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Lung Cancer

Outcomes of Palliative Radiotherapy in Metastatic Epidural Spinal Cord Compression in Lung Cancer—A Prospective Observational Study from Tata Memorial Hospital

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Abstract

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Background Metastatic epidural spinal cord compression (MESCC) secondary to lung cancer (LC) is a debilitating complication associated with poor prognosis and is commonly treated with radiotherapy (RT). There is no consensus for RT dose fractionation in spinal cord compression.

Methods Forty consecutive patients of LC with radiological evidence of MESCC treated with palliative RT were evaluated for functional outcomes (pain, ambulation, and sphincter function) at 2-, 4-, and 24-week post RT completion. Pain assessment was done using visual analogue scale (VAS) and response was categorized according to international consensus criteria, ambulation status (AS) using Tomita's scale, and sphincter function by the presence or absence of a catheter. Overall survival (OS) was assessed using Kaplan-Meier method and compared using log-rank test. Impact of potential prognostic factors on survival was also analyzed and *p*-value ≤0.05 was considered significant.

Results Sixteen, 22, and two patients received 8 Gy single fraction (SF), 20 Gy in five fractions (20/5), and 30 Gy in 10 fractions (30/10), respectively. At 2 weeks, overall response (OR) rates of pain, ambulation, and sphincter control were 73, 81, and 81%, respectively. At 4 and 24 weeks, 93.7, 84.3, 87.5% and 88, 94, 76.5% had OR, respectively. Median OS was 4 months. Six- and 12-months OS was 50 and 37.5%. Nonsignificant difference in OS was seen between SF and 20/5 fractions (median 2.2 vs. 7.1 months, $p = 0.39$). Age ≤50 years was the only significant factor ($p < 0.05$) in univariate analysis for OS.

Conclusion Radiotherapy provided equivalent pain control, ambulation, and sphincter function compared with reported literature in MESCC. Nonsignificant difference in OS exists between SF and multifraction RT regimens.

Keywords

- cord compression
- radiotherapy
- lung cancer
- ambulation

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Introduction

Metastatic epidural spinal cord compression (MESCC) can be defined as the compression of spinal cord and/or cauda equina, by direct pressure and/or induction of vertebral collapse or instability by metastatic spread or direct extension of malignancy that threatens or causes neurological disability.[1] It occurs in 5 to 15% of all cancer patients and is the second most common neurological complication of cancer after brain metastasis.[2] The incidence of MESCC in lung cancer is approximately 25 to 30%.[2] It is an oncological urgency that may result in irreversible neurological damage such as paraplegia or tetraplegia depending upon the level of the lesion.

The treatment of MESCC includes urgent surgical decompression or radiotherapy (RT) alone or in combination. The choice of treatment depends on duration of symptoms, performance status (PS), presence/absence of spinal instability, extent of vertebral disease, sensitivity of the tumor, and expected survival.[3,4] De-compressive surgery followed by RT gives better outcome in terms of pain, ambulation, and use of steroids.[5,6] However, decompressive surgery is performed in less than 10% and majority receive palliative external beam RT. Radiotherapy to the affected sites also improves pain control, motor function, and sphincter function. The acceptable dose fractionation for MESCC are 30 Gy in 10 fractions delivered daily over a period of 2 weeks, 20 Gy in five fractions delivered daily over 1 week, 16 Gy in two fractions once weekly, or 8 to 10 Gy single fraction (SF).[7-10] Expected life expectancy, logistics of bringing the patient daily to RT department, and physician's preference usually decides dose fractionation. Commonly, long course RT schedules are preferred for patients with good life expectancy and short course or SF treatment are preferred for limited life expectancy.

Various randomized studies have compared different RT regimens for MESCC; however, consensus for a single RT regimen for all MESCC patients is still lacking. These studies compared different fractionation schedules and end points using different response evaluation criteria.[7-12] Patient and caregivers face extreme physical, logistical, and financial challenges to come daily to the RT department for longer RT schedules. Hence, the use of protracted RT schedules is less preferred than short course. At our institute, we use 20 Gy in five fractions or 16 Gy in two fractions 1 week apart. However, there are no strict criteria of using either two regimens.

