3 (5.08%), while these were not represented in Group A.

Table 2. Primary tumor site distribution among patients with brain metastases by study group

Primary Tumor site	Group A (n=59) n (%)	Group B (n=59) n (%)
Lung	46 (77.97)	35 (59.32)
CUP	5 (8.47)	0 (0.00)
Head and neck	3 (5.08)	8 (13.56)
Oesophagus	5 (8.47)	0 (0.00)
Breast	0 (0.00)	8 (13.56)
Testes	0 (0.00)	3 (5.08)
Colon	0 (0.00)	5 (8.47)

Adenocarcinoma was the most common histology in both groups, particularly in Group B, 35 (59.32%) vs 27 (45.76%) in Group A. Squamous cell carcinoma was the next most frequent, 11 (18.64%) in Group A and 9 (15.25%) in Group B, while small cell carcinoma was higher in Group A, 8 (13.56%) vs 4 (6.78%). Notably, undifferentiated carcinoma, 10 (16.95%), and adenosquamous carcinoma, 3 (5.08%), occurred only in Group A, whereas infiltrating ductal carcinoma was present only in Group B, 8 (13.56%), consistent with the breast primary distribution.

Table 3. Histopathological types of the primary tumor by study group

Histopathology	Group A (n=59) n (%)	Group B (n=59) n (%)
Adenocarcinoma	27 (45.76)	35 (59.32)
Squamous cell carcinoma	11 (18.64)	9 (15.25)
Small cell carcinoma	8 (13.56)	4 (6.78)
Undifferentiated carcinoma	10 (16.95)	0 (0.00)
Adenosquamous carcinoma	3 (5.08)	0 (0.00)
Infiltrating ductal carcinoma	0 (0.00)	8 (13.56)
Seminoma and others	0 (0.00)	3 (5.08)

Metachronous presentation was the dominant pattern in both groups, 48 (81.36%) in Group A and 51 (86.44%) in Group B, indicating that most patients developed brain metastases after the initial diagnosis of the primary disease. Synchronous metastasis at presentation was less common, 11 (18.64%) in Group A and 8 (13.56%) in Group B.

Table 4. Timing of brain metastasis diagnosis, synchronous versus metachronous, by study group

Diagnosis of primary disease	Group A (n=59) n (%)	Group B (n=59) n (%)
Synchronous	11 (18.64)	8 (13.56)
Metachronous	48 (81.36)	51 (86.44)

Multiple brain metastases were overwhelmingly more common than single inoperable lesions in both groups, 51 (86.44%) in Group A and 52 (88.14%) in Group B. Single, inoperable lesions accounted for a small minority, 8 (13.56%) and 7 (11.86%), respectively, suggesting a generally high intracranial metastatic burden at baseline.

Table 5. Number of brain metastatic lesions at baseline by study group

Number of brain metastases	Group A (n=59) n (%)	Group B (n=59) n (%)
Single, inoperable	8 (13.56)	7 (11.86)
Multiple	51 (86.44)	52 (88.14)

Most patients had a moderate functional status at presentation, with a KPS of 80 being the most frequent category, 30 (50.85%) in Group A and 36 (61.02%) in Group B. A KPS of 70 was also common appearing in 24 (40.68%) Vs 20 (33.90%) patient respectively, while relatively few patients were in the highest category, KPS of 90 [5(8.47%) in Group A and 3(5.08%) in Group B].

Table 6. Baseline Karnofsky Performance (KPS) Status distribution by study group

KPS	Group A (n=59) n (%)	Group B (n=59) n (%)
KPS 70	24 (40.68)	20 (33.90)
KPS 80	30 (50.85)	36 (61.02)
KPS 90	5 (8.47)	3 (5.08)

Clinical response at 8 weeks showed improvement across key symptoms in both groups, with statistically significant between-group differences for headache and nausea. Moderate to severe headache (Grade 2–3) was reduced from 42 (71.19%) to 19 (32.20%) in Group A, and from 28 (47.46%) to 10 (16.95%) in Group B; with response proportions of 54.76% vs 64.29%, $p < 0.01$. Grade 2 nausea was decreased from 33 (55.93%) to 15 (25.42%) in Group A, and from 16 (27.12%) to 7 (11.86%) in Group B, response proportion were 54.55% vs 56.25%, $p < 0.001$. Vomiting (Grade 2) was improved substantially in both groups-27.12% to 5.08% in Group A and 20.34% to 3.39% in Group B, but without a significant between-group difference, $p = 0.8988$. Convulsion was also declined sharply from 27.12% to 5.08% in Group A and 40.68% to 6.78% in Group B, $p = 0.2806$, while cognitive dysfunction showed a modest improvement from 20.34% to 15.25% in Group A and 25.42% to 15.25% in Group B, $p = 0.7674$.

