World Journal of Clinical Oncology

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DOI: 10.5306/wjco.v7.i3.308

World J Clin Oncol 2016 June 10; 7(3): 308-320
ISSN 2218-4333 (online)

Extrapulmonary small cell carcinoma of lymph node: Pooled analysis of all reported cases

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Conflict-of-interest statement: None.

Data sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author at navneetchd@yahoo.com.

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Received: February 1, 2016
Peer-review started: February 2, 2016
First decision: March 21, 2016
Revised: March 28, 2016
Accepted: April 14, 2016
Article in press: April 18, 2016
Published online: June 10, 2016

Abstract

AIM: To study clinical outcomes and management of lymph nodes extrapulmonary small cell carcinoma (LNEPSCC).

METHODS: Herein, we perform a systematic search of published literature in the PubMed and EMBASE databases for studies describing LNEPSCC. For uniformity of reporting, LNEPSCC was staged as limited if it involved either single lymph node station or if surgery with curative intent had been undertaken. The disease was staged extensive if it involved two or more lymph node regions.

RESULTS: The systematic literature review yielded eight descriptions (n = 14) involving cervical, submandibular and inguinal lymph nodes. Eleven (64.7%) patients had limited disease (LD) and six (35.3%) had extensive disease (ED) at presentation. Chemotherapy (n = 6, 35.3%) or surgery (n = 4, 23.5%) were the most common form of treatment given to these patients. Complete response was achieved in 12 (70.6%) of the patients. Median (interquartile range) progression free survival and overall survival was 15 (7-42) mo and 22 (12.75-42) mo respectively. Of the three illustrative cases, two patients each had ED at presentation and achieved complete remission with platinum based combination chemotherapy.

CONCLUSION: LNEPSCC is a rare disease with less than 15 reported cases in world literature. Surgical resection with curative intent is feasible in those with LD while platinum based combination chemoradiation is associated with favorable outcomes in patients with ED. Prognosis of LNEPSCC is better than that of small cell lung cancer in general.

Key words: Extrapulmonary; Small cell; Carcinoma; Lymph node; Small cell lung cancer

Core tip: Extrapulmonary small cell cancer confined to lymph nodes (LNEPSCC) is extremely rare. A systematic literature review yielded 3 index and 14 previous case descriptions. Chemotherapy or surgery was most common treatments given with complete response achieved in 70% of the cases. Surgical resection with curative intent is feasible in those with limited disease. Prognosis of LNEPSCC is better than that of small cell lung cancer in general.

Sehgal IS, Kaur H, Dhooria S, Bal A, Gupta N, Behera D, Singh N. Extrapulmonary small cell carcinoma of lymph node: Pooled analysis of all reported cases. *World J Clin Oncol* 2016; 7(3): 308-320 Available from: URL: http://www.wjgnet.com/2218-4333/full/v7/i3/308.htm DOI: http://dx.doi.org/10.5306/wjco.v7.i3.308

INTRODUCTION

Extrapulmonary small cell carcinoma (EPSCC) is a rare disorder that is characterized by histological evidence of small cell carcinoma (SCC) from body organs other than the lungs[1]. First described in 1930[2], much needs to be determined about natural history and clinical behaviour of EPSCC. EPSCC is known to involve gastrointestinal tract (esophagus, stomach, liver, bile ducts, intestines and pancreas)[3-5], genitourinary tract (kidney, ureter, pelvis, bladder)[6-10], head and neck region (tonsils, larynx, nasopharynx, and paranasal sinuses)[11-14], bones[15] and lymph nodes (locoregional or distant)[16-23]. Although, EPSCC has histological similarity with small cell lung cancer, it has a different biological behaviour[1,24,25]. Also, the biological behaviour varies with the site of origin and the extent of the cancer. The disease limited to the site of origin and female genital tract is associated with a better survival[26,27]. Amongst the various types of EPSCC, patients with EPSCC of the lymph nodes have an even better overall survival and is considered to be a separate subgroup amongst patients with EPSCC[28]. Due to the paucity of evidence not much is known regarding the optimal schema for staging and classification of lymph node EPSCC (LNEPSCC). Further, the best treatment modality and the diagnostic approach remains to be determined. Herein, we describe three cases of LNEPSCC involving the cervical lymph nodes. We also perform a systematic review of the literature describing LNEPSCC.

MATERIALS AND METHODS

Search strategy

We searched the PubMed and EMBASE databases for articles published until August 15, 2015 using the free text terms: ("extra pulmonary small cell cancer" or "extra pulmonary small cell carcinoma" or "extra pulmonary small cell malignancy" or "extra pulmonary small cell tumor" or "extra thoracic small cell cancer" or "extra thoracic small cell carcinoma" or "extra thoracic small cell tumor" or "extra thoracic small cell malignancy"). We reviewed the reference list of all the included articles and previous review articles.

Inclusion criteria

We included full-text, peer-reviewed, cross-sectional studies, cohort studies and case-reports that described SCC of the lymph node (LN). We excluded the following studies: (1) abstracts, comments, editorials, and reviews; (2) studies published in non-English language; (3) studies done in pediatric age group; and (4) animal studies. We also excluded the studies describing LNSCC involving the mediastinal LNs and studies or case reports that did not provide details about the site of LN station involved or follow up.

Initial review of studies

The database thus created from the electronic searches was assimilated in the reference manager package Endnote (version X7.4; Thomson Reuters) and all duplicate citations were discarded. Two authors (Sehgal IS and Singh N) screened these citations by review of the title and abstract to identify the relevant studies. Any disagreement was resolved by discussion between the authors. The full text of each of these studies was obtained and reviewed in detail.

