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Gastroesophageal reflux disease and paraneoplastic neurological syndrome associated with long-term survival in limited stage small-cell lung cancer

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Abstract

Introduction: Patients with small-cell lung cancer (SCLC) have a very poor prognosis. However, a subset of SCLC achieves long-term survival. The objective of this study was to investigate factors and pattern of long-term survival in patients with limited-stage small cell lung cancer (LS-SCLC) who achieved a complete response (CR) after chemoradiotherapy.

Patient and Methods: This was a single-center retrospective study. The analysis of hazard ratio (HR) and 95% confidence interval (CI) was performed using Cox proportional hazards model. For pattern analysis, the date of recurrence was used as the endpoint. The nominal categorical variables were analyzed by the χ^2 test. Survival was estimated using the Kaplan–Meier model, and the results were reported as the median and interquartile range.

Results: We identified 162 patients, median age was 64.7 (56.2–70.2) years, and 94 (58%) were females. Eighty-one patients (50%) had recurrence during follow-up. Gastroesophageal reflux disease (GERD) (HR, 0.65; 95% CI, 0.45–0.93; $p = 0.016$) and neurological paraneoplastic syndrome (PNS) (HR, 0.46; 95% CI, 0.29–0.72; $p < 0.001$) were independent factors associated with improved overall survival (OS). Patients with GERD had prolonged recurrence free survival (RFS) compared to patients without GERD (median, 29.1 months vs. 13.9 months, $p < 0.001$), whereas patients with neurological PNS had a reduced recurrence rate compared to those patients without neurological PNS (No. [%], 8 [20.5] vs. 73 [59.3], $p < 0.001$).

Conclusions: Patients with LS-SCLC achieving a CR after chemoradiotherapy, GERD, and neurological PNS were associated with improved OS. GERD and neurological PNS were associated with longer RFS and lower recurrence rate, respectively.

KEYWORDS
cancer, chemoradiation, lung, paraneoplastic, prognosis

INTRODUCTION

Lung cancer is the leading cause of cancer related death worldwide. In 2020, there were an estimated 228 820 new cases of lung cancer in the United States (US).[1] The

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incidence of small-cell lung cancer (SCLC) has been declining over the last few decades, however, it still accounts for about 10%–15% of all the lung cancers.[2] This subtype of lung cancer has historically been classified as extensive-stage SCLC (ES-SCLC) and limited-stage (LS-SCLC). The median survival is ~15–30 months for LS-SCLC, and 8–13 months for ES-SCLC.[3] The standard of care treatment for patients with LS-SCLC consists of platinum and etoposide concurrently with chest radiation. This strategy offers a high complete response rate, improved survival, and the potential for a cure.[4]

Despite the dramatic response to treatment, SCLC survival is still dismal. Nevertheless, ~25% of LS-SCLC patients