Lung cancer patients with MESCC have a dismal prognosis. However, with systemic targeted therapy survival has improved considerably in positive oncogene mutation like epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase. As MESCC patients require urgent RT treatment, decision of appropriate dose fractionation is of critical importance to have durable pain control, ambulation status (AS), and local control.

Materials and Methods

We conducted a prospective observational study of lung cancer patients with radiological evidence of MESCC. Patients were accrued in this study from March 2016 to November 2017 after written informed consent. This study was approved by Institutional Review Board. The primary objective of this study was to evaluate pain control and functional outcomes of ambulation status and sphincter function and secondary objective was overall survival (OS). Eligibility criteria included pathologically confirmed lung cancer with radiological evidence of MESCC and no prior surgical intervention or RT to the affected spinal segments. Diagnosis of MESCC was done either with magnetic resonance imaging or computerized tomography (CT). The decision of palliative RT was done in a multidisciplinary tumor board and the fractionation schedule was decided by the treating radiation oncologist (RO) depending upon patient PS, expected survival, and logistics. All patients were assessed for baseline physical and neurological examination prior to radiation commencement. Pain, ambulation, and sphincter function assessment was done at baseline and at 2 weeks, 4 weeks, and at 6 months post RT completion. Each aspect was evaluated separately. Patients who were unable to come for follow-up were contacted telephonically for response assessment.

Radiotherapy Treatment

Palliative RT was planned with CT scan. Target volume included the diseased vertebra with associated soft tissue mass if any and one vertebra above and below the diseased vertebra. RT was delivered using megavoltage radiation with single posterior portal. Depth of prescription was kept such that the affected body of vertebrae is covered by at least 90% of the prescription dose. RT was started within 24 to 48 hours of diagnosis of MESCC. Different fractionation schedules used were 8 Gy SF, 20 Gy in five fractions, and 30 Gy in 10 fractions.

All patients received supportive care, i.e., corticosteroids, analgesics, and appropriate systemic treatment. Oral dexamethasone (8 mg bid) was administered from the first day of clinical-radiological diagnosis, and then gradually tapered off during the next 2 weeks. In addition, patients received analgesics as per the WHO ladder of analgesia and supportive care including anti emetics, bisphosphonates, and physiotherapy.

Assessment

Pain assessment was done using visual analogue scale (VAS) with a score of 0 indicating no pain and score of 10 indicating worst pain in the last 24 hours. Pain score was categorized as 1 to 3 mild pain, 4 to 7 moderate pain, and 8 to 10 severe pain for clinical purpose. Pain response assessment was done as per the updated international consensus criteria as a combination of pain score and oral morphine equivalent dose (OMED).[13] It comprises of four categories namely, complete response, partial response, pain progression, and indeterminate response. Complete response is pain score of zero at the treated site with no concomitant increase in OMED, partial response is reduction in pain score of 2 or more without OMED increase or OMED reduction of ≥25% from the baseline without an increase in pain score, pain progression is increase in pain score by 2 or more from baseline with stable OMED or ≥ 25% increase in OMED with baseline pain score

stable or 1 above baseline. All other responses were classified as indeterminate response.

Ambulation assessment was done with modified Tomita's scale[14] which comprises of grade 0—normal strength, grade 1—walking without support, grade 2—walking with support, Grade 3—inability to walk, and grade 4—complete paraplegia. Ambulation response has been categorized as responders—if there is an improvement in grade of ambulation or stable grade of ambulation after RT, progression—worsening of grade of ambulation. Sphincter function was recorded in terms of presence or absence of an indwelling catheter.

Percentage response for pain, ambulation and sphincter function, duration of response, reirradiation rate, and OS was also evaluated. Toxicity was documented using RTOG criteria.