Study selection and data abstraction

Two authors (Sehgal IS and Singh N) independently assessed all the articles for inclusion in the systematic review and extracted the data; the data was entered into a standard data extraction form. The following items were extracted: (1) publication details (authors, year of publication); (2) study design (prospective, retrospective or case-report); (3) number of patients (including the demographic profile) and inclusion criteria; (4) details such as LN region involved, size of the LN, number of LNs involved; (5) stage of the disease; (6) details of the treatment given (surgical or chemotherapy); (7) response to treatment (complication of chemotherapy progression free survival, overall survival, site of relapse, second line treatment given); and (8) final outcome. Any differences in the study selection and data extraction process between the two authors were resolved by discussion. For uniformity of

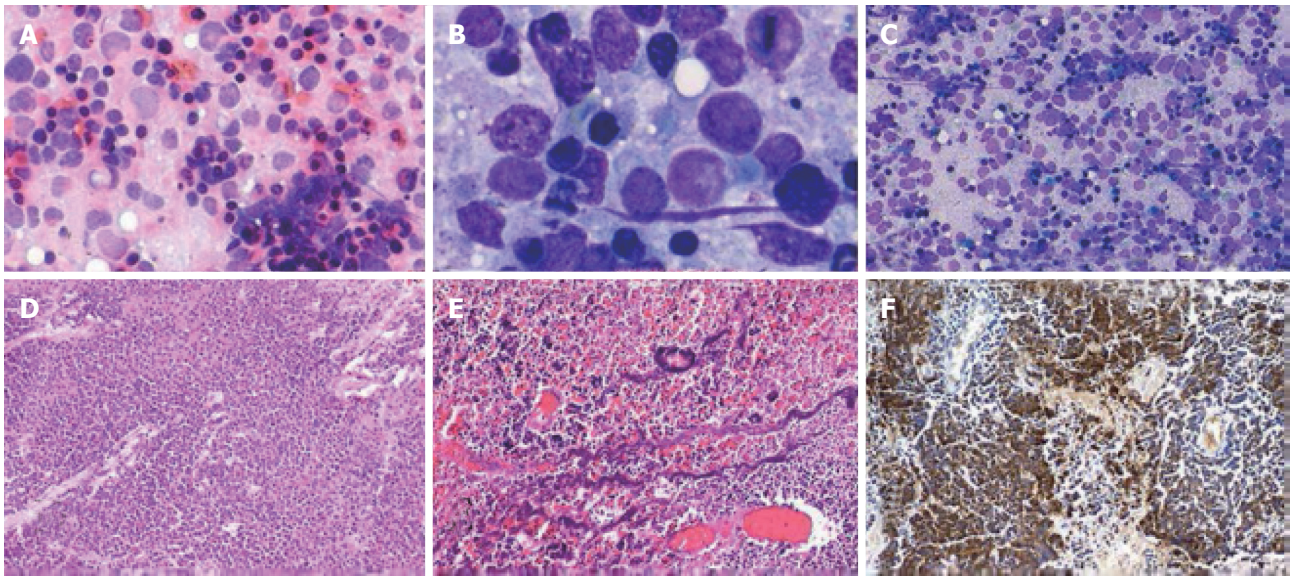

Figure 1 Histopathology and cytology of lymph node samples of illustrative case 1. A: Microphotograph showing predominantly dispersed population of tumor cells (MGG × 20 ×); B: Microphotograph showing tumor cells with very high nuclear cytoplasmic ratio, scant cytoplasm, round nuclei and fine granular chromatin (MGG × 100 ×); C: Microphotograph showing tumor cells with many apoptotic bodies (HE × 40 ×); D: Photomicrographs showing clusters of tumour cells with small hyperchromatic nuclei, scanty cytoplasm and apoptosis; E: Photomicrographs showing Azzopardi phenomena (basophilic nuclear chromatin spreading to wall of blood vessels); F: Photomicrographs showing synaptophysin immunostain showing intense cytoplasmic positivity.

reporting, LNEPSCC was staged as limited if it involved either single LN station or if surgical resection with curative intent had been undertaken. The disease was staged extensive if it involved two or more LN regions and/or other body organs.

Statistical analysis

Data from all individual patients (case reports or case series) were entered into a spreadsheet (Microsoft Excel 2016). Data was analyzed using the commercial statistical package SPSS (version 22, IBM Inc.) and is presented in a descriptive fashion as proportions, mean (95%CI) or median (IQR). χ^2 and Mann Whitney *U* tests were used to compare the categorical and numerical data, respectively.

RESULTS

Illustrative cases

Case 1: A 59-year-male, a known case of chronic obstructive pulmonary disease, presented with progressively increasing swelling in the left cervical region of 9-mo duration. He denied any history of fever or night sweats. On examination a 3 cm × 3 cm hard mass was identified in the left cervical region. FNAC and LN biopsy revealed clusters of tumour cells with hyperchromatic nuclei, nuclear molding and scanty cytoplasm (Figure 1). The pancytokeratin staining showed patchy dot like positivity and synaptophysin immunostain had an intense cytoplasmic positivity with an overall morphology suggestive of small cell carcinoma. Contrast enhanced computed tomography of the neck revealed a conglomerate mass of left cervical LN of size 2 cm × 1.2 cm abutting the left sternocleidomastoid muscle (Figure 2). Further evaluation with CECT thorax and abdomen did not show a primary anywhere and a diagnosis of limited disease (LD) LNEPSCC involving the left cervical LN was considered. Patient was unwilling for radical neck dissection and hence was started on platinum based doublet chemotherapy regimen. He was started on a combination of irinotecan (100 mg/m^2) and cisplatin (60 mg/m^2) each on D_1 of three weekly cycle for six cycles. After third cycle of chemotherapy patient developed grade Ⅱ hematological toxicity. A repeat CT of the neck revealed complete resolution of the LN mass. He achieved complete remission and was kept on follow up. Nine months after chemotherapy he again had a locoregional relapse of his disease and presented with a LN swelling of 5 cm × 4 cm. He was reinitiated on the same chemotherapy regimen (sensitive disease) to which he had responded and is currently doing well on follow up with no evidence of metastasis elsewhere in the body.

Case 2: A 65-year-old female with no previous comorbid illness presented with a progressively increasing mass over the right side of the neck. She also complained of loss of weight and appetite. She denied any history of cough, hemoptysis, hoarseness of voice, and fever. On examination there was a 6.8 cm × 4.2 cm hard mass in the right cervical and submandibular region that was fixed to the underlying structures. FNAC and a subsequent biopsy from the LN mass was suggestive of SCC morphology (Figure 3). Further evaluation with CECT thorax, paranasal sinuses, and abdomen did not reveal any primary in the lung, sinuses, or the abdomen. CECT of the neck revealed a right LN

