

Response to reviewers: We thank the reviewers for their comments. The manuscript has benefited immensely from their comments

Response to reviewer 1

Comment: The research article is well written and informative; I think that this article is suitable for publication on this journal.

Response: Thank you very much.

Response to reviewer 2

Comment: This review is well-written.

Response: Thank you very much.

Response to the reviewer 3

Comment: One of the very rare tumours seen in clinical practice, may not fascinate a usual reader. The total number of cases very small.

Response: We agree with the reviewer that extrapulmonary small cell lung cancer is an extremely rare entity. Infact, in our more than two decade of experience with lung cancer, we have only seen three patients. However, this is an important condition as if identified then the treatment can result in good response and clinical outcomes, in contrast to SCLC. This is likely to benefit in the patient care and management. We have now added this point in the manuscript. (Page 12, lines 228-232)

Comment: Is there a rationale behind classifying the localized vs. extensive disease or it is extrapolated from small cell carcinoma

Response: The localized form of LNEPSCC can be treated surgically with a curative intent and had a trend towards better outcomes (In patients with limited disease the median [IQR] overall and progression free survival was not significantly different from those with extensive disease LNEPSCC at presentation (22 [15-42] and 28.5 [11.3-52.5] months versus 13 [4-38] and 7 [3.5-21] months respectively). We have added this information in the manuscript. (Page 13, lines 242-253)

Comment: The chemotherapy was given in 6 patients and radiotherapy in 4 patients, while CR is mentioned in 12 cases

Response: The complete response was seen in two patients who underwent surgical resection. This information has been provided in Table 1.

Comment: What was the reason in selecting Irinotican + Cisplatin rather than Cisplatin + Etoposide

Response: Although, Cisplatin and Etoposide is now the current standard chemotherapy regimen, at our centre a combination of irinotecan and cisplatin is preferred. This is because this combination is cost effective and is better tolerated by our patients as the patients. This has now been added as a limitation in the manuscript. (Page 15, lines 286-290)

Comment: In the case 2, if RT was refused why surgery was not offered?

Response: Case 2 by definition was extensive disease and the surgical cure is not the option for extensive disease LNEPSCC

Comment: Why PET scan was done in one case only?

Response: The facility of PET scan was not available at our center previously; however after its availability it was done in one patient with suspected LNEPSCC. Infact, before diagnosing a patient with LNEPSCC, PET scan should be done routinely.

Comment: PET may be useful in multiple ways, and should be done in each and every case.

Response: We agree with the reviewer that PET scan should be done in all the patients. We have now included this in the manuscript. (Page 14, lines 263-273)

Comment: The cases which progressed, was it local or systematic?

Response: Case 1 had locoregional progression whereas, case 2 had both loco-regional and systemic progression (central nervous system). In case 3 the disease progressed despite treatment and the patient died after four weeks. This has now been added in the manuscript. (page 7, lines 134-138 & page 8, lines 154-159). In the systematic review of cases, this information has now been provided in table 1 about the cases where this information was available.

Comment: How a primary SCC was excluded?

Response: The CT scan of thorax, abdomen, and bone scan did not reveal a primary lung SCC in the three illustrative cases and all the cases that were included in the systematic review. Even at follow-up and repeat CT thorax did not reveal a primary lung. However, a PET CT should be done to rule out SCLC. This has been added in the manuscript. (Page 10, lines 195-197) We now provide an algorithm for the diagnostic evaluation of patients with suspected LNEPSCC (Figure 7)

Comment: Was RT given prophylactic to cases in CR, for intracranial relapse?

Response: Prophylactic cranial RT was given to one patients who achieved CR. This information has been provided in table 1. In the three index cases cranial irradiation was given in case 2, who presented with CNS extension. In case 1, however it was not given.