TABLE 1 Baseline characteristics

Characteristics	Total ($n = 162$)	Characteristics	Total ($n = 162$)
Age, median (interquartile range), y	64.7 (56.2–70.2)	Family history of cancer	
Gender, No. (%)		Family history of lung cancer, No. (%)	
Male	68 (42.0)	No	139 (85.8)
Female	94 (58.0)	Yes	23 (14.2)
Race, No. (%)		Family history of other cancer, No. (%)	
Caucasian	131 (80.9)	No	105 (64.8)
Non-Caucasian	31 (19.1)	Yes	57 (35.2)
BMI, No. (%)			
Underweight	7 (4.3)	Personal history of diseases	
Normal	50 (30.9)	Personal history of other cancer, No. (%)	
Overweight	54 (33.3)	No	140 (86.4)
Obese	36 (22.2)	Yes	22 (13.6)
Unknown	15(9.3)	Respiratory comorbidity, No. (%)	
Smoke status, No. (%)		No respiratory comorbidity	87 (53.7)
Never smoker	1 (0.6)	COPD	52 (32.1)
Former smoker	58 (35.8)	Non-COPD respiratory comorbidity	23 (14.2)
Current smoker	103 (63.6)	Cardiovascular comorbidity, No. (%)	
Smoking classification, No. (%)		No cardiovascular comorbidity	86 (53.1)
Never/light	47 (29.0)	Heart disease	20 (12.3)
Heavy	62 (38.3)	Vascular disease	13 (8.0)
Super-heavy	53 (32.7)	Hypertension	43 (26.5)
T stage, No. (%)		GI comorbidity, No. (%)	
T1	58 (35.8)	No GI comorbidity	79 (48.8)
T2	78 (48.1)	GERD	42 (25.9)
T3	26 (16.0)	GERD with GI polyps	25 (15.4)
N stage, No. (%)		GI polyps	16 (9.9)
N0	36 (22.2)	Neurological PNS, No. (%)	
N1	25 (15.4)	No	123 (75.9)
N2	87 (53.7)	Yes	39 (24.1)
N3	14 (8.6)	Diabetes mellitus II, No. (%)	
Tumor location, No. (%)		No	144 (88.9)
Central	120 (74.1)	Yes	18 (11.1)
Peripheral	42 (25.9)		
Recurrence, No. (%)			
No	81 (50.0)		
Yes	81 (50.0)		
PCI, No. (%)			
No	105 (64.8)		
Yes	57 (35.2)		

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; GI, gastrointestinal; PCI, prophylactic cranial irradiation; PNS, paraneoplastic syndrome; SCLC, small-cell lung cancer.

treated with definitive chemoradiation can achieve long-term survival.[5] Knowledge of the factors that predict the clinical outcome of patients with SCLC is critical both for guiding treatment and for determining prognosis. The most reproducible prognostic factor is stage. Other less established prognostic indicators include age, performance status, gender, race, smoking status, and lactate dehydrogenase (LDH). Within this context, we sought to better understand the prognostic factors and patterns of long-term survival in patients with LS-SCLC that achieved a complete response (CR) after chemoradiation.

MATERIAL AND METHODS

Patients and protocols

We performed a retrospective analysis using the Mayo Clinic electronic medical records (EMR) to identify possible prognostic factors and pattern of long-term survival in patients with LS-SCLC treated with chemoradiation. All patients diagnosed with LS-SCLC and treated with definitive chemoradiation at Mayo Clinic in Minnesota between January of 1997 and December of 2016 were included in this study. LS-SCLC was defined as according to the 7th edition of the American Joint Committee on Cancer (AJCC) as stage I-III (T any, N any, M0) that can be safely treated with definitive radiation doses, excluding T3–4 because of multiple lung nodules or tumor/nodal volume too large to be encompassed in a tolerable radiation plan.[6] Patients provided written informed consent, which was approved by the Mayo Clinic Institutional Review Boards (IRB). For each patient, medical records were reviewed for eligibility and the following information was collected: demographic characteristics, cigarette smoking history, family history, comorbidities, TNM stage, tumor location, treatment modality, and disease recurrence. We did not include Eastern Cooperative Oncology Group (ECOG) performance status because ECOG performance status was not an independent survival predictor in our previous study.[7] LDH was only obtained in a small number of patients, so it was excluded from the analysis. The detailed information above was supplemented with additional information from structured subject interviews, follow-up questionnaires, or both. For patients who have received medical care outside of Mayo Clinic, copies of the relevant medical records were requested. Follow-up data were collected through comprehensive medical record abstraction and self-administered questionnaires, including current health information and treatment updates starting within 6 months after diagnosis and annually thereafter. Annual verification of patients' status was performed through the Mayo Clinic's EMR and registration database, death certificates, next-of-kin reports, obituary documents filed in the patients' medical records through the Mayo Clinic Tumor Registry and the Social Security Death Index website. Our manually abstracted data were used as a gold standard to train a natural language processing (NLP) tool for accurately retrieving medical records such as smoking status. While training the algorithms of the NLP tool, we discovered human errors (~1/1000) in our original data, for which we made the needed correction. Histologic specimens of the patients were all from biopsy; surgically treated patients were not included in this study. Biopsies were obtained by bronchoscopy, endobronchial ultrasound (EBUS), mediastinoscopy, and computed tomography (CT) guidance.