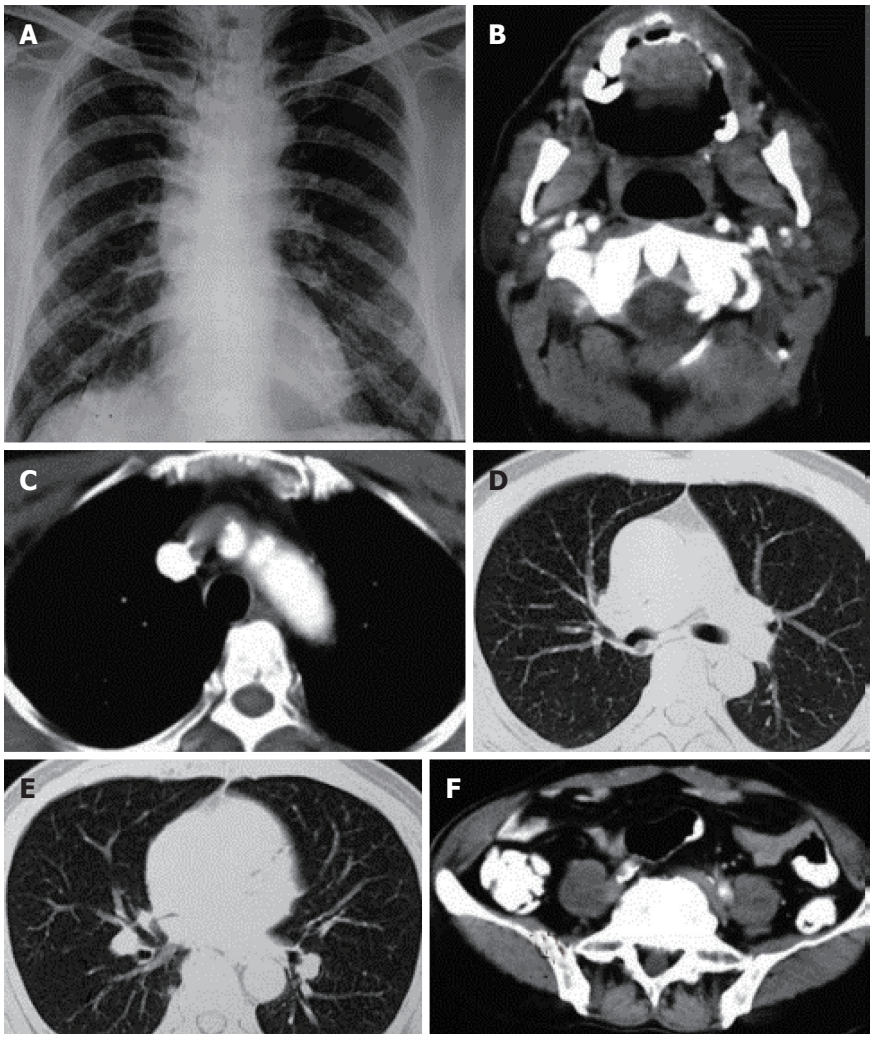

Figure 2 Thoracic imaging at baseline and after treatment of illustrative case 1. A: Chest radiograph revealing hyperinflated lung fields with no evidence of any parenchymal abnormality; B: Contrast enhanced computed tomography (CECT) of the neck revealing enlarged right sided cervical group of lymph nodes; C: Mediastinal window of CECT of the thorax with no evidence of mediastinal lymph node enlargement; D and E: Lung window of CECT thorax with no evidence of primary in the lung; F: CECT of the abdomen with no evidence of any abnormality in the abdomen.

mass extending from the submandibular region to the supra sternal region (Figure 4). Patient was diagnosed with extensive disease (ED) EPSCC of lymph node (submandibular and cervical) and was initiated on platinum based combination chemotherapy regimen [intravenous irinotecan (65 mg/m^2) and intravenous cisplatin (30 mg/m^2) each on D_1 and D_8 of three weekly cycle for six cycles]. The patient developed grade Ⅱ constipation, and hematological complication (anaemia and leukopenia) that responded to conservative treatment with hematinics and stool softening agent. A partial response was achieved with the chemotherapy. Patient was advised radiotherapy but was unwilling for any further treatment. Three months after the last cycle of chemotherapy she presented with an increase in the size of submandibular lymph node mass and was restarted on same regimen (sensitive disease) to which she had initially responded. The submandibular mass reduced in size clinically. After third cycle of chemotherapy she presented in the emergency department with generalized tonic-clonic seizures and altered sensorium. CECT head revealed bony metastasis to the skull bone invading the underlying brain parenchyma. She was given the option of cranial irradiation but she denied the same and succumbed to her illness 13 mo after her initial presentation.

Case 3: A 38-year-old previously healthy male presented with history of gradually increasing swelling in the neck region and loss of weight of nine-month duration. He also complained of fever of three-month duration. He denied any history of cough, hemoptysis, night sweats or hoarseness of voice. On physical examination he had bilateral enlarged cervical LNs (3 cm × 3 cm; 3 cm × 2 cm) that were firm to feel and were freely mobile. Fine-needle cytological examination was performed and he was diagnosed as non-Hodgkin's lymphoma and was referred to our center for further management. At presentation to our center (six months after initial presentation), he had jaundice and the LN size had increased (5 cm × 4 cm; 4 cm × 4 cm). A repeat FNAC was performed from the

