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Presentation, management patterns and outcome of small cell lung cancer and stage III non-small cell lung cancer in Saudi Arabia: a multicentre retrospective observational study (REVEAL Study)

Abstract

Background: The advent of immune checkpoint inhibitors (ICIs) and targeted therapy has resulted in a significant paradigm shift in the small (SCLC) and non-small cell lung cancer (NSCLC) management landscape. However, limited real-world evidence is available regarding the standard of care practice and treatment outcomes of both in the Kingdom of Saudi Arabia (KSA). Thus, the REVEAL study evaluated the clinical presentation, treatment patterns, and outcomes of SCLC and stage-III NSCLC in KSA prior to the availability of ICIs.

Methods: The REVEAL was a multicentre retrospective study that retrieved data from adult patients diagnosed with primary SCLC (extensive or limited stage) or stage-III NSCLC between 2015 and 2019. Retrieved records included demographic and clinical characteristics, treatment regimens, disease response, and survival outcomes.

Results: The cohort comprised 23 patients with SCLC, predominantly extensive stage 17 (73.9%). Systemic chemoradiotherapy was the common first-line treatment for limited-stage SCLC patients, 4 (66.7%), while extensive-stage patients, 7 (41.2%), received systemic chemoradiotherapy. The distribution of second-, third and later-lines of treatment was similar across subtypes. At first-line, the extensive-stage SCLC had a mean treatment duration of 5.9 ±8.1months, while limited-stage SCLC had 3.25±1.49months. About 3(37.5%) of limited-stage patients and 7 (29.2%) of extensive-stage discontinued first-line treatment due to disease progression. The median first-line progression-free survival (PFS) was six months for extensive-stage SCLC. The median overall survival (OS) was 38 months for limited-stage SCLC and 11 months for extensive-stage SCLC. 17 patients with stage-III NSCLC were included. First-line chemoradiation was administered for 12(70.5%). At first-line, stage-III NSCLC had a mean treatment duration of 2.29 ±2.98months. The median first-line PFS was six months, and the median OS was 20 months.

Conclusion: The current data provide real-world insights into the presentation and management landscape of both SCLC and stage-III NSCLC in KSA. Further studies with a larger sample size are recommended.

Keywords: SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; Stage-III; KSA, Kingdom of Saudi Arabia; limited stage; extensive stage

Volume 16 Issue 4 - 2025

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Received: September 4, 2025 | **Published:** September 24, 2025

Introduction

Lung cancer (LC) remains the leading cause of cancer-related mortality worldwide, even in high-income countries.[1] The global burden of LC is profound, with an estimated 2.2 million new cases and 1.8 million deaths in 2020.[2] Recent statistics estimated that the global LC incidence will increase by 23% and 2% by 2035 in the male and female populations, respectively.[3] Despite advancements in diagnostic techniques and treatment modalities, the overall survival (OS) rate remains low (5-year OS =20.5%), particularly for patients diagnosed at advanced stages who exhibit a 5-year OS of 5.8% only.[4] LC accounts for nearly 4% of the cancer cases in the Kingdom of Saudi Arabia (KSA) and substantially impacts its healthcare system. LC lower prevalence of LC in KSA is speculated to stem from the ban of smoking until 1960, which remains a culturally unacceptable practice.[5] Nonetheless, previous reports showed a sustained increase in LC incidence in KSA, with a 3.5-fold increase from 1990 to 2016, ranking it the fourth leading cause of cancer death in KSA.[5,6]

Small-cell LC (SCLC) and non-small-cell LC (NSCLC) are the primary histological subtypes exhibiting distinct molecular characteristics, clinical behaviours and responses to treatment.[7] NSCLC accounts for the majority (85%) of LC cases, with nearly one-third of the patients presenting with stage-III[8] This clinical group typically refers to locally advanced disease, including up to massive parenchymal localization with contralateral lymph node (LN) involvement (T3-T4 and N3)[9] Patients with stage-III NSCLC usually present with unresectable disease, and platinum-based chemotherapy combined with radiotherapy[10,11] Although chemotherapeutic regimens have relatively improved stage-III NSCLC survival[12,13] current data still show a poor prognosis, with a 5-year OS rate of 34.5%[14] The advent of immune checkpoint inhibitors (ICIs) and targeted therapy has resulted in a significant paradigm shift in NSCLC management landscape, with promising survival benefits in perioperative settings and unresectable disease[10] In the PACIFIC trial, the 5-year OS rate for durvalumab after chemoradiotherapy was 42.9%.[15]