Toxicity was generally mild and tended to improve by 8 weeks. Fatigue was common on 1 week, any grade of fatigue was 45 (76.27%) in Group A versus 34 (57.63%) in Group B, and Grade 2 fatigue was higher in Group A, 20 (33.90%) vs 14 (23.73%); by 8 weeks any grade of fatigue decreased to 33 (55.93%) in Group A and 26 (44.07%) in Group B, $p = 0.429$. Skin reactions were infrequent; any grade at 1 week was seen in 3 (5.08%) in Group A and 4 (6.78%) in Group B, rising slightly by 8 weeks to 5 (8.47%) and 8 (13.56%), respectively, $p = 0.675$. Hair loss remained low and stable. Grade 1 was about 10% in Group A at both time points, 6 (10.17%), and 12% to 14% in Group B, 7 (11.86%) at 1 week and 8 (13.56%) at 8 weeks, $p = 0.7769$.

Table 7. Symptom response at 8 weeks after radiotherapy by study group

Symptom (response category used)	Group A (n=59)			Group B (n=59)			P-value
	Baseline n (%)	At 8 weeks n (%)	Response %	Baseline n (%)	At 8 weeks n (%)	Response %	
Headache (Grade 2–3)	42 (71.19)	19 (32.20)	54.76	28 (47.46)	10 (16.95)	64.29	<0.01
Nausea (Grade 2)	33 (55.93)	15 (25.42)	54.55	16 (27.12)	7 (11.86)	56.25	<0.001
Vomiting (Grade 2)	16 (27.12)	3 (5.08)	81.25	12 (20.34)	2 (3.39)	83.33	0.8988
Convulsion (present)	16 (27.12)	3 (5.08)	81.25	24 (40.68)	4 (6.78)	83.33	0.2806
Cognitive dysfunction (present)	12 (20.34)	9 (15.25)	25.00	15 (25.42)	9 (15.25)	40.00	0.767

Table 8. Treatment-related toxicities at 1 week and 8 weeks after radiotherapy by study group

Toxicity	Time point	Group A (n=59)			Group B (n=59)			P-value
		No Fatigue n (%)	Grade 1 n (%)	Grade 2 n (%)	No Fatigue n (%)	Grade 1 n (%)	Grade 2 n (%)	
Fatigue	1 week	14 (23.73)	25 (42.37)	20 (33.90)	25 (42.37)	20 (33.90)	14 (23.73)	0.429
	8 weeks	26 (44.07)	21 (35.59)	12 (20.34)	33 (55.93)	16 (27.12)	10 (16.95)	
Skin reaction	1 week	56 (94.92)	2 (3.39)	1 (1.69)	55 (93.22)	2 (3.39)	2 (3.39)	0.675
	8 weeks	54 (91.53)	3 (5.08)	2 (3.39)	51 (86.44)	5 (8.47)	3 (5.08)	
Hair loss	1 week	53 (89.83)	6 (10.17)	NA	52 (88.14)	7 (11.86)	NA	0.7769
	8 weeks	53 (89.83)	6 (10.17)	NA	51 (86.44)	8 (13.56)	NA	

Discussion

This quasi-experimental comparison of two commonly used palliative WBRT schedules, 12 Gy in 2 fractions versus 20 Gy in 5 fractions, was undertaken in a real-world, resource-limited setting where treatment time, travel burden, and rapid symptom relief are central clinical priorities. The baseline pattern in both groups, older age, lung cancer predominance, metachronous presentation, multiple intracranial lesions, and KPS mainly 70–80, mirrors the case-mix typically described in palliative WBRT cohorts and supports the external plausibility of the study population.[13-17] Prognostically, most participants would be expected to fall into intermediate

survival strata on diagnosis-specific tools such as the graded prognostic assessment (GPA), where KPS, age, extracranial disease, and number of metastases are dominant drivers of outcome and, in turn, influence how aggressively intracranial therapy should be pursued.[13]