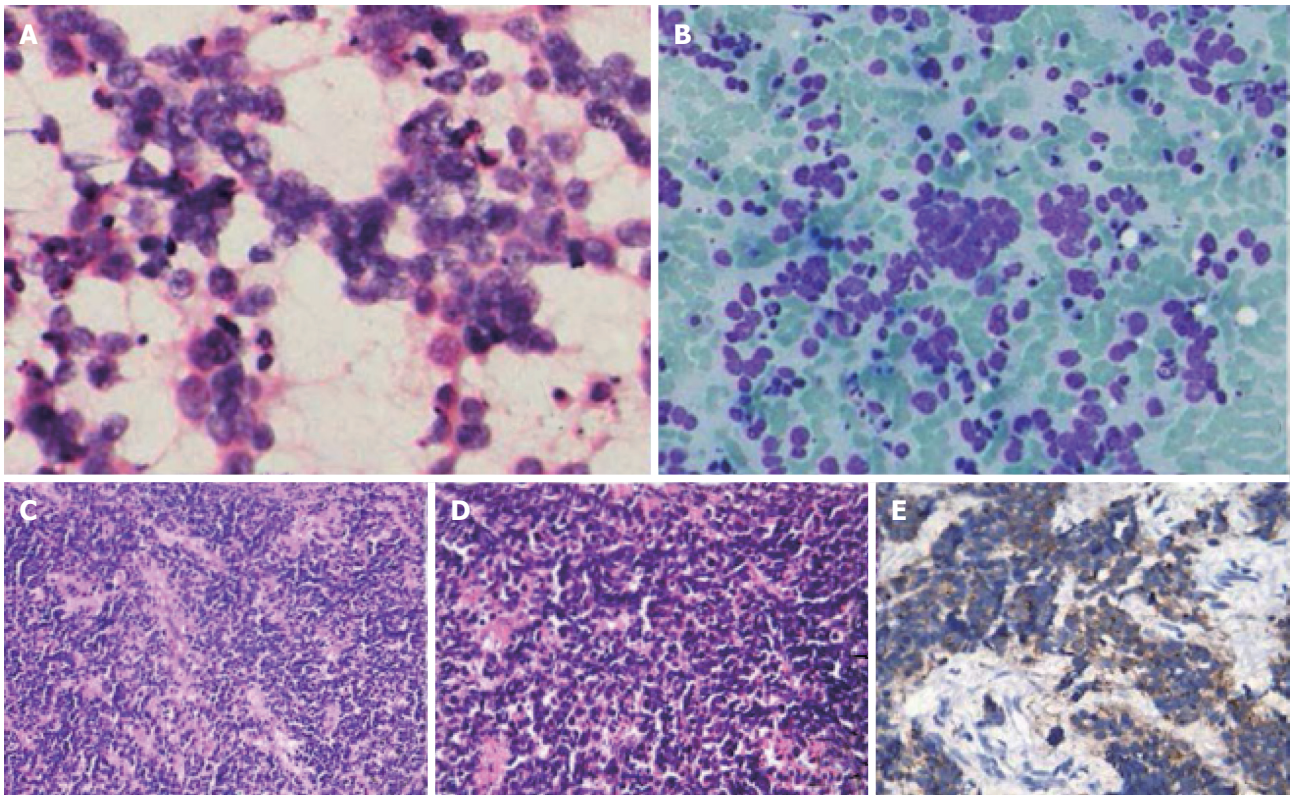

Figure 3 Histopathology and cytology of lymph node samples of illustrative case 2. A: Microphotograph showing dispersed population of tumor cells along with few loose clusters. The tumor cells with high nuclear cytoplasmic ratio and showing nuclear moulding (MGG × 20 ×); B: Microphotograph showing small tumor cells with high N:C ratio, salt and pepper type chromatin and inconspicuous nucleoli (HE × 40 ×); C: Photomicrographs showing tumour with extensive crushing artefact; D: Tumour cells having hyperchromatic nuclei, scanty cytoplasm and apoptosis; E: Synaptophysin immunostain showing cytoplasmic positivity.

right cervical LN that revealed small sized tumor cells that were positive for cytokeratin, and synaptophysin and negative for CD-3, CD-20 suggestive of SCC (Figure 5). A whole body 18F-fluorodeoxyglucose positron emission tomography (FDG-PET CT) was performed that revealed FDG avid LNs in bilateral cervical region with diffuse FDG uptake over background uptake in liver and entire skeleton. A diagnosis of ED LNEPSCC (primary in cervical LN with metastasis to liver and skeletal system) was made. The patient was initiated on palliative platinum based chemotherapy [irinotecan (65 mg/m^2) and cisplatin (30 mg/m^2) on D_1 and D_8 of 3 weekly cycle]. He developed grade Ⅳ hematological toxicity (neutropenia and anemia) and deranged liver function test (more than four times the baseline) due to which further chemotherapy was deferred. He succumbed to his illness four week after his presentation at our centre due to disease progression.

Systematic review

Our initial search of the PubMed and EMBASE databases yielded 1189 citations of which 954 were excluded after initial review. Eight studies (n = 14) were included in the current analysis (Figure 6)[16-23]. Studies that did not provide separate information for patients with LNEPSCC[29-41], and the treatment given or follow up were not included in the current review[42-50]. A total of 17 patients including the three index cases (mean ± SD, 59.5 ± 10.8 years; 81.8% males) with LNEPSCC were included in the current analysis (Table 1). There was no difference in the age and gender distribution based on the stage of the disease at presentation (61 ± 10.3 years in LD *vs* 57.6 ± 12.3 years in ED; P = 0.931). Cervical group (9, 52.9%) of LN region followed by submandibular LNs (4, 23.5%) was the most common site of primary disease. Two patients had inguinal LN enlargement while in two patients both submandibular and cervical LNs were involved. Eleven (64.7%) patients had LD as the disease involved only single LN region whereas 6 (35.3%) had ED at presentation. One patient had evidence of involvement of liver and skeletal system, and in two patients' central nervous system was involved at presentation, while three patients were labelled ED as they involved two LN regions (bilateral cervical LN; submandibular and cervical LNs). To rule out primary at other sites, chest radiograph, flexible bronchoscopy, CECT thorax and abdomen was performed in all patients. Whole body PET-CT was done in only one patient (index case 2). Chemotherapy (n = 6, 35.3%) or surgery (n = 4, 23.5%) were the most common form of treatment given to the patients. A combination of chemotherapy with radiation (n = 2, 11.8%) and surgery with radiation (n = 2, 11.8%) were the other forms of treatment. Five patients received radiation (one only radiotherapy, two each combined radiotherapy and chemotherapy, and combined

