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RESEARCH ARTICLE

COMPARISION OF TWO DIFFERENT RADIO THERAPY FRACTIONATIONS FOR METASTATIC SPINAL CORD COMPRESSION

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Abstract

Background: Indian population experiences most common 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 cord compression so regularly that we need to frame a protocol for this cases on priority and 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 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.

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.

Introduction:-

Compression of spinal cord by metastatic tumour is an emergency scenario in oncology. If not treated appropriately it can lead to serious neurological compromise. It commonly occurs due to extension of vertebral metastases into the epidural sac Metastatic spinal cord compression (MSCC) is the compression of the dural sac and its contents by extradural mass. Neurological impairment occurring due to compression of the spinal cord if not treated early will become irreversible leading to permanent neurological deficit.

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Aim of study:-

The primary endpoint is to compare the overall response regarding motor function defined as improvement or no further progression at the end of 1 month 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.

Place of study:
Government general hospital/ Guntur medical college NATCO cancer centre, Guntur.

Study design:
A prospective comparative study.
Sample size: 60 patients(30 patients in each arm)
Study duration: 1 year.

Inclusion Criteria
- Biopsy proven malignancy of anyprimary site
- Lower extremity motor dysfunction
- Radiological evidence of spinal cord compression
- Age20 to 70 years
- No previous surgery to index site
- No previous irradiation to index site
- Patients with intermediate or poor survival prognosis.

Exclusion Criteria
- No radiological evidence of bone metastasis
- Age <20 or >70 years
- Previous irradiation of the same spine
- Previous surgery of the same spine
- Metastasis of the cervical spine only
- Brain metastasis
- Primary Brain Tumour
- Majorneurological disorders
- Established pathological fracture
- Spinal instability warranting surgical intervention.

Materials and Methods:-

Pre treatment requirements
1. Biopsy from primary tumour
2. CT or MRI –spine
3. Complete blood count, blood grouping
4. Liver function test
5. Renal function test
6. Chest X ray – PA view
7. ECG, Cardiology evaluation
8. Ortho spine surgery consultation
9. Medical records from previous consultations

Treatment Protocol
Patients with a biopsy proven primary tumour 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 randomisation.

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

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.
$RE = 1 + d\ (\alpha/\beta)$ 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
$BED = n\ d\ x\ [1+d(\alpha/\beta)]$
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
$EQD2 = BED / 1+[2 /(\alpha/\beta)]$

Radiobiological Comparison

		Arm A 4 Gy x 5#	Arm B3Gy x 10#
Tumour			
BED	10	28 Gy10	39 Gy10
EQD2	10	23.3 Gy	32.5 Gy
Cord			
BED	3	46.67 Gy3	60 Gy3
EQD2	3	28 Gy	36 Gy

Response Assesment
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

Statistical Analysis
Data was entered in Microsoft excel and SPSS software with Mann-Whitney U test was used for statistical analysis

Analysis And Results:-

Total Number Of Patients 60 Patients were allocated to both arms by simple randomization

ARM	NUMBER OF PATIENTS
A – 4 Gy x 5 fractions	30
B – 3 Gy x 10 fractions	30

Table 1:- TOTAL PATIENTS

Age Distriburion In Entire Cohort

AGE GROUP	NUMBER	PERCENTAGE
< 50	17	31.66%
50 – 60	30	50%
> 60	13	18.33%
TOTAL	60	100%

Table 2:- Age Distribution In Cohort.

50% of patients in the protocol were between 50 and 60 years of age. 31.3%patients had age less than 50 years and 18.3% had age more than 60 years.

Gender Distribution

	ARM A		ARM B		
GENDER	NUMBER	PERCENT	NUMBER	PERCENT	p-value
FEMALE	13	43.33%	12	40%	
MALE	17	56.66%	18	60%	
TOTAL	30	100%	30	100%	.79

Table 3:- Gender Distribution.

43.33% patients in ARM A were females and 56.66% were males. 40% patients in ARM B were females and 60% were males.

Age Distribution In Each Arm.