Body mass index (BMI) was categorized according to the World Health Organization classification into underweight (BMI, <18.5 kg/m^2), normal weight (BMI, 18.5–24.9 kg/m^2), overweight (BMI, 25–29.9 kg/m^2), and obese (BMI, ≥30.0 kg/m^2).[8] The patients were staged according to the seventh edition of the TNM staging system of the AJCC. CT was the preferred diagnostic approach for the identification of tumor location. Central SCLC was defined as a tumor originating in the bronchi or large bronchi proximal to the segmental bronchi or located near the hilum of the lung. Peripheral SCLC was defined as a tumor that occurred in the bronchi distal to the segmental bronchi. For the evaluation of treatment response, Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used. Response was divided into CR, partial response (PR), stable disease (SD), and progressive disease (PD). The diagnosis of recurrence was made with a combination of CT images and biopsy of the new suspected disease. Smoking status was based on the adult tobacco use information from the National Health Interview Survey (NHIS) into never smoker, an adult who had never smoked, or who had smoked <100 cigarettes in his or her lifetime; former smoker, an adult who had smoked at least 100 cigarettes in his or her lifetime, but who had quit smoking at the time of interview; current smoker, an adult who had smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes. Smokers were classified as: never, if they never smoked; light, if smoked less than 30 pack-years; heavy, if smoked 30–60 pack-years; and super-heavy, if smoked more than 60 pack-years.[9] The preliminary study found that specific gastrointestinal comorbidities may have a positive impact on survival. Then, two major gastrointestinal (GI) comorbidities were evaluated: gastroesophageal reflux disease (GERD) and GI polyps. The presence of a

TABLE 2 Paraneoplastic neurological syndromes

Type of neurologic PNS	N = 39
Lambert-Eaton (LEMS)	6 (15.3)
Autonomic neuropathy	2 (5.1)
Cerebellar degeneration/ataxia	5 (12.8)
Sensory neuropathy	11 (28.2)
Peripheral neuropathy	2 (5.1)
Chorea/dystonia	1 (2.5)
Myelopathy	2 (5.1)
Unknown	10 (25.6)

Abbreviations: LEMS, Lambert-Eaton myasthenic syndrome; PNS, paraneoplastic syndromes.

