Section: Radiotherapy

Original Research Article

COMPARISION OF TWO DIFFERENT RADIO THERAPY FRACTIONATION SCHEDULES FOR METASTATIC SPINAL CORD COMPRESSION

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ABSTRACT

Background: Indian population experiences cancers of Lung, Breast, prostate most commonly where the disease is systemic to start with, and a high chance of metastasis to bones. Our institute experience most common radiotherapy emergency of spinal cord compression so regularly that we need to frame a protocol for this cases on priority basis and to save the linac machine time is also so precious. **Objectives:** To compare the overall response in patients treated with two different fractionation schedules of 4 Gy x 5 fractions versus 3 Gy x 10 fractions for metastatic spinal cord compression.
Materials and Methods: It is a prospective comparative study with total number of patients enrolled in the study is 60. After obtaining informed consent, then patients were enrolled in the study. Patients with known biopsy proven tumour presenting with metastatic spinal cord compression causing lower limb motor dysfunction.
Results: Results showed that overall response to radiation and ambulatory status of patients post irradiation were similar in both arms. There was no significant difference between the arms.
Conclusion: Comparatively no difference in over all response and ambulatory status of patient by different fractionation. In general patients with MSCC have a poor survival and short course fractionation with 4 Gy x 5 fractions can be considered instead of the standard 3 Gy x 10 fractions.
Keywords: Bone secondaries, spinal cord compression, palliative radiotherapy,30Gy/10 frctions,20 Gy /five fractions

INTRODUCTION

MSCC, which stands for metastatic spinal cord compression, is a well-known consequence of cancer that typically manifests itself as an oncological emergency of the highest severity. There are a few cases in which direct tumour extension into the vertebral column can be the cause of metastatic spinal cord compression (MSCC).[1] However, the most common cause of MSCC is the collapse or compression of a vertebral body that contains metastatic disease. A reversible oedema, venous congestion, and demyelination are the early symptoms that are brought on by the compression of the spinal cord. Injuries to the blood vessels, necrosis of the spinal cord, and irreversible damage can result with prolonged compression. The likelihood of improvement is low for patients who have been without neurological function for more than forty-eight hours.[2]

MATERIAL AND METHODS

A prospective comparative study is conducted at king George hospital/KGH Visakhapatnam with a sample size of 60 patients, divided equally into two arms. Over a period of one year, the study included biopsy-proven malignancy from any primary site, presenting with lower extremity motor dysfunction and radiological evidence of spinal cord compression, aged between 20 to 70 years, and with intermediate or poor survival prognosis. Patients with no prior surgery or irradiation to the index site are included, while those with cervical spine metastasis only, brain metastasis, primary brain tumors, major neurological disorders, established pathological fractures, or spinal instability requiring surgical intervention are excluded from the study.

Before initiating the comparative study on two different radiotherapy fractionation schedules for metastatic spinal cord compression, several pre-treatment requirements are essential for patient evaluation and readiness. These include obtaining a biopsy from the primary tumor site for histopathological confirmation, conducting CT or MRI scans of the spine to assess the extent of metastasis and spinal cord compression, as well as routine blood tests such as complete blood count and blood grouping, liver function tests, and renal function tests to evaluate overall health status. Additionally, a chest X-ray in PA view is necessary to rule out any thoracic pathology, while an ECG and cardiology evaluation ensure cardiac fitness for treatment. Consultation with orthopedic spine surgery specialists is sought to assess spinal stability and potential surgical interventions if warranted. Gathering medical records from previous consultations aids in understanding the patient's medical history and prior treatment modalities, facilitating informed decision-making regarding the radiotherapy fractionation schedules to be compared in the study.

Treatment Protocol

Patients with a biopsy proven primary tumor diagnosed to have metastatic spinal cord compression causing lower limb dysfunction were identified. Imaging and clinical examination were correlated with deficit. Ortho spine surgeon consultation was done to rule out surgery. After getting consent patients were assigned to treatment arms by simple randomization.

Patients in both arms received Inj. Dexamethasone 16 mg IV before start of

Radiation and were tapered over the period of treatment. All patients with vertebral metastases were given Inj. Zolendronate 4 mg every 28 days as per institution protocol followed.

Treatment by EBRT 3DCRT & volume included one vertebra above and below

the involved vertebrae. Lateral margins encompassed the transverse process on either side.

Equipment

EBRT under LINAC Varian Eclipse treatment planning system.

Treatment EBRT

CBCT was done on the initial day of treatment and alternate day for setup verification.

PTV was verified in relation to planning CT.