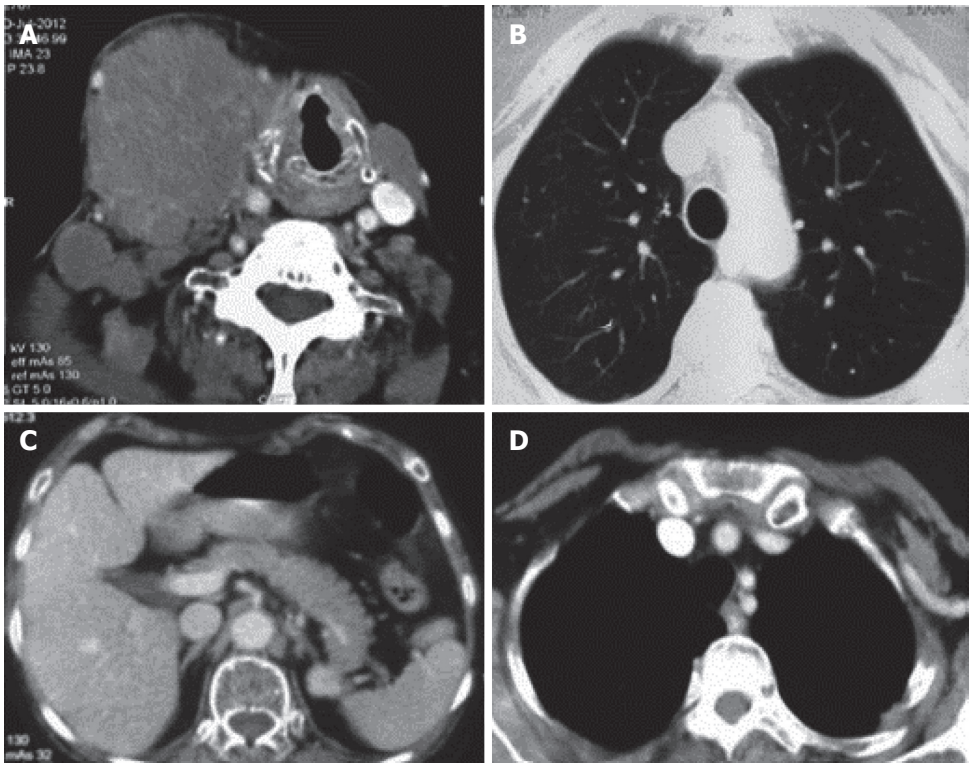

Figure 4 Thoracic imaging at baseline and after treatment of case 2. A: Contrast enhanced computed tomography of the neck revealing a conglomerate lymph node mass of size 7 cm × 4 cm involving the right submandibular region. The mass is pushing the larynx towards the left side; B: Contrast enhanced computed tomography of the thorax (lung window) with no evidence of primary in the lung; C: Contrast enhanced computed tomography of the abdomen with normal abdominal organs and no evidence of any primary in the abdomen; D: Mediastinal window of CECT thorax revealing no enlarged lymph node stations in the mediastinum. CECT: Contrast enhanced computed tomography.

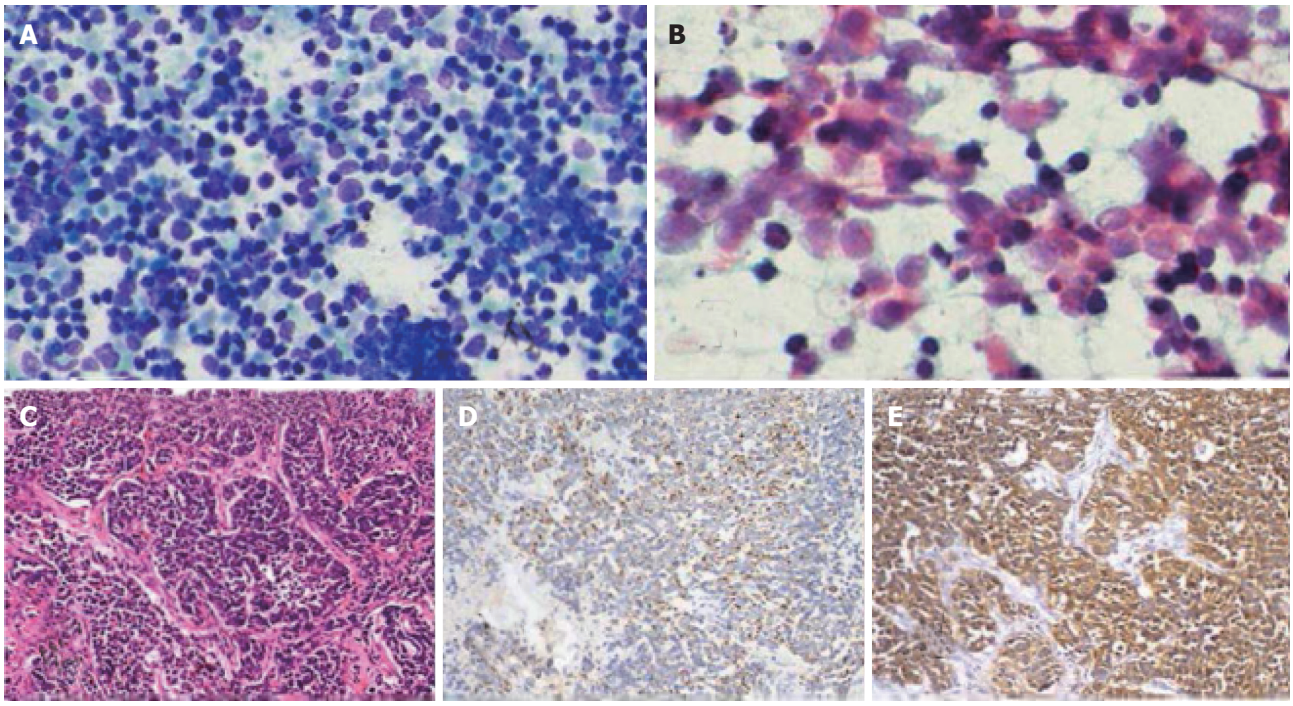

Figure 5 Histopathology and cytology of lymph node samples of case 3. A: Microphotograph showing dispersed population of small sized tumor cells with high nuclear cytoplasmic ratio along with many degenerated cells (MGG × 20 ×); B: Microphotograph showing nuclear threading and crushing along with tumor cells with round nuclei, high N:C ratio, salt and pepper type chromatin and inconspicuous nucleoli (Pap × 40 ×); C: Photomicrographs showing clusters of tumour cells with hyperchromatic nuclei, nuclear molding and scanty cytoplasm; D: Pancytokeratin staining showing patchy dot like positivity; E: Synaptophysin immunostain showing intense cytoplasmic positivity.

Table 1 Details of studies included in the review

Ref.	No. of patients	Gender	Age	Stage	Lymph node area involved	Investigations performed to rule out primary elsewhere	Treatment regimen used	No. of cycles received	Response	Complication of treatment	PFS, in months	Overall survival, in months	Site of relapse	Final outcome
Levenson *et al*[23]	1	Male	49	LD	Cervical	CXR, FB, radionuclide scan of liver, bone, spleen and brain	CMC-VAP + local RT	NA	CR	NA	15+	15+	None	Alive with disease
Kasimis *et al*[22]	2	Male	60	ED	Right submandibular	CXR, panendoscopy of larynx, pharynx, bronchial tree and esophagus	Surgery (radical neck dissection) + RT (5860 rads); cyclophosphamide and doxorubicin + cranial irradiation	NA	SD	None	24	36	Left cervical LN, left scapular region, left parotid gland, left submandibular LN, right tonsil, right testis	Died of disease
		Male	70	ED	Right submandibular and posterior cervical	CXR, sputum cytology, bone and liver scan, panendoscopy of larynx, pharynx, bronchial tree and esophagus	None (patient refused treatment)	-	SD	None	18+	40+	Locoregional enlargement of submandibular LN at 18 mo	Alive with disease
Remick *et al*[21]	1	Male	52	LD	Left cervical LN	CXR, CECT thorax and abdomen, bone scan	RT (46 Gray)	NA	CR	None	NA	84+	None	Alive with disease
Hainsworth *et al*[20]	2	Female	77	LD	Inguinal	CXR, CECT thorax and abdomen	Surgery	-	CR	None	12+	12+	None	Alive with disease
		Male	61	LD	Cervical	CXR, CECT thorax and abdomen, bone scan	CAV + RT	NA	CR	NA	100+	100+	None	Alive with disease
Van Der Gaast *et al*[19]	2	NA	55 (26-72)	LD	Cervical LN	CXR, CECT thorax and abdomen, bone scan	CDE (*iv* cyclophosphamide 1 g/sq.m on day 1, *iv* doxorubicin 45 mg/sq.m on day 1 and *iv* etoposide 100 mg/sq.m on days 1, 3 and 5)	Five	CR	Hematological (grade 3-4 leukopenia, neutropenia, thrombocytopenia), nausea and vomiting, alopecia	NA	22+	Locoregional	Alive with disease
		NA	55 (26-72)	LD	Cervical LN	CXR, CECT thorax and abdomen, bone scan	CDE (*iv* cyclophosphamide 1 g/sq.m on day 1, *iv* doxorubicin 45 mg/sq.m on day 1 and *iv* etoposide 100 mg/sq.m on days 1, 3 and 5) + RT (6000 cGy)	Five	CR	Hematological (grade 3-4 leukopenia, neutropenia, thrombocytopenia), nausea and vomiting, alopecia	12+	12+	None	Alive with disease
Galanis *et al*[18]	4	NA	NA	LD	Submandibular LN	CXR, CECT thorax and abdomen, bone scan	Surgery	Nil	CR	None	42+	42+	None	Alive at with disease
		NA	NA	LD	Submandibular LN	CXR, CECT thorax and abdomen, bone scan	Surgery	Nil	CR	None	42+	42+	None	Alive with disease