Statistical Methods

The primary objective of pain control, AS, and sphincter function was assessed at 2 and 4 weeks. All the analyses were done for assessable patients at follow-up. Continuous data were reported as frequencies and percentages. Fisher's exact test and Chi-square test were applied for all categorical data. Mean change in pain score and AS of 1 or 2 were compared using Wilcoxon sign rank test in assessable patients. Secondary objective of OS was measured from the date of RT starting to the date of death from any cause. OS and impact of potential prognostic factors were calculated by the Kaplan-Meier method and compared by the log-rank test. A *p*-value of ≤0.05 was considered statistically significant.

Results

A total of 40 consecutive patients were accrued in this study. Patient and tumor characteristics were summarized in ►Table 1. Thirty-seven patients were eligible for assessment at first follow-up of 2 weeks (three patients expired before first follow-up), 32 patients at 4 weeks (five additional patients expired after first follow-up), and 17 patients at 6 months (12 additional patients expired after second follow-up and three lost to follow-up). The baseline pain score, ambulation grade, sphincter function are given in ►Table 2. Median follow-up was 5.5 months (range 10 days to 49 months).

Pain Control

Distribution of pain scores is given in ►Table 3 and pain response is given in ►Table 4. At first follow-up of 2 weeks, out of 37 assessable patients, 73% had partial response, 16.2% had indeterminate response, and 10.8% had progression. At 4 weeks, out of 32 assessable patients, 6.25% had complete response, 87.5% had partial response, and 6.25% had progression. At 6 months, out of 17 assessable patients, 5.8% had complete response, 82.3% had partial response, and 11.7% had progression. Mean change in pain score was significant at 2 weeks, 4 weeks, and 6 months from baseline score (p <0.000).

Table 1 Baseline patient characteristics

Patient characteristics at baseline	N-40 (%)
Age (median)	52
<50 y	14 (35%)
≥50 y	26 (65%)
Gender	
Female	07 (17.5%)
Male	33 (82.5%)
Performance status	
1–2	30 (75%)
3–4	10 (25%)
MESCC as presenting manifestation	
Yes	34 (85%)
No	06 (15%)
Mode of diagnosis	
CT	09 (42.5%)
MRI	23 (57.5%)
Duration of symptoms/deficits	
1–7 d	07 (17.5%)
8–14 d	08 (20%)
>14 d	25 (62.5%)
Histology	
NSCLC	36 (90%)
SCLC	04 (10%)
Location	
Cervical	05 (12.5%)
Thoracic	26 (65%)
Lumbosacral	09 (22.5%)
No. of vertebrae affected	
Single	09 (22.5%)
Multiple	31 (77.5%)
Contiguity of involvement	
Contiguous	30 (75%)
Noncontiguous	10 (25%)
Pain (VAS score)	
Mild pain[1,2,7]	05 (12.5%)
Moderate pain[3-6]	25 (62.5%)
Severe pain[8-10]	10 (25%)
Ambulation	
Walking	27
Without support	14 (35%)
With support	13 (32%)
Not walking	13
Inability to walk	06 (15%)
Complete paraplegia	07 (17%)
Sensory deficits	
Present	17 (42.5%)

(*Continued*)

Table 1 (Continued)

Patient characteristics at baseline	N-40 (%)
Absent	23 (57.5%)
Sphincter function	
Affected	09 (22.5%)
Preserved	31 (77.5%)
Other visceral metastasis	
Present	16 (40%)
Absent	24 (60%)
Fractionation used	
Long course (30 Gy/10)	02 (5.0%)
Short course (20 Gy/5)	22 (55%)
Single fraction (8 Gy)	16 (40%)
Systemic therapy	
Chemotherapy	33 (82.5%)
Targeted therapy	07 (17.5%)
Bisphosphonates	
Received	24 (60%)
Not received	16 (40%)

Abbreviations: CT, computed tomography; MESCC, metastatic epidural spinal cord compression; MRI, magnetic resonance imaging; NSCLC, nonsmall cell lung cancer; SCLC, small cell lung cancer; VAS, visual analogue scale.

Ambulation

Distribution of ambulation scores is given in ►Table 5 and ambulation response in ►Table 4. At first follow-up of 2 weeks (n = 37), 81% patients showed response and 19% showed progression. At 4 weeks (n = 32) and 6 months (n = 17), 84.3 and 94.1% showed response and 16.7 and 5.9% showed progression, respectively. Mean change in ambulation score of 1 or 2 was not different at any time point from baseline. This suggests that patient maintained the walking ability with or without support compared with baseline.