	ARM A		ARM B		
AGE GROUP	NUMBER	PERCENT	NUMBER	PERCENT	p-value
< 50	8	26.66%	9	30%	
50 – 60	14	46.66%	16	53.33%	
> 60	8	26.66%	5	16.66%	.64
TOTAL	30	100%	30	100%	

Table 4:- Age Distribution.

Arm A had 26.66% patients below 50 years, 46.66% patients between 50 and 60 years, 26.66% patients above 60 years. Youngest patient in Arm A was 40 years old and oldest patient was 72 years old. Arm B had 30% patients below 50 years, 53.33% patients between 50-60 years and 16.66% patients above 60 years. The youngest patient in Arm B was 37 years old and oldest patient was 68 years old.

Performance Status

	ARM A		ARM B		
ECOG STATUS	NUMBER	PERCENT	NUMBER	PERCENT	p-value
1-2	5	16.66%	6	20%	.73
3-4	25	83.33%	24	80%	
TOTAL	30	100%	30	100%	

Table 5:- Performance Status.

Number Of Vertebra Involved

	ARM A		ARM B		
VERTEBRAL INVOLVEMENT	NUMBER	PERCENT	NUMBER	PERCENT	p-value
SINGLE	13	43.33%	12	40%	

MULTIPLE	17	56.66%	18	60%	
TOTAL	30	100%	30	100%	.79

Table 6:- Vertebral Involvement.

43.3% in ARM A had single vertebral involvement. 56.6% had multiple vertebral involvements. 40% in ARM A had single vertebral involvement.60% had multiple vertebral involvements.

Presence Other Bone Metastases

	ARM A		ARM B		
OTHER BONE METASTASES	**NUMBER**	**PERCENT**	**NUMBER**	**PERCENT**	**p-value**
YES	21	70%	20	66.66%	
NO	9	30%	10	33.3%	
TOTAL	30	100%	30	100%	.78

Table 7:- Other Bone Metastasis.

70 % patients in ARM A 66.66% patients in ARM B had multiple bone metastases

Presence Of Visceral Metastases

	ARM A		ARM B		
VISCERAL METASTASES	**NUMBER**	**PERCENT**	**NUMBER**	**PERCENT**	**p-value**
YES	22	73.33%	21	70%	
NO	8	26.66%	9	30%	
TOTAL	30	100%	30	100%	.77

Table 8:- Visceral Metastasis.

More than 70% patients had visceral metastases in both arms.

Interval Between Tumur Diagnosis And MSCC

	ARM A		ARM B		
INTERVAL	**NUMBER**	**PERCENT**	**NUMBER**	**PERCENT**	**p- value**
< 6 MONTHS	12	40%	10	33.33%	
> 6 MONTHS	18	60%	20	66.66%	
TOTAL	30	100%	30	100%	.59

Table 9:- Interval Between Tumur Diagnosis And MSCC.

40% patients in ARM A and 33.33% in ARM B developed MSCC within 6months from tumor diagnosis.

Primary Site

	ARM A		ARM B	
PRIMARY SITE	**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	33.33%	0	-
RCC	1	33.33%	1	33.33%
THYROID	0	-	1	33.33%
TOTAL	30	100%	30	100%

Table 10:- Primary Site.

Lung and breast primaries formed the majority of cases in both arms. 33.33%in AMR A and 23.33% in ARM B had lung primary. 23.33% in ARM A and 26.66% in ARM B had breast primary. Prostate was the next common primary

constituting 16.66% patients in ARM A and 20% in ARM B. Other primaries found in study population were rectum, oesophagus, stomach, pancreas, thyroid, and renal cell carcinoma

Ambulatory Status Before Radiation

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

23.33% in ARM A and 26.66% in ARM B were ambulant without any aid.33.33% in ARM A and 36.66% in ARM B were ambulant with aid.

43.33% in ARM A and 36.66% in ARM B were non ambulant.

Response To Radiation At 1 Month

All patients were available for follow-up at one month after radiation. Clinical examination was done to assess overall response to radiation.