In this study, all the patients were above 18 years of age, majority of patients 49 (83.05%) in Group A and 43 (72.88%) in Group B were in the age group of 50-70 years which is consistent with the finding of one study conducted by Asghar et al. in 2009 that shows peak incidence occurring in the age range of 40-60 years.[18] According to Emiline et al. (2012), the median age at diagnosis ranged from 57 to 63 years, which also correlates with this study.[19] Regarding sex, the male patients were found to be dominant in both groups, with the percentages of 64% (38) in Group A and 86% (51) in Group B. The percentages of female patients were 36% (21) and 14% (8) in Groups A and B, respectively. Regarding economic status, most of the patients were found to be in the middle-class group. It was 55.93% and 59.32% in Group A and Group B, respectively. In this study, the primary tumor site in most patients was the lung (68.64%) in both groups combined, followed by the head and neck (9.32%) and breast (6.78%), and other primary sites, which is relatively similar with respect to lung origin in most other studies and texts.[2,20] In a study conducted in various hospitals in Germany[21], it was also found that the primary site of brain metastases is the lung in most patients. They also concluded that dose escalation beyond 30 Gray in palliative whole brain radiotherapy does not prolong survival. Zomosa et al. (2018) showed that lung cancer (50%) and breast cancer (15%) were the common primary sites of origin for brain metastases.[22] Histopathology of primary tumor among the study population showed that most patients suffered from non-small cell lung cancer; among them, 52.54% patients had adenocarcinoma and 16.95% had squamous cell carcinoma. Other common histopathology revealed 10.17% small cell carcinoma and 6.78% infiltrating ductal carcinoma. Pekmezci et al. (2013) showed that the incidence of metastases varies by the histologic subtype of the tumors.[23] Non-small cell lung carcinomas were more likely to metastasize to the brain as compared with small cell carcinomas, and among the former, adenocarcinomas were more likely to metastasize than squamous cell and large-cell carcinomas, which correlates with this study.

This study suggested most patients were in the metachronous group, accounting to 83.9% combinedly in both groups, and the remaining presented with synchronous brain metastases. According to DeVita et al. (2019), one-third of brain metastases are synchronous, and the remaining are metachronous.[2] A study showed 36% of patients had synchronous brain metastases and 64% were in the metachronous group[24], although instead of 1 month, they included a duration of 2 months from the diagnosis of the primary, as the definition of synchronous brain metastases.

Most patients (87%) in both groups presented with multiple metastases in the brain. According to Emiline et al. (2012), the number of patients with a single metastatic lesion in the brain is 29%, whereas the proportion of patients with three or more metastatic lesions has increased, which is consistent with this study finding.[19] Regarding the performance status, all patients were within Karnofsky Performance Status 90 and 70. The maximum patient load had a KPS of 80, which was 50.8% and 61%, respectively, in Groups A and B. Besides, KPS 70 was found in 40.7% in Group A, and 33.9% in Group B. Emiline et al. (2012) showed that at the time of brain metastases diagnosis.[19], the performance status of patients was most frequently preserved, with a median KPS of 70. In this study, the most common symptoms associated with brain metastases were headache, nausea, vomiting, convulsion, and cognitive dysfunction, which correlate strongly with most other studies.[17,25]

This study showed significant improvement in headache by ultra-short fraction and short fraction whole brain radiotherapy in metastatic brain cancer. In case of grade 3 headache, the response rate was 76.19% and 75.00% in the ultra-short fraction and short fraction radiotherapy, respectively. In respect of grade 2 nausea, 54.55% & 56.25% response rates were observed in Groups A and B, respectively, which were also statistically significant. In case of vomiting, convulsion, and cognitive dysfunction, the response rate was mostly similar in both groups. In this study, it was found that fatigue, skin reaction, and hair loss were common acute toxicities of whole brain radiotherapy by both ultra-short and short fraction schedules. Although there was no statistical significance, the frequency of these acute toxicities was similar in both groups, which could be managed by adequate supportive measures. Considering all the above finding in this study, it was revealed that, ultra-short course whole brain radiation therapy i.e. 12 Gray in 2 fractions in consecutive days, can effectively achieve response in metastatic brain cancer with minimal acute toxicities, in addition, it can cut the long patient queue in radiotherapy department, as there are huge patient burden and lack of adequate number of radiotherapy machine in Bangladesh.

Limitations of the study

Despite appropriate conduct at each stage, this study has important limitations. It was carried out in only two tertiary-

level centers in Dhaka, which may limit the generalizability to the broader national population, particularly patients managed in peripheral facilities where case-mix, access to imaging and radiotherapy, and supportive care resources may differ. Another important limitation is baseline imbalance of sex and primary tumor sites and types, which can be minimize by studying large number of sample.

Conclusion

Ultra-short course whole brain radiotherapy (12 Gy in 2 fractions on consecutive days) is similarly effective as short-course whole brain radiotherapy (20 Gy in 5 fractions) in palliation of symptoms of metastatic brain cancer, and explored the concept to treat a larger number of patients with the existing facilities with manageable toxicities.

Recommendations

- Further multicenter studies across Bangladesh with larger samples and longer follow-up are recommended to improve generalizability and assess sustained symptom control, survival, and late effects.
- Prospective studies using standardized toxicity grading should also be conducted to better define acute and delayed adverse events for each WBRT fractionation schedule.

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