Sphincter Function

At 2 weeks, 4 weeks, and 6 months, 81.1, 87.5, and 76.5% patients were continent and 18.9, 12.5, and 23.5% required indwelling catheter, respectively (►Table 5). A total of five out of nine patients showed improvement in sphincter function, three patients at 2 weeks and two patients at 4 weeks. Two showed worsening in sphincter function (1 at 2 weeks and other at 6 months). Mean change in sphincter function was not different at any time point from baseline.

Survival and Toxicity

The median OS was 4 months, and 50 and 37.5% were alive at 6 and 12 months, respectively. Age ≤ 50 years was the only significant factor (p <0.05) in univariate analysis for OS. No

Table 2 Baseline scores for pain, ambulation, and sphincter function

Baseline scores					
Pain scores	***N* (%)**	**Ambulation**	***N* (%)**	**Sphincter function**	***N* (%)**
Mild (VAS 1–3)	5 (12.5%)	Walking without support	14 (35%)	Incontinence	09 (22.5%)
Moderate (VAS 4–7)	25 (62.5%)	Walking with support	13 (32.5%)	Continence	31 (77.5%)
Severe (VAS 8–10)	10 (25%)	Inability to walk	06 (15%)		
		Complete paraplegia	07 (17.5%)		

Abbreviation: VAS, visual analogue scale.

Table 3 Distribution of pain scores—numbers (percentage)

	Baseline	At 2 wk	1 mo	6 mo
Mild pain (VAS 1–3)	5 (12.5%)	16 (43.2%)	19 (59.4%)	13 (76.47)
Moderate pain (VAS 4–7)	25 (62.5%)	18 (48.6%)	11 (34.4%)	4 (23.53)
Severe pain (VAS 8–10)	10 (25%)	03 (8.1%)	02 (6.3%)	0
Expired/loss to follow-up	–	03	08	23
Total	40 (100%)	37 (100%)	32 (100%)	17 (100%)

Abbreviation: VAS, visual analogue scale.

Table 4 Pain and ambulation response compared with baseline

Functions		2 wk (n = 37)	1 mo (n = 32)	6 mo (n = 17)
Pain	CR	0	2 (6.25%)	1 (5.8%)
	PR	27 (73%)	28 (87.5%)	14 (82.3%)
	IR	6 (16.2%)	00	00
	Progression	4 (10.8%)	2 (6.25%)	2 (11.7%)
Ambulation	Improvement	08 (21.62%)	08 (24.9%)	08 (46.06%)
	Stable	22 (59.46%)	19 (59.4%)	08 (47.06%)
	Progression	7 (18.9%)	5 (15.6%)	01 (5.8%)

Abbreviations: CR, complete response; IR, indeterminate response; PR, partial response.

Table 5 Distribution of ambulation and sphincter function

		At baseline	2 wk	1 mo	6 mo
Ambulation	Walking without support	14 (35%)	13 (35.14%)	13 (40.63%)	08 (47.06%)
	Walking with support	13 (32.5%)	10 (27.03%)	10 (31.25%)	06 (35.29%)
	Inability to walk	06 (15%)	10 (27.03%)	06 (18.75%)	02 (11.76%)
	Complete paraplegia	07 (17.5%)	04 (10.81%)	03 (9.38%)	01 (5.08%)
Sphincter function	Incontinence	09 (22.5%)	07 (18.9%)	04 (12.5%)	04 (23.5%)
	Continence	31 (77.5%)	30 (81.1%)	28 (87.5%)	13 (76.5%)
	Expired	–	03	08	23
	Total (*n*)	40 (100%)	37 (100%)	32 (100%)	17 (100%)