		NA	NA	LD	Inguinal	CXR, CECT thorax and abdomen, bone scan	Surgery	Nil	CR	None	42+	42+	None	Alive with disease
		NA	NA	ED	Submandibular	CXR, CECT thorax and abdomen, bone scan	NA	NA	NA	None	NA	42+	None	Alive with disease
Orhan *et al*[17]	1	Male	55	ED	Right cervical LN and multiple cranial metastasis	CXR, CT (thorax and abdomen), FB	Etoposide (100 mg/sq.m on days 1, 3, 5) and cisplatin (80 mg/sq.m on day 1)	Six	CR	None	7	7+	None	Alive with disease
Ochsenreither *et al*[16]	1	Male	68	LD	Cervical LN	CECT thorax and FB	Surgery and RT	-	CR	None	5	22	NA	Died of disease
Current report	3	Male	59	LD	Unilateral LN (left cervical LN)	CXR, CECT, neck, thorax and abdomen, FB	Irinotecan (100 mg/sq.m) and cisplatin (60 mg/sq.m) each on D1 of 3 weekly cycle	6 (3 weekly)	CR	None	9	16+	Locoregional	Alive with disease
		Male	38	ED	Bilateral cervical LNs	CXR, CECT thorax and abdomen and whole body PET CT	Irinotecan (65 mg/sq.m) and cisplatin (30 mg/sq.m) each on D1 and D8 of 3 weekly cycle	1 (C1D1)	NR	Grade IV hematological (pancytopenia), deranged liver enzymes	Not assessable	1	Systemic	Died of disease
		Female	65	ED	Right sided submandibular and cervical LNs	CXR, CECT neck, thorax, abdomen and; CT head	Irinotecan (65 mg/sq.m) and cisplatin (30 mg/sq.m) each on D1 and D8 of 3 weekly cycle	4 (twice weekly; C1D1 and C1D8)	PR	Nausea and vomiting, constipation (grade II) and grade II hematological (anaemia and leucopenia)	7	13	Increase in cervical LN size and skull bone metastasis with invading the bone	Died of disease

CAV: Cyclophosphamide, doxorubicin and vincristine; CDE: Cyclophosphamide, doxorubicin, etoposide; CMC-VAP: Cytoxan, methotrexate, CCNU [1-(2-chlorethyl)-3-cyclohexyl-1-nitrosourea] alternating with vincristine, adriamycin, and procarbazine; CECT: Contrast enhanced computed tomography; CR: Complete response; CXR: Chest radiograph; FB: Flexible bronchoscopy; ED: Extensive disease; LD: Limited disease; LN: Lymph node; NA: Not available; PR: Partial response; RT: Radiotherapy; SD: Stable disease.

surgery and radiotherapy). All patients who had ED at presentation received platinum based chemotherapy except one who refused any form of treatment and was kept on follow up. A complete response (CR) was achieved in 12 (70.6%) of the patients whereas one had partial response, and in two patients the disease remained stable. Eleven patients with LD achieved CR whereas only one with ED had CR (P = 0.008). Median (IQR) PFS and overall survival (OS) was 15 (7-42) mo and 22 (12.25-42) mo respectively. In patients with LD the median (IQR) overall and PFS was not significantly different from those with ED LNEPSCC at presentation [22 (15-42) and 28.5 (11.3-52.5) mo *vs* 13 (4-38) and 7 (3.5-21) mo respectively; P value 0.145 and 0.129]. Overall 4 (23.5%) patient died while 13 (76.5%) subjects were labelled as alive with disease at the time of reporting of their individual publications. One patient with LD and three patients in ED died (P = 0.057). Adverse events due to chemotherapy were reported in 4 (23.5%) patients and included grade 2 hematological complications, alopecia, constipation, nausea and vomiting.

DISCUSSION

The results of the systematic review and the illustrative cases highlight that LNEPSCC is a distinct clinical entity. Patients with disease limited to only one LN region responded well to surgical management consisting of radical neck dissection or regional LN dissection. Patients with ED at presentation responded favorably to