TABLE 3 Survival factors in univariate and multivariate Cox regression analysis

Variables[a]	Case	Events, no. (%)	Median overall survival, month (95% CI)	Univariate		Multivariate	
				HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, y	162	133 (82)	52.4 (41.8–66.9)	1.02 (1.00,1.04)	0.036	1.02 (0.99,1.04)	0.116
BMI[b]					0.185		
Underweight/obese	43	38 (88)	41.8 (31.0–52.7)	1.27 (0.81,1.97)			
Normal	50	44 (88)	57.2 (31.1–76.9)	–			
Overweight	54	41 (76)	65.8 (47.5–96.1)	0.84 (0.54,1.29)			
T stage					0.080		0.333
T1–T2	136	111 (82)	53.8 (44.8–75.2)	–		–	
T3	26	22 (85)	41.4 (26.3–61.7)	1.51 (0.95,2.41)		1.27 (0.79,2.05)	
N stage					0.388		0.434
N0–N2	148	123 (83)	53.6 (44.8–72.2)	–		–	
N3	14	10 (71)	31.5 (25.7–60.6)	1.33 (0.70,2.55)		1.32 (0.68,2.57)	
Tumor location					0.270		
Central	120	97 (81)	47.8 (36.6–65.8)	–			
Peripheral	42	36 (86)	63.6 (48.3–88.8)	0.80 (0.55,1.19)			
PCI					0.079		0.101
No	105	87 (83)	47.5 (36.0–60.1)	–		–	
Yes	57	46 (81)	75.2 (50.1–94.2)	0.72 (0.50,1.04)		0.72 (0.49,1.07)	
Smoke status					0.679		
Never/former smoker	59	49 (83)	61.7 (36.6–76.9)	1.08 (0.76,1.54)			
Current smoker	103	84 (82)	52.0 (41.3–75.0)	–			
Smoking classification					0.813		
Never/light	47	37 (79)	35.1 (25.7–76.9)	1.15 (0.75,1.76)			
Heavy	62	51 (82)	52.7 (41.0–90.1)	—			
Super-heavy	53	45 (85)	58.3 (46.8–82.4)	1.04 (0.70,1.56)			
Family history of lung cancer					0.094		0.076
No	139	113 (81)	53.8 (47.5–75.2)	–		–	
Yes	23	20 (87)	32.6 (24.0–60.1)	1.50 (0.93,2.43)		1.62 (0.97,2.65)	
Personal history of other cancer					0.007		0.058
No	140	112 (80)	53.8 (44.8–75.2)	–		–	
Yes	22	21 (95)	37.6 (23.3–60.1)	1.90 (1.08,3.06)		1.77 (0.98,2.94)	
Respiratory comorbidity					0.155		
Non-COPD	110	85 (77)	53.6 (41.8–79.2)	–			
COPD	52	48 (92)	50.5 (36.0–65.8)	1.30 (0.91,1.85)			
Cardiovascular comorbidity					0.117		
No cardiovascular disease	86	71 (83)	41.8 (35.1–61.7)	–			
Cardiovascular disease	76	62 (82)	48.5 (31.1–89.0)	0.83 (0.52,1.24)			
GI comorbidity					0.013		0.016
Non-GERD	95	82 (86)	41.4 (31.0–50.5)	–		–	
GERD	67	51 (76)	83.3 (64.7–103.2)	0.64 (0.45,0.91)		0.65 (0.45,0.93)	
Neurologic PNS					<0.001		<0.001
No	123	102 (83)	44.8 (36.0–52.0)	–		–	
Yes	39	31 (79)	96.1 (72.2–131.6)	0.45 (0.29,0.70)		0.46 (0.29,0.72)	
Diabetes mellitus II					0.869		
No	144	120 (83)	53.6 (41.5–72.2)	–			
Yes	18	13 (72)	48.3 (31.0–164.2)	1.03 (0.54,1.69)			

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; GI, gastrointestinal; HR: hazard ratio; PCI, prophylactic cranial irradiation; PNS, paraneoplastic syndrome.

[a]Gender, race, and family history of cancer were also evaluated; none was significant.

[b]Fifteen patients with missing BMI were not analyzed in Cox regression model.

neurological paraneoplastic syndrome (PNS) was also noted. We focused our analysis on a subset of PNS rather than the broader group of paraneoplastic disorders, which was supported by our previous finding that PNS was the only subgroup associated with exceptional survival among LS-SCLC patients. We excluded the patients with chemotherapy-induced peripheral neuropathy, brain metastasis, or comorbid conditions such as diabetes. This subgroup of patients was analyzed previously and was not included in the current study.[10] The diagnosis of GI comorbidities and PNS were made by Mayo Clinic physicians. Our study did not define and/or interpret these diagnoses.

Statistical analysis

For survival analysis, end points were analyzed as time-to-event data from the start of chemoradiotherapy to the respective events, which were subject to censoring at the last follow-up if no events were observed. The survival of patients with recurrence was recorded as recurrence-free survival (RFS), which is defined as the time from diagnosis to the first progression of the disease. The analysis of hazard ratios (HRs) and 95% confidence intervals (CIs) was performed using Cox proportional hazards model. Factors with a p value <0.1 in the Cox univariate analysis (log-rank) were included in the multivariate analysis, and other statistical analysis all considered that p value <0.05 was statistically significant. For pattern analysis, the date of recurrence was used as the endpoint. The nominal categorical variables were analyzed by the χ^2 test. Survival was estimated using the Kaplan–Meier model, and the results were reported as the median and interquartile range. All statistical analyses were performed using SAS 9.3 (SAS Institute).