Table 6 Randomized studies comparing different fractionation regimens in MESCC

	Maranzano 2005 (*n* = 276)	Maranzano 2009 (*n* = 303)	ICORG 05–03 (*n* = 116)	SCORE-2 (*n* = 203)	SCORAD (*n* = 686)	Our study (*n* = 40)
Study arms	16 Gy/2Fr vs. Split course	16 Gy/2Fr vs. 8 Gy SF	20 Gy/5Fr vs. 10 Gy SF	20 Gy/5 Fr vs. 30 Gy/10Fr	8 Gy SF vs. 20 Gy/5Fr	8 GySF (*n* = 16) 20 Gy/5Fr, (*n* = 22),
Eq. D2	24 vs. 35 Gy	24 vs. 12 Gy	23.3 vs. 17 Gy	23.3 vs. 32.5 Gy	12 vs. 23.3 Gy	
Primary end point at 1 mo	Pain, Motor, Sphincter function	Pain, Motor, Sphincter function	Change in mobility at 5 wk	Motor function	Ambulatory score of 1 or 2 at week 8	Pain relief and ambulation
Pain relief	56 vs. 59%	53 vs. 52%	–	–	–	93.75%
Ambulation	68 vs. 71%	69 vs. 62%	68 vs. 79%	87 vs. 90%	69.3 vs. 72.7%	84.3%
Sphincter function	90 vs. 89%	87 vs. 85%	76 vs. 87%	–	–	81%,87%
Median duration of relief	3.5 mo	5 vs. 4.5 mo	–	–	–	–

Abbreviations: Eq. D2, equivalent dose in 2 Gy fraction calculated using α/beta ratio of 10 Gy, Split course: 5 Gy × 3 fractions; 4 d gap, 3 Gy × 5 fractions; Total dose: 30 Gy in 2 wk; Fr, fractions; MESCC, metastatic epidural spinal cord compression; SF, single fraction.

patient reported any grade 2 toxicity. Nonsignificant difference in OS was noted in patients who received 20 Gy in 5 versus 8 Gy SF (median OS 7.1 vs. 2.2 months, $p = 0.39$). We also analyzed pain response (complete response and partial response) between 20 Gy in five fractions ($n = 22$) and 8 Gy in SF ($n = 16$). At 2 weeks, 4 weeks, and 6 month, response rates were 68.75, 87.5, and 31.25% in SF group compared with 68.18, 63.63, and 41% in five fraction group, respectively (p = NS).

Discussion

MESCC is an oncological urgency for early intervention with either surgery or RT. To the best of our knowledge, this is the first prospective study from our country on MESCC in lung cancer. Pain response at 2 and 4 weeks were 73 and 93.75% and ambulation rates of 81 and 84.3%, respectively. In our study, although varied fractionation schedules have been used but patients were predominantly treated with short course (20 Gy in five fractions, $n = 22$) and single 8 Gy fraction ($n = 16$). Pain control and functional outcomes were similar to those reported in literature (►Table 6).

Maranzano et al in their first noninferiority randomized study in patients with limited life expectancy (≤6 months) had compared 8 Gy times two fractions (total dose of 16 Gy in 1 week) with protracted split course regimen 5 Gy times three fractions, 4-day rest, and then 3 Gy times five fractions, (total dose of 30 Gy in 2 weeks) and showed equivalent pain relief rate of 56 versus 59% and ambulation rate of 68 versus 71%, respectively, at 1-month post RT.[7] In their second randomized study, authors compared 8 Gy times two fractions versus 8 Gy SF in patients with limited life expectancy and showed equivalent pain relief rate of 53 versus 52% and ambulation rate of 69 versus 62%, respectively.[8] They established that 8 Gy SF is noninferior to 16 Gy in two fractions and 30 Gy split course. Our results showed higher response rates of both pain (94%) and ambulation (85%) at 1-month post RT and possible explanation could be different pain response criteria, small sample size, and nonrandomized comparison of our study. We used international consensus criteria published by Chow et al in 2002. Rades et al have compared short course (20 Gy in five fractions daily) with long course (30 Gy in 10 fractions daily) in patients with poor or intermediate survival based on their prognostic scoring system.[3] They reported overall response rates of motor function at 1 month of 87.2 versus 89.6%, respectively ($p = 0.73$).[9] Their results corroborated with our findings of 84.3%. Ambulation without aid in 20 Gy × 5 arm was seen in 44.9% at 1 month compared with our study finding of 37.5% in patients treated with 20 Gy × 5 ($n = 22$). We understand that our results cannot be directly compared with the randomized study findings and suggest caution while interpreting our findings.