Protocol Design

PROTOCOL	ARM A	ARM B
Dose per fraction	4 Gy	3 Gy
Number of fractions	5	10
Total dose	20 Gy	30 Gy
Duration of treatment	1 week	2 weeks

Biologically equivalent dose is the equivalent dose in 2-Gy fraction i.e, total

dose in 2-Gy fractions that would give the same log kill as the given schedule

EQD2 = BED / 1+ [2 /(α/β)]

Radiobiological Comparison

Biological effective dose is the product of total dose and relative effectiveness.

Relative effectiveness of a regimen is the relative effectiveness per unit dose

for that fractionated treatment.

RE = 1 + d (α/β) d – Dose per fraction α – Cell kill by linear component

β – Cell kill by quadratic component

Value of α/β:

Early reacting tissue (Tumour): 10 Late reacting tissue (Spinal cord): 3

BED = n d x [1+d(α/β)]

Radiobiological Comparison

		Arm A 4 Gy x 5#	Arm B3Gy x 10#
Tumour			
BED	10	28 Gy	39 Gy
EQD2	10	23.3 Gy	32.5 Gy
Cord			
BED	3	46.67 Gy	60 Gy
EQD2	3	28 Gy	36 Gy

Response Assessment

Clinical examination of lower limb motor function was done at baseline before

radiation and 1, 3 and 6 months following radiation. It was scored as follows

0 – Total paralysis

1 – Palpable or visible contractions

3 – Active movement, full range of motion, against gravity

4 – Active movement, full range of motion, against gravity and provides some resistance.

5 – Active movement, full range of motion, against gravity and provides normal resistance.

Improvement of motor function was defined by improvement of point in scoring system compared to baseline. Deterioration of motor function defined by reduction of point in scoring system compared to baseline. No further progression defined by no change in score compared to baseline. Primary end point was 1-month overall response regarding motor function defined as improvement or no further progression of motor deficits.

RESULTS

Overall response to radiation was not significantly different between the arms. It was not affected by age, gender, performance status, number of vertebra involved, duration to development of MSCC, primary tumour and ambulatory status. For all these factors the overall response was not significantly different between the arms. [Table 6]

Patients were assessed for acute toxicities of skin, oesophagus, upper gastrointestinal tract and haematological toxicity. None of the patients had grade 3 or 4 toxicities as per RTOG grade. Both treatment arms were tolerated well.

Assessment at 6 Months

At six months of follow-up some patients in both arms had died. 24 patients in ARM A were alive after 6 months and were available for follow-up assessment. 25 patients in ARM B were alive.

4 patients in ARM A had deterioration in motor function after radiation and 3 of them had died by 6 months. The remaining 1 patient had paralysis lower limb muscle and was non ambulant. 6 other patients who had response to radiation died by 6 months.

Out of the 24 patients available at follow-up 4 had developed second vertebral metastases within 6 months and were irradiated.

3 patients in ARM B had deterioration in motor function after radiation and one among them had died by 6 months. The remaining 2 patients had paralysis in lower limb muscle and were non ambulant. 4 other patients who had response to radiation died by 6 months. Out of the 25 patients available at follow-up 3 had developed second vertebral metastases within 6 months and were irradiated.

There was no statistically significant difference between the ambulatory status in the study arms at the end of six months. [Table 7]

Table 1: Distribution of Patients with Different Variables

	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
AGE GROUP					
< 50	8	26.66%	9	30%	
50 – 60	14	46.66%	16	53.33%	
> 60	8	26.66%	5	16.66%	.64
GENDER					
FEMALE	13	43.33%	12	40%	**0.79**
MALE	17	56.66%	18	60%	
ECOG STATUS					
1-2	5	16.66%	6	20%	.73
3-4	25	83.33%	24	80%	
VERTEBRAL INVOLVEMENT					
SINGLE	13	43.33%	12	40%	
MULTIPLE	17	56.66%	18	60%	.79
OTHER BONEMETASTASES					
YES	21	70%	20	66.66%	
NO	9	30%	10	33.3%	.78
VISCERAL METASTASES					
YES	22	73.33%	21	70%	
NO	8	26.66%	9	30%	.77
INTERVAL BETWEEN TUMUR DIAGNOSIS AND MSCC					
< 6 MONTHS	12	40%	10	33.33%	
> 6 MONTHS	18	60%	20	66.66%	.59