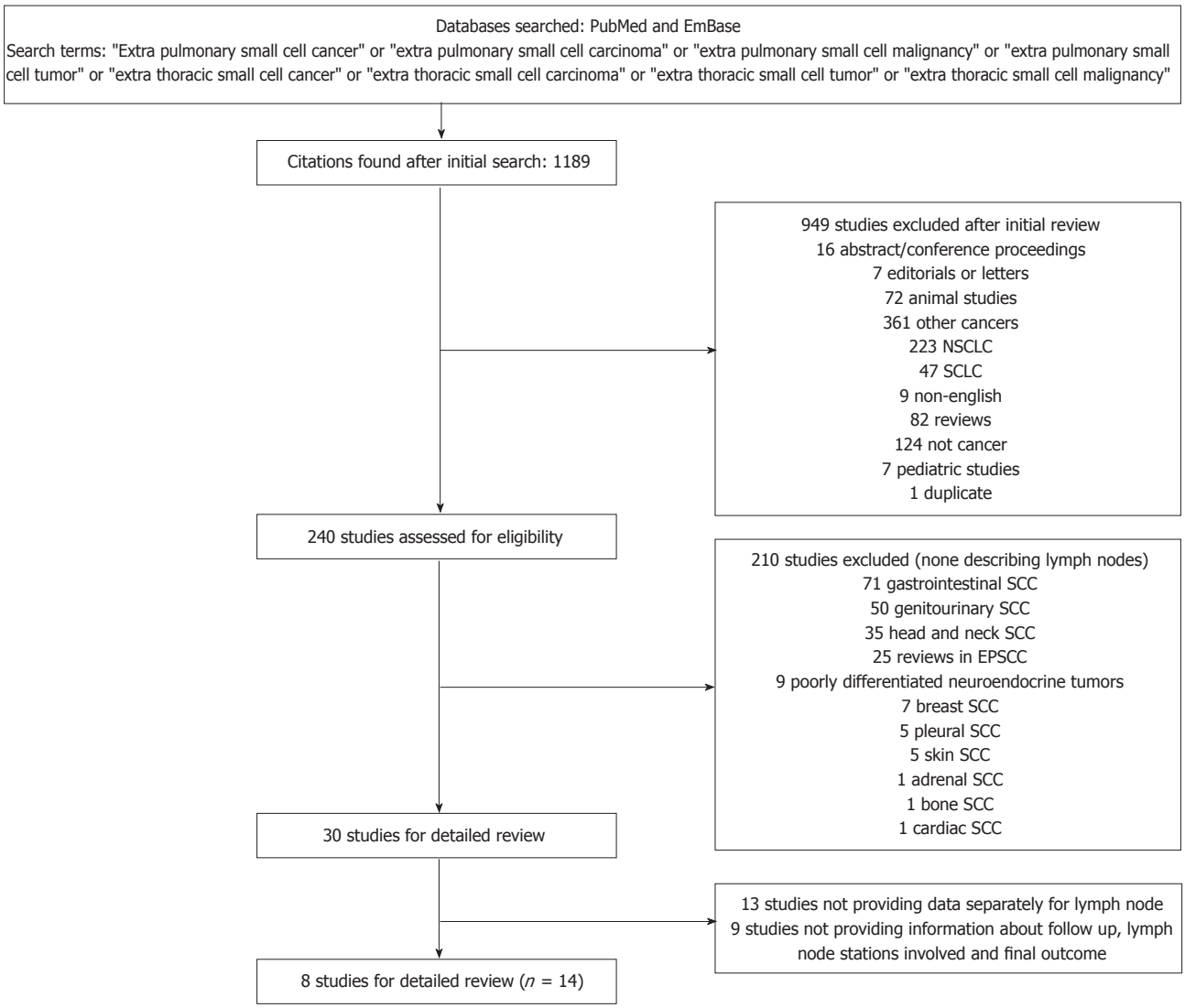

Figure 6 Study selection process for systematic review. NSCLC: Non small cell lung cancer; SCLC: Small cell lung cancer; SCC: Small cell cancer; EPSCC: Extrapulmonary small cell cancer.

chemotherapy with or without radiation.

Small cell carcinoma of the lung (SCLC) accounts for 18%-20% of all lung cancers and is invariably associated with a dismal prognosis[51,52]. Median overall survival is 9-10 mo despite treatment in extensive SCLC and 18-24 mo in case of LD SCLC[53,54]. Role of surgical resection in SCLC is limited with treatment being primarily combined chemoradiation[54]. However, SCC has also been described in various other parts of the body including the gastro-intestinal tract, male and female genital tract, musculoskeletal system and others[5,15,55-57]. Extrapulmonary SCLC, especially in the lymph nodes, 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.

The exact pathogenesis of LNEPSCC is controversial, although several hypotheses exist[28,58,59]. It is believed to arise from multipotent stem cells in the LN and hence a slow growing nature of the LNEPSCC. It can also be due to a primary elsewhere in the body with secondary metastasis to the LNs and spontaneous regression of the primary tumor. However, the fact that patients with LD LNEPSCC had a prolonged survival (median survival 22 mo) makes this theory unlikely. Further, LNEPSCC is cytogenetically different from SCLC as the loss of chromosome 3p, 10q and deletion of chromosome 13 are not seen in EPSCC[60]. It may also be plausible that EPSCC is derived from neuroendocrine amine precursors uptake and decarboxylation cells as neurosecretory granules are frequently seen in the tumor[60].

Apart from pathogenesis, the schema for the staging of LNEPSCC is also uncertain. In the systematic review we could only identify 14 patients with LNEPSCC suggesting it to be a rare disease. An attempt was made to stage LNEPSCC in the current analysis on the basis of ability to perform curative surgery and the number of LN regions involved, and involvement of other organs. If TMN staging process was to be followed, then the stage