RESULTS

Selection and characteristics of patients

We identified a total of 635 LS-SCLC patients, 233 of them were excluded because they did not receive standard chemotherapy (etoposide plus platinum) combined with chest radiation. Another 240 were excluded, because they have not achieved a CR. Therefore, 162 patients were included in the analysis and their demographic (Table 1) were as follow: median age at diagnosis, 64.7 years (interquartile range [IQR], 56.2–70.2); female, 94 (58%); median follow-up time was 50.6 (IQR, 26.4–91.5) months; 133 (82.1%) died during follow-up, and 81 (50.0%) had recurrence with a median RFS of 16.4 (IQR, 11.3–30.9) months. The median dose of radiation was 5040 cGy. Tumor related information, selected family/personal history, and comorbidities are shown in Table 1. The different subtypes of neurological PNS are listed in Table 2. All patients with GERD were treated with proton pump inhibitors (PPI); two of them also received a histamine H2 antagonist.

Overall survival analysis

In Cox regression analysis (Table 3), univariate analysis identified age (HR, 1.02; 95% CI, 1.00–1.04; $p = 0.036$), T3 stage (HR, 1.51; 95% CI, 0.95–2.41; $p = 0.080$), prophylactic cranial irradiation (PCI) (HR, 0.72; 95% CI, 0.50–1.04; $p = 0.079$), family history of lung cancer (HR, 1.50; 95% CI, 0.93–2.43; $p = 0.094$), personal history of other cancer (HR, 1.90; 95% CI, 1.08–3.06; $p = 0.007$), GERD (HR, 0.64; 95% CI, 0.45–0.91; $p = 0.013$), and neurological PNS (HR, 0.45; 95% CI, 0.29–0.70; $p < 0.001$) as potential risk factors affecting survival. Multivariate Cox analysis revealed that only GERD (HR, 0.65; 95% CI, 0.45–0.93; $p = 0.016$), and neurological PNS (HR, 0.46; 95% CI, 0.29–0.72; $p < 0.001$) were associated significantly with improved overall survival (OS) in LS-SCLC patients who achieved a CR after chemoradiotherapy.

Patterns analysis

After determining GERD and neurological PNS as survival factors, it was found that their prognostic effects were different. Patients with GERD or neurological PNS had significantly better overall survival than those without these comorbidities (GERD vs. no-GERD, median [IQR], 69.4 [36.6–105.4] months vs. 41.4 [23.2–75.0] months, $p < 0.001$; neurological PNS vs. no-PNS, median [IQR], 82.4 [60.1–

TABLE 4 Prognostic patterns

	GERD			Neurologic PNS		
Patterns of all 162 patients	**Yes (N = 67)**	**No (N = 95)**	***p* value**	**Yes (N = 39)**	**No (N = 123)**	***p* value**
Overall survival, median (IQR), month	69.4 (36.6, 105.4)	41.4 (23.2, 75.0)	<0.001	82.4 (60.1, 131.6)	41.8 (25.5, 79.2)	<0.001
Recurrence rate, no. (%)			0.151			**<0.001**
No	38 (56.7)	43 (45.3)		**31 (79.5)**	**50 (40.7)**	
Yes	29 (43.3)	52 (54.7)		**8 (20.5)**	**73 (59.3)**	
Patterns of 81 recurrent patients						
	Yes (N = 29)	No (N = 52)	*p* value	Yes (N = 8)	No (N = 73)	*p* value
Recurrence survival (RFS), median (IQR), month	**29.1 (15.0, 59.5)**	**13.9 (10.1, 19.4)**	**<0.001**	17.2 (13.1, 47.6)	15.7 (11.3, 29.3)	0.527

Abbreviations: GERD, gastroesophageal reflux disease; IQR, interquartile range; PNS, paraneoplastic syndrome; RFS, recurrence-free survival.
Note: Bold values are indicates *p*-value is in the next column, a line up.