Improvement of motor function was defined by improvement of point inscoring system compared to baseline.

Deterioration of motor function defined by reduction of point in scoringsystem compared to baseline.

No further progression defined by no change in score compared to baseline.

Overall response regarding motor deficits defined as improvement or no furtherprogression at the end of 1 month.

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 12:- Response To Radiation In Entire Cohort.

At the end of one month 21 patients had an improvement in motor function.7 patients deteriorated further.
32 patients did not show improvement but did not deteriorate.

MOTOR FUNCTION ATONE MONTH	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
IMPROVEMENT	10/30	33.33%	11/30	36.66%	
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%	0.9

Table 13:- Response To Radiation At 1 Month.

33.3% patients in ARM A and 36.66% patients in ARM B had improvement in motor function. 53.33% patients in both arm had no progression in deficit. 13.33% patients in ARM A and 10% in AMR B deteriorated.

Ambulatory Rate At One Month After Radiation

Table 14:- Ambulatory Rate At One Month After Radiation

AMBULATORY STATUS AT ONEMONTH	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
AMBULANT	20	66.66%	21	70%	
NOT AMBULANT	10	33.33%	09	30%	

TOTAL	30	100%	30	100%	0.78

Age Distribution And Overall Response

Table 15:- Age Distribution And Response.

	ARM A	**ARM B**	**p-value**
< 50 YEARS	7/8	8/9	
50 – 60 YEARS	12/14	15/16	
> 60 YEARS	7/8	4/5	**0**.54
TOTAL	26/30	27/30	

Gender Distribution And Overall Response

Table 16:- Gender Distribution And Response.

	ARM A	**ARM B**	**p-value**
FEMALE	11/13	11/12	
MALE	15/17	16/18	
TOTAL	26/30	27/30	.90

Performance Status And Overall Response

Table 17:- Performance Status And Response.

ECOG STATUS	**ARM A**	**ARM B**	**p-value**
1-2	5/5	6/6	
3-4	21/25	21/24	
TOTAL	26/30	27/30	.78

Number Of Vertebra Involved And Overall Response

Table 18:- Vertebral Involvement And Response.

	ARM A	**ARM B**	**p-value**
SINGLE	12/13	11/12	
MULTIPLE	14/17	16/18	
TOTAL	26/30	27/30	.69

Onset Of Mscc And Overall Response

Table 19:- Onset Of Mscc And Response.

	ARM A	**ARM B**	**p- value**
< 6 MONTHS	10/12	9/10	
> 6 MONTHS	16/18	18/20	
TOTAL	26/30	27/30	.69

Primary Site And Overall Response

Table 20:- Primary Site And Response.

PRIMARY SITE	**ARM A**	**ARM B**
LUNG	8/10	6/7
BREAST	6/7	7/8
PROSTATE	5/5	6/6
RECTUM	3/3	¾
EOPHAGUS	2/3	2/2
STOMACH	0	1/1
PANCREAS	1/1	0
RCC	1/1	1/1
THYROID	0	1/1
TOTAL	26/30	27/30

Ambulatory Status Before Radiation And OverallResponse

Table 21:- Ambulatory Status Before Radiation OverallResponse.

	ARM A	ARM B	p-value
AMBULATORY WITHOUT AID	7/7	8/8	
AMBULATORYWITH AID	10/10	11/11	
NON AMBULATORY	9/13	8/11	
TOTAL	26/30	27/30	.54

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.

Acute Toxicity

Table 22:- Acute Toxicity.

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

Patients were assessed for acute toxicities of skin, oesophagus, upper gastrointestinal tract and haematological toxicity. None of the patients had grade 3 or4 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 by6 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 A had deterioration in motor function after radiation and one among them had died by 6 months. The remaining 2 patient 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.

AMBULATORY STATUS AT SIXMONTHS	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
AMBULANT	12	50%	14	56%	
NOT AMBULANT	12	50%	11	44%	
TOTAL	24	100%	25	100%	0.67

Discussion:-

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.

Results:-

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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