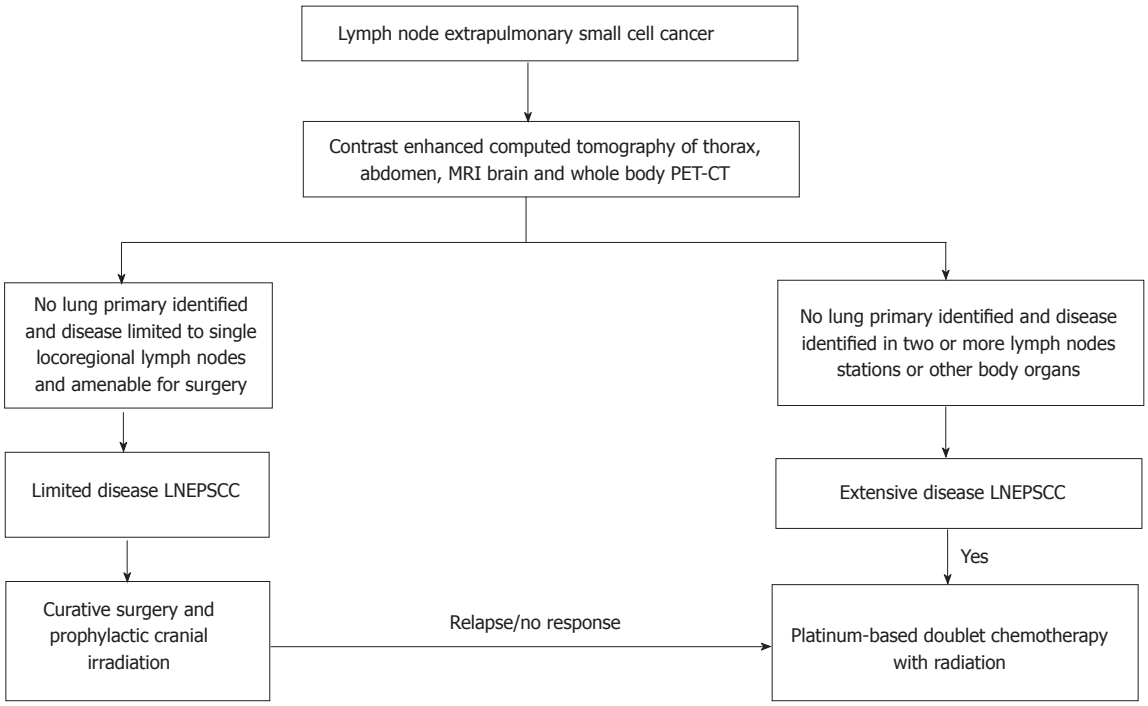

Figure 7 Algorithm for the diagnostic work-up and treatment of lymph node extrapulmonary small cell carcinoma. LNEPSCC: Lymph nodes extrapulmonary small cell carcinoma; PET: Positron emission tomography; CT: Computed tomography; MRI: Magnetic resonance imaging.

of all the LNPSCC would have been stage Ⅳ disease or ED that is associated with a poor prognosis and survival outcome[54]. However, this was in contrast to our index cases and the results of the systematic review, where patients with LD LNEPSCC had a longer survival. The PFS and OS in both the LD LNEPSCC and in ED LNEPSCC was higher than that of the SCLC. Thus the staging schema adopted in the current analysis seems appropriate. This has important clinical implications as contrary to LD SCLC where surgery has no role, surgery has a definite role in patients with LD LNEPSCC[18,20,22].

SCC limited to LNs usually develops slowly as highlighted by a prolonged stable disease despite no treatment[22]. However, at an unpredictable time there may be rapid dissemination of the disease and the tumor enters its aggressive phase with an outcome similar to progressive SCLC[20,22]. This was highlighted in one of the index cases that had a fulminant course after diagnosis. Hence, patients presenting with LD LNEPSCC should be treated early with curative surgery (regional LN dissection)[18]. Patients with ED LNEPSCC should also be treated aggressively and early in contrast to SCLC where despite treatment the results are dismal[54]. Treatment with combination chemotherapy, concurrent chemoradiation resulted disease stabilization in five of the six patients with ED LNEPSCC. However, due to the paucity of data and various chemotherapy regimen used with or without radiotherapy, the best treatment option for EDLNSCC remains uncertain. Thus, patients with ED LNEPSCC may be treated similar to patients with ED SCLC until further good quality evidence is available.

Finally, the role of FDG-PET CT (18F-fluorodeoxyglucose positron emission tomography) in evaluating the cases of LNEPSCC needs to be discussed. The studies included in the current systematic review do not clarify this issue. The authors in the various studies have used a combination of chest radiograph, CECT thorax and abdomen and bone scan along with blind mucosal biopsies to investigate the patients with LNEPSCC. This seems reasonable as most patients who were still alive in the studies did not demonstrate primary in the lung or at any other site. However, the advent of PET CT and its inclusion in the diagnostic algorithm will further clarify and enable a better staging process[61,62]. This was highlighted in one of the index cases where performance of PET CT upstaged the tumor to ED with FDG uptake in liver and the entire skeletal system. Hence, future studies should include PET-CT in the diagnostic evaluation of patients with presumed LNEPSCC.

Our systematic review has several limitations. Most of the studies included were either case reports or retrospective data and included only a small number of patients. Further, most studies did not have a complete follow-up data and hence the interpretation of overall survival may not be correct with most patients still alive with disease at the time of publication of studies. However, in rare diseases it is not possible to conduct randomized trials and generate good quality evidence. Also, most reports did not utilize PET-CT in the diagnostic evaluation of the cases. In current era, the authors believe that PET-CT may enable a better understanding and staging of disease and may also pick up small primaries in the lung and should be incorporated in the diagnostic algorithm (Figure 7). Although, Cisplatin and Etoposide is now the current standard chemotherapy regimen, at our center a

combination of irinotecan and cisplatin is preferred and was used in the three illustrative cases[52]. This is because this combination is cost effective and is better tolerated by our patients as the patients. The use of this combination might have resulted in unfavorable outcomes in the illustrative cases.

In conclusion, LNEPSCC is a rare disease and seems to be distinct from SCLC and other EPSCCs. LNEPSCC that remains confined to single group of LN region should be considered for surgical resection with curative intent combined with chemotherapy. Those patients who present late or with an ED should be offered treatment with a combination of concurrent chemoradiation. Prognosis of LNEPSCC seems to be better than that of SCLC in general emphasizing the need for recognition of this unusual entity.

COMMENTS

Background

Lymph node extrapulmonary small cell carcinoma (LNEPSCC) is a rare disorder that is characterized by histological evidence of small cell carcinoma in lymph nodes without a primary in the lungs.

Research frontiers

Contrary to small cell carcinoma of the lungs, LNEPSCC is associated with better overall survival. However, due to the rarity of this disease much needs to be ascertained regarding the staging schema and the appropriate management of patients affected with this entity.

Innovations and breakthroughs

The current study provides a pooled analysis of all the reported cases in literature and provides a schema for management of subjects with LNEPSCC. The study highlights that subjects who are affected with LNEPSCC have a better overall survival than those with extensive disease (ED) small cell lung carcinoma. For staging purpose, a primary in the lungs should be ruled out with the help of contrast enhanced computed tomography of thorax and a whole body 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) to detect the overall extent of the disease. LNEPSCC should be staged as limited if it involves either a single LN station or if surgical resection with curative intent can be undertaken. The disease is staged extensive if it involves two or more LN regions and/or other body organs. Subjects who have disease limited to only one LN region should be offered surgical management consisting of radical neck dissection or regional LN dissection with a curative intent. Subjects with ED at presentation respond favorably to chemotherapy with or without radiation.

Applications

This review suggests that LNEPSCC is a rare disease and seems to be distinct from small cell lung cancer (SCLC) and other EPSCCs. The diagnostic algorithm for future studies should include whole body PET-CT. LNEPSCC that remains confined to single group of LN region should be considered for surgical resection with curative intent combined with chemotherapy. Those patients who present late or with an ED should be offered treatment with a combination of concurrent chemoradiation.

Terminology

Prognosis of LNEPSCC seems to be better than that of SCLC in general emphasizing the need for recognition of this unusual entity.

Peer-review

This review is well-written.

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