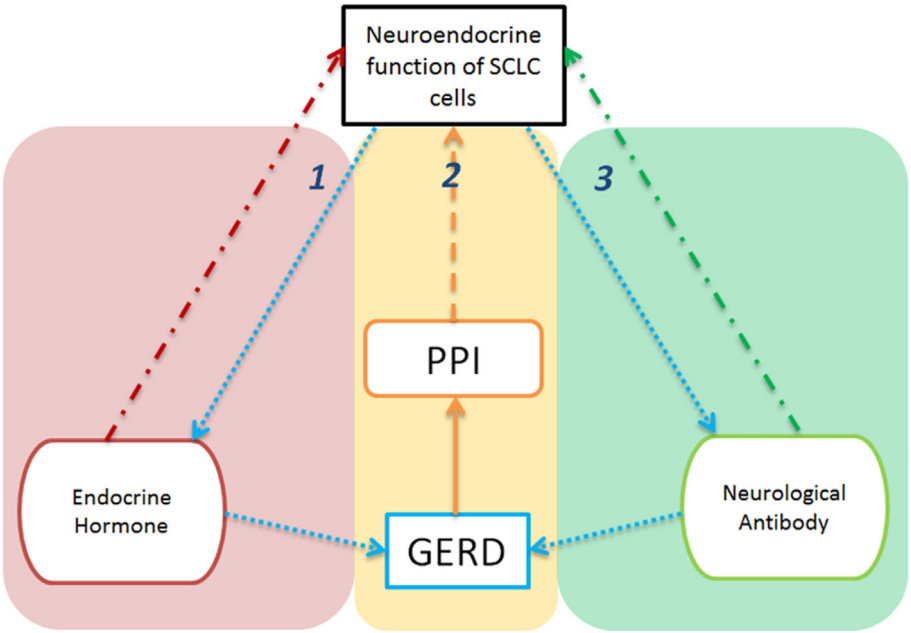

FIGURE 1 Hypothetical association between GERD and long-term survival of small cell lung cancer (SCLC). Pathway 1: paraneoplastic endocrine hormone induces GERD while inhibiting SCLC. Pathway 2: PPI is an anti-cancer drug. Pathway 3: paraneoplastic antibody causes GERD and increases curative effect of chemo- and radiation therapy. Abbreviations: GERD, gastroesophageal reflux disease; PPI, proton pump inhibitors; SCLC, small-cell lung cancer