Table 2: Primary Site

PRIMARY SITE	ARM A		ARM B	
	NUMBER	PERCENT	NUMBER	PERCENT
LUNG	10	33.33%	7	23.33%
BREAST	7	23.33%	8	26.66%
PROSTATE	5	16.66%	6	20%
RECTUM	3	10%	4	13.33%
EOPHAGUS	3	10%	2	6.66%
STOMACH	0	-	1	3.33%
PANCREAS	1	3.33%	0	-
RCC	1	3.33%	1	3.33%
THYROID	0	-	1	3.33%
TOTAL	30	100%	30	100%

Table 3: Ambulatory Status Before Radiation

AMBULATORYSTATUS	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
AMBULATORYWITHOUT AID	7	23.33%	8	26.66%	.94
AMBULATORY WITH AID	10	33.33%	11	36.66%	
NON AMBULATORY	13	43.33%	11	36.66%	
TOTAL	30	100%	30	100%	

Table 4: Response to Radiation in Entire Cohort

MOTOR FUNCTION AFTER RADIATION	NUMBER	PERCENT
IMPROVEMENT	21/60	35%
NO PROGRESSION	32/60	53.33%
DETERIORATION	07/60	11.66%
OVERALL RESPONSE TO RADIATION	53/60	88.33%

Table 5: Response to Radiation at 1 Month

MOTOR FUNCTION ATONE MONTH	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
IMPROVEMENT	10/30	33.33%	11/30	36.66%	0.9
NO PROGRESSION	16/30	53.33%	16/30	53.33%	
DETERIORATION	04/30	13.33%	03/30	10%	
OVERALL RESPONSE TO RADIATION	26/30	86.66%	27/30	90%	

Table 6: Overall Response

	ARM A (26/30)	ARM B (27/30)	p-value
< 50 YEARS	7/8	8/9	0.54
50 – 60 YEARS	12/14	15/16	
> 60 YEARS	7/8	4/5	
GENDER DISTRIBUTION			
FEMALE	11/13	11/12	0.90
MALE	15/17	16/18	
ECOG STATUS			
1-2	5/5	6/6	0.78
3-4	21/25	21/24	
NUMBER OF VERTEBRA INVOLVED			
SINGLE	12/13	11/12	0.69
MULTIPLE	14/17	16/18	
ONSET OF MSCC			
< 6 MONTHS	10/12	9/10	0.69
> 6 MONTHS	16/18	18/20	
	PRIMARY SITE		
LUNG	8/10	6/7	
BREAST	6/7	7/8	
PROSTATE	5/5	6/6	
RECTUM	3/3	3/4	
EOPHAGUS	2/3	2/2	
STOMACH	0	1/1	
PANCREAS	1/1	0	
RCC	1/1	1/1	
THYROID	0	1/1	
AMBULATORY STATUS BEFORE RADIATION			
AMBULATORY WITHOUT AID	7/7	8/8	0.54
AMBULATORYWITH AID	10/10	11/11	
NON AMBULATORY	9/13	8/11	

Table 7: Acute Toxicity

ACUTE TOXICITY	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
GRADE 1	10	33.33%	11	36.66%	.90
GRADE 2	4	13.33%	4	13.33%	
GRADE 3	0	-	0	-	
GRADE 4	0	-	0	-	

DISCUSSION

In this study comparing two different radiotherapy fractionation schedules for metastatic spinal cord compression (MSCC), a total of 60 patients were randomly allocated to each treatment arm. Demographic analysis revealed that 50% of patients in both arms were aged between 50 and 60 years, with 31.3% younger than 50 and 18.3% older than 60. Gender distribution showed slight variations, with ARM A comprising 43.33% females and 56.66% males, while ARM B had 40% females and 60% males. The majority of patients in both arms had multiple vertebral involvements (56.6% in ARM A and 60% in ARM B), and over 70% had multiple bone metastases. More than 70% of patients in both arms had visceral metastases. Within six months of tumor diagnosis, 40% of ARM A and 33.33% of ARM B developed MSCC. The most common primary tumor sites were lung and breast in both arms. At the end of one month after radiation, 21 patients showed improvement in motor function, deteriorated further, and 32 showed no improvement but did not deteriorate. There was no significant difference in overall response to radiation between the arms, regardless of demographic or clinical factors. Acute toxicities were well tolerated, with no grade 3 or 4 toxicities observed. At six months, some patients had died in both arms, with similar rates of deterioration in motor function. The ambulatory status did not significantly differ between the arms at six months.