Recently published another randomized study compared 20 Gy in five fractions daily with SF of 8 Gy in patients with life expectancy of ≥8 weeks with primary end point of ambulatory status of 1 or 2 at 8 weeks post RT. The results demonstrated no significant difference between the two regimens 72.7 and 69.3%, respectively.[12] They also reported AS of 1 or 2 at 1 month of 67.6 and 66.8%, respectively, compared with our study findings of 68.75% (n = 22) and 71% (n = 16), respectively. A meta-analysis published in 2019 also concluded that there was no difference between short course and long course for motor response, bladder function, and OS with limited prognosis.[15]

All the above randomized studies were done mainly in patients with solid tumors with limited survival using various fractionation schedules and different end points. All RT fractionation schedules demonstrated almost similar outcomes as far as pain and ambulation are concerned. But there are still different dose fractionation used despite using similar criteria for selecting dose fractionation in an international survey.[4] Our study selectively recruited MESCC patients of lung cancer only which has limited life expectancy, median OS of 4 months. However, with the rapidly changing treatment paradigms of metastatic lung cancer with survival extending to years in oncogene driver mutated patient populations,[16,17] long course RT schedules are needed. In our study, we had seven oncogene mutated patients with a median OS of 25.6 months with three alive at the time of analysis.

Long course RT schedules like 30 Gy in 10 fractions or 40 Gy in 20 fractions have been shown to reduce the local recurrence rate in patients with favorable prognoses or longer expected survival.[18,19] Patients receiving short course or SF treatment do not live long enough to experience recurrence. In this study, reirradiation for clinical or radiological worsening at the treated site was done in two patients (5%), with a median duration of 10.5 months from last RT. Both of them have received 20 Gy in five fractions. Favorable prognostic criteria like good PS, ambulatory status of 1 or 2, no visceral metastases at the time of RT, more time to develop motor deficits have been described to have better OS by Rades et al.[20] They created three risk groups (A, B, and C) based on the points given to each of the four prognostic criteria and showed significant difference in OS. In our study, we did not find any of these factors to be prognostic for OS except age ≤50 years. We could not find any survival difference in our patients after assigning them into these three risk groups as described by Rades et al (small cell excluded). The possible explanation is very less numbers in each group to have a meaningful difference.

The median OS of 4 months in our study corroborated with the median OS of retrospective study of Rades et al and Silva et al in NSCLC.[20,21] The OS at 6 and 12 months was 50 and 37.5%, respectively. We found a nonsignificant difference in survival in patients treated with SF versus multifraction (median OS of 2.2 vs. 7.1 months, p = 0.39). This explains that the treating RO decided the dose fractionation considering patient life expectancy in mind. Better OS at 1 year in our study could be explained by the fact that majority presented with MESCC rather than metachronous presentation and all have received subsequent systemic therapy including targeted therapy. In our study 7/36 (19%) of the NSCLC patients were EGFR mutation positive which are expected to have better outcomes.

Our study also had some limitations. First, we did not restrict fractionation schedules for a formal comparison between the two most common regimens, SF (8 Gy) and multifraction (20 Gy in five fractions). Second, we did not document the patient-reported outcomes using EORTC quality of life questionnaires. Third, our sample size of only 40 patients did not allow us to make any formal conclusions. However, our study demonstrates the real-world treatment patterns for MESCC in lung cancer from a tertiary cancer center in a third world setting.

In conclusion, our study demonstrates equivalent pain control and ambulation rates as reported in the literature. However, further research is warranted in MESCC of NSCLC regarding optimal dose fractionation considering its rapidly evolving management and improving survival outcomes. With this background, we initiated a randomized controlled trial comparing 16 Gy in two fractions 1 week apart to 20 Gy in five fractions once daily in MESCC from NSCLC.

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Conflict of Interest

None declared.

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