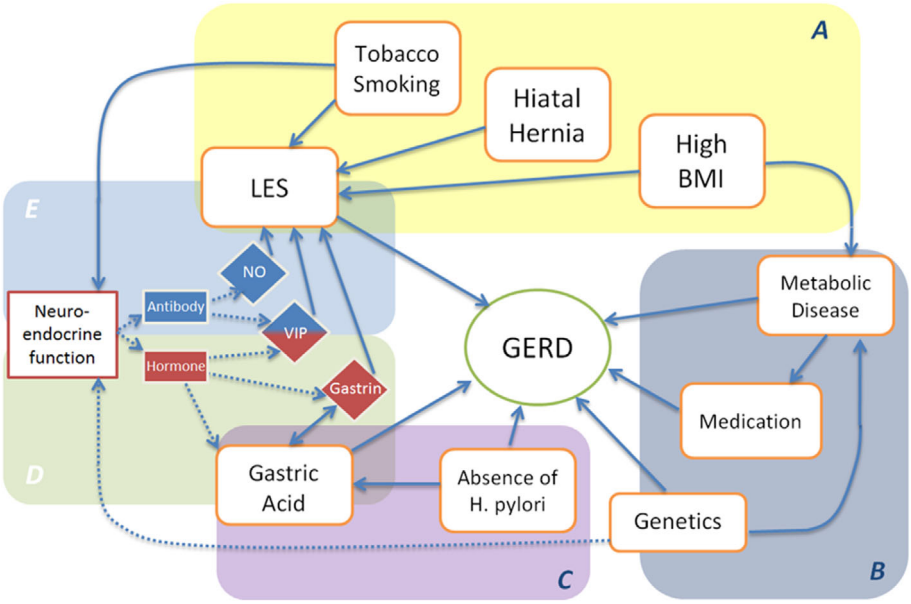

FIGURE 2 Mechanisms of gastroesophageal reflux disease (GERD). (a) Lower esophageal sphincter (LES) motor dysfunction. (b) Biochemical dysfunction. (c) Absence of *Helicobacter Pylori*. (d) Paraneoplastic endocrine hormone could decrease LES pressure by 1) inhibiting gastrin; 2) increasing gastric acid secretion; or 3) increasing levels of vasoactive intestinal polypeptide (VIP) (hypothetical). (e) Paraneoplastic neurological antibody could increase the level of VIP and NO, decreasing LES pressure (hypothetical). Abbreviations: BMI, body mass index; GERD, gastroesophageal disease; LES, lower esophageal sphincter; NO, nitric oxide; VIP, vasoactive intestinal polypeptide

131.6] months vs. 41.8 [25.5–79.2] months, $p < 0.001$). Eighty-one patients had disease recurrence, those with GERD had significantly improved RFS than those without GERD (GERD vs. no-GERD, median [IQR], 29.1 [15.0–59.5] months vs. 13.9 [10.1–19.4] months, $p < 0.001$); neurological PNS did not affect the RFS (neurological PNS vs. no-PNS, median [IQR], 17.2 [13.1–47.6] months vs. 15.7 [11.3–29.3] months, $p = 0.527$). We also found that recurrence rate was not associated with GERD, whereas it was significantly associated with neurological PNS (GERD vs. no-GERD, recurrence rate, No. [%], 29 [43.3] vs. 52 [54.7], $p = 0.151$; neurological PNS vs. no-PNS, recurrence rate, No. [%], 8 [20.5] vs. 73 [59.3], $p < 0.001$). Detailed data are provided in Tables 3 and 4.

DISCUSSION

To the best of our knowledge, this is the first report to demonstrate the correlation between GERD and survival in patients with LS-SCLC treated with chemoradiation. Based on our results, GERD and neurological PNS are additional factors associated with improved overall survival in patients with LS-SCLC who achieve a CR after chemoradiation.

Patients with GERD have a longer RFS, whereas patients with neurological PNS have a lower recurrence rate. Therefore, GERD and neurologic PNS affect OS, but possibly through different underlying mechanisms.

SCLC is the most frequent cancer associated with PNS. The pathophysiology of neurologic PNS involves the ectopic production of biologically active hormones/peptides by the primary tumor, or alternatively by immune-mediated processes, including antibody and cell-mediated mechanisms. It has been previously demonstrated that the presence of an antibody-mediated neurologic PNS is generally associated with a more favorable outcome as compared to the absence of PNS or antibodies.[11–14] Maddison et al.[15] compared the OS of 15 patients with SCLC and Lambert-Eaton Myasthenic Syndrome (LEMS) to SCLC patients without LEMS, and the OS median OS was 17.3 months and 10 months, respectively. Another study evaluated 31 patients with LEMS and again demonstrated a significant survival improvement in patients with LEMS as compared to the subgroup without LEMS.[16] Studies have consistently shown that most of the patients with LEMS present with LS-SCLC (50%–65%) compared to patients with SCLC without neurological disorder.[16,17] Iams et al.[18] recently demonstrated that patients with neurologic PNS experienced improved OS compared to endocrinologic and control (median OS of 24 months vs. 12 months, vs. 13 months, respectively). Of the 25 patients, 4 were diagnosed with LEMS and 3 with limbic encephalitis.