Rades and Barbara et al compared short-course radiotherapy (RT) (4 Gy × 5) to longer-course RT (3 Gy × 10) for metastatic epidural spinal cord compression (MSCC). Two-hundred three patients with MSCC and poor to intermediate expected survival were randomly assigned to 4 Gy × 5 in 1 week (n = 101) or 3 Gy × 10 in 2 weeks (n = 102). Patients were stratified according to ambulatory status, time developing motor deficits, and primary tumor type. Seventy-eight and 77 patients, respectively, were evaluable for the primary end point, 1-month overall response regarding motor function defined as improvement or no further progression of motor deficits. Other study end points included ambulatory status, local progression-free survival, and overall survival. End points were evaluated immediately after RT and at 1, 3, and 6 months thereafter. At 1 month, overall response rates regarding motor function were 87.2% after 4 Gy × 5 and 89.6% after 3 Gy × 10 (P = .73). Improvement rates were 38.5% and 44.2%, respectively, no further progression rates 48.7% and 45.5%, respectively, and deterioration rates 12.8% and 10.4%, respectively (P = .44). Ambulatory rates at 1 month were 71.8% and 74.0%, respectively (P = .86). At other times after RT, the results were also not significantly different. Six-month local progression-free survival was 75.2% after 4 Gy × 5 and 81.8% after 3 Gy × 10 (P = .51); 6-month overall survival was 42.3% and 37.8% (P = .68). and finally concluded that Short-course RT with 4 Gy × 5 was not significantly inferior to 3 Gy × 10 in patients with MSCC and poor to intermediate expected survival.[3]

Rades D, Stalpers et al studied five radiotherapy (RT) schedules and potential prognostic factors for functional outcome in metastatic spinal cord compression (MSCC). One thousand three hundred four patients who were irradiated from January 1992 to December 2003 were included in this retrospective review. The schedules of 1 × 8 Gy in 1 day (n = 261), 5 × 4 Gy in 1 week (n = 279), 10 × 3 Gy in 2 weeks (n = 274), 15 × 2.5 Gy in 3 weeks (n = 233), and 20 × 2 Gy in 4 weeks (n = 257) were compared for motor function, ambulatory status, and in-field recurrences. The following potential prognostic factors were investigated: age, sex, performance status, histology, number of involved vertebra, interval from cancer diagnosis to MSCC, pretreatment ambulatory status, and time of developing motor deficits before RT. And results were motor function improved in 26% (1 × 8 Gy), 28% (5 × 4 Gy), 27% (10 × 3 Gy), 31% (15 × 2.5 Gy), and 28% (20 × 2 Gy); and posttreatment ambulatory rates were 69%, 68%, 63%, 66%, and 74% (P = .578), respectively. On multivariate analysis, age, performance status, primary tumor, involved vertebra, interval from cancer diagnosis to MSCC, pretreatment ambulatory status, and time of developing motor deficits were significantly associated with functional outcome, whereas the RT schedule was not. Acute toxicity was mild, and late toxicity was not observed. In-field recurrence rates at 2 years were 24% (1 × 8 Gy), 26% (5 × 4 Gy), 14% (10 × 3 Gy), 9% (15 × 2.5 Gy), and 7% (20 × 2 Gy) ($P < .001$). Neither the difference between 1 × 8 Gy and 5 × 4 Gy (P = .44) nor between 10 × 3 Gy, 15 × 2.5 Gy, and 20 × 2 Gy (P = .71) was significant. And concluded that five RT schedules provided similar functional outcome. The three more protracted schedules seemed to result in fewer in-field recurrences. To minimize treatment time, the following two schedules are -1 × 8 Gy for patients with poor predicted survival and 10 × 3 Gy for other patients. [4]

Maranzano et al. intended to conduct a randomised trial in order to evaluate the clinical result and toxicity of two distinct hypofractionated radiation therapy regimens. Three hundred patients diagnosed with MSCC were randomly randomised to receive either short-course radiation therapy (eight Gy over two days) or split-course radiation therapy (five Gy over three days or three Gy over five days). Patients with a limited life expectancy were the only ones who participated in the programme. A follow-up period of 33 months was the median, with a range of 4 to 61 months. The total number of patients who were able to be evaluated was 276 (92%): 142 (51%) were treated with the short course regimen, and 134 (49%) were treated with the split course regimen of radiation therapy. The two arms did not differ significantly in terms of response, survival, duration of response, or toxicity. There was no significant difference identified here. A comparison was made between short-course and split-course regimens, and the results showed that following RT, 56% and 59% of patients experienced alleviation from their back pain, 68% and 71% were able to walk, and 90% and 89% had good bladder function, respectively. For both groups, the median length of improvement was 3.5 months, and the median survival time was four months per patient. A grade 3 oesophagitis or pharyngitis was documented in four patients (1.5%), grade 3 diarrhoea occurred in four patients (1.5%), and grade 3 vomiting or nausea happened in ten patients (6%). The proportion of patients who experienced toxicity was equal between the two arms. None of the late toxicity was ever documented. Both of the hypofractionated RT were successful and had a level of toxicity that was tolerable, in terms of patient convenience and machine time, hypofractionated RT regimen is of choice in clinical practice for patients with MSCC.[5]