Figure 1 describes three possible pathways that associates GERD with improved survival in patients with LS-SCLC treated with chemoradiation. The first pathway hypothesizes that paraneoplastic endocrine hormones produced by SCLC could potentially contribute to the development of GERD, or perhaps be associated with the eradication of tumor cells. The second possible pathway is related to the use of PPI intended to treat GERD symptoms. Numerous studies have shown effects of PPI on tumor cell growth, metastasis, chemo-resistance, and autophagy. Therefore, PPIs may actually be acting as an anti-neoplastic agent.[19] In our study, all patients with GERD had been on PPI. The third possible pathway is built on the hypothesis that GERD may be secondary to PNS antibodies causing transient lower esophageal sphincter relaxation (TLESR). Lower esophageal sphincter (LES) tone relaxation is the most important factor related to GERD and is regulated by a variety of neurotransmitters, which could include PNS antibodies. In addition, the PNS antibodies may also increase tumor sensitivity to the treatment, therefore, prolonging RFS. Support for this hypothesis is that the presence of anti-Hu antibodies (one of the most frequently antibody associated with PNS) is a strong and independent predictor of complete response to treatment.[20]

Based on these hypotheses, GERD could represent yet another endocrine or neurological paraneoplastic syndrome in SCLC. We propose that GERD could be classified into four categories (Figure 2). Figure 2(a) shows that LES motor dysfunction is frequently associated with hiatal hernia, high BMI, and smoking.[21,22] Figure 2(b) shows less well characterized GERD associations, including metabolic diseases, medications, and genetics.[21,23–25] Figure 2(c) shows that the presence of *Helicobacter pylori (H. pylori)* protects from GERD by causing the atrophy of the esophagus and gastric mucosa. Consequently, this reduces gastric acid exposure and GERD.[26] In Figure 2(d), paraneoplastic endocrine hormones could decrease the LES pressure by inhibiting gastrin, increasing the production of gastric acid, or increasing the levels of vasoactive intestinal peptide (VIP). In Figure 2(e), paraneoplastic neurological antibodies would upregulate the expression of neurotransmitters like nitric oxide (NO) or VIP. N is the major mediator of nerve-induced LES relaxation.[27,28] VIP also has the neurological function, which can relax gastrointestinal smooth muscle and inhibit LES tension.[29,30]

In summary, GERD and neurologic PNS are associated with improved survival in patients with LS-SCLC who experience a complete response to chemoradiotherapy. Our study demonstrates that SCLC patients with GERD have a longer RFS. We encourage further studies to evaluate the pathogenesis of GERD in SCLC and the potential anti-neoplastic properties of PPI, which might shed light on the exact mechanisms responsible for our findings. Our results support other studies, which have shown that SCLC patients with neurologic PNS have significant survival benefits.[16,31,32] Our study also revealed that neurologic PNS might be associated with decreased disease recurrence after chemoradiation.

This study has several limitations. First, we studied a very small subset of patients with SCLC, a group that is known to have better survival. We do not know whether our findings are applicable to all SCLC patients, including those with extensive-stage disease or PR to treatment. Therefore, similar studies in all SCLC patients are warranted. We did not include many prognostic factors such as LDH, race, white blood cell count, and performance status. The study also did not distinguish patients that received concurrent chemoradiation from those that received a sequential treatment (chemotherapy followed by radiation). Another limitation of our analysis was the small number of patients that were tested for paraneoplastic antibodies. However, the clinical significance of these antibodies has been primarily used to assist in the diagnosis of PNS. Moreover, because of the long period of this study (~20 years), these antibodies have not been used as a routine detection method in the early days. Last, the study was retrospective, so further prospective studies are necessary to confirm these findings.

CONCLUSIONS

In this cohort of patients with LS-SCLC treated with definitive chemoradiation in a tertiary academic center, we found that patients with GERD have a longer recurrence-free survival rate, whereas patients with neurologic PNS have a lower recurrence rate. We also propose that GERD could potentially be a manifestation of a paraneoplastic syndrome

in this subgroup of patients. Further studies to elucidate this mechanism are needed to corroborate our conclusion.

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