Rades and karstens et al compared three distinct schedules. There were three different schedules that were examined for post treatment functional and ambulatory outcomes. These schedules were as follows: 30 Gy in 10 fractions (n = 93), 37.5 Gy in 15 fractions (n = 80), and 40 Gy in 20 fractions (n = 74). Before and after the completion of RT, as well as three, six, and twelve months later, motor function was assessed using a scale with six points. In order to determine the functional outcome, a multivariate analysis was carried out. This analysis took into account the fractionation schedule as well as the three key prognostic criteria, which were the primary tumour type, the time at which motor impairments began to develop prior to RT, and the ambulatory status. There was no discernible difference found between the three schedules in terms of post-treatment motor function or ambulatory rates. A multivariate analysis revealed that the radiation schedule did not have a significant impact on the functional outcome ($p = 0.223$). This is in contrast to the three prognostic factors, which were found to have a substantial impact ($p <0.001$, $p <0.001$, and $p = 0.012$). There was no significant difference in the functional outcome across the three fractionation regimes. When treating patients who have a significantly shorter life expectancy, it is important to take into consideration the schedule that requires the least amount of time (30 Gy in 10 fractions).[6]

Larsen and et al investigated the statistical significance of a number of clinical and radiological factors in relation to post-treatment ambulatory function and survival. A total of 153 consecutive patients who were diagnosed with spinal cord compression due to metastatic disease were enrolled in the study, which was conducted over a period of three and a half years. Regular neurological examinations were performed on the patients by the same neurologist for a minimum of eleven months or until the conclusion of their lives, whichever came first. An investigation into the relevance of five variables in terms of their impact on gait function and survival time following therapy was carried out. There was a significant relationship between the type of original tumour and the duration of time that passed between the diagnosis of the primary malignancy and the incidence of spinal cord compression ($p < 0.0005$). Additionally, the type of primary tumour had a direct impact on the ambulatory function available at the time of diagnosis ($p = 0.016$). There was a significant relationship between the degree of myelographic obstruction and gait function as well as sensory abnormalities ($p = 0.000$). There was a significant relationship between the final gait and the gait function at the time of diagnosis ($p < 0.0005$). Survival time after diagnosis was directly dependent on the amount of time that passed between the diagnosis of the main tumour and the compression of the spinal cord ($p = 0.002$), as well as on the ambulatory function that was present at the time of diagnosis ($p = 0.018$), and on the ambulatory function that was present after treatment. The primary factor that determines the gait function after therapy is the ambulatory function that was present before treatment. The survival time is rather short, particularly in patients who are unable to walk, and the only way to improve survival time is to restore gait function in patients who are unable to walk via treatment that is administered immediately.[7]

Individually tailored radiation approach is necessary in metastatic cord compression. Expected life span and socio economic status of the patient play a significant role in decision making. Several radiation fractionations have been employed. Shorter courses from one day to one week and longer ones from two to four weeks can be used. Retrospective and prospective data have shown that motor function and ambulatory status do not vary significantly between various regimens. Results of the present study also showed no significant difference in motor function and ambulatory status. In-field recurrence should be considered in choosing fractionation regimen in patients expected to have a longer survival. Non randomized retrospective data have shown that shorter courses are associated with more recurrences beyond two years. Future research is needed to find patient population who could benefit from a shorter fractionation of single 8 Gy alone. Development of tools to predict the longer survival and recurrence patterns can help in deciding radiation fractionation.

CONCLUSION

Results of the study showed that overall response to radiation and ambulatory status of patients post irradiation were similar in both arms. There was no significant difference between the arms.

Age, gender, performance status, number of vertebra involved, time to develop MSCC, ambulatory status did not influence a difference between study arms.

However, recurrence rates between arms were not analyzed due to shorter follow-up period. Considering the fact that expected survival of many patients is poor it might not make an impact. For a small proportion of patients who might survive longer recurrence pattern might influence radiation fractionation.

In general patients with MSCC have a poor survival and short course fractionation with 4 Gy x 5 fractions can be considered instead of the standard 3 Gy x 10 fractions.

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