On the other hand, SCLC is a poorly differentiated neuroendocrine tumor affecting 15% of all LC cases[16] Chemoradiotherapy is the recommended first-line regimen for limited-stage SCLC patients, alongside prophylactic brain irradiation in patients without progression after chemoradiotherapy. For patients with extensive disease, chemotherapy combinations, mainly a platinum agent and etoposide, are recommended[17] Nonetheless, SCLC remains a highly aggressive malignancy with poor prognosis (median OS = 7-12 months)[18] Although SCLC management landscape remained largely stable for two decades, targeted therapy and ICIs have gained significant attention in treating SCLC, moving away from the traditional platinum and etoposide-based regimens. Recent trials showed that ICIs significantly improved OS when combined with traditional chemotherapy in advanced SCLC.[19]

Despite the LCs growing burden in KSA, limited real-world evidence is available regarding the standard of care practice and treatment outcomes of both entities in KSA. Thus, the REVEAL study evaluated the clinical presentation, treatment patterns, and outcomes of SCLC and stage-III NSCLC in KSA. The results of this study can contribute to identifying the unmet treatment needs and provide baseline data for evaluating treatment outcomes of stage-III NSCLC and SCLC in KSA. The data collection prior to ICIs' availability in KSA would provide helpful information about how ICIs may improve the survival outcomes of patients compared to the historic standard of care.

Materials and methods

The study was conducted in accordance with the Declaration of Helsinki[20] and applicable local regulatory laws. The study has been registered on CT.gov under ClinicalTrials.gov Identifier: NCT06039683. Ethical approval was obtained from the two participating centers' Institutional Review Boards (IRBs) (NGH-Riyadh IRB approval no. SRC21R-010-10 and KFMC-Riyadh IRB approval no. 21-427. As this was a retrospective observational study, informed consent from individual patients was waived by the IRBs. The present report was prepared in concordance with the STROBE statement.[21]

Study design and data source

The REVEAL study (NCT04836975) was a multicentre retrospective chart review that retrieved the records of adult patients (aged ≥18years) with SCLC or stage-III NSCLC between January 2015 and December 2019 (index-window). Anonymized data were received from the medical records in two-centers in Riyadh-KSA: King Abdulaziz Medical City and King Fahad Medical City. Patients diagnosed with SCLC or stage-III NSCLC during the index window were included if they had a follow-up period of at least nine months. The study assessed SCLC and NSCLC extent using the 7th or 8th editions of the American Joint Commission on Cancer, excluding patients with concomitant cancer (diagnosed within five-years of LC diagnosis), other than stage I-III skin cancers, or in situ/benign lesions. Patients' medical records who progressed to stage-III NSCLC or received durvalumab were excluded.

Variables and definitions

The following sociodemographic data were retrieved from the medical records of the eligible patients: age, sex, ethnicity, weight, body-mass-index (BMI), and smoking history. Additionally, data regarding the clinical characteristics of the patients were collected, including the extent of SCLC, NSCLC-stage, tumor-site, pathological subtype, Eastern Cooperative Oncology Group (ECOG) performance status[22] comorbidity burden using the Charlson comorbidity index (CCI) and distant metastasis presence and type[23] Concerning treatment, we collected data regarding administrated regimens number, treatment-patterns, treatment lines, dose and each line cycles number, radiotherapy administration, surgical procedures, and treatment discontinuation reasons.

The study collected from the chart review the best responses for each treatment line as per clinicians' assessment in the medical records. The patient's response was categorized into complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The investigator assessed response-rate, defined as CR or PR, and disease control rate (DCR), defined as CR, PR, or SD. Data regarding survival outcomes, including PFS and OS, and the development of distant metastasis were collected. The PFS and OS were calculated as the time from diagnosis date to progression/death and death, respectively. For patients who were alive, did not progress, or lost to follow-up at the time of analysis, the data were censored at the date of the last tumor evaluation. Lastly, healthcare resource utilization (HCRU) data were collected, including hospitalization frequency and setting, medical or surgical treatments number, and other diagnostic procedures use.

Statistical analysis

All analyses were done using IBM SPSS Statistics for Windows (Version 24.0). Continuous data were summarized using the mean ± standard deviation (SD) or median and interquartile range (IQR) according to data normality. At the same time, counts were used for categorical variables. The Kaplan-Meier method estimated the OS and PFS for the overall cohort, and the estimates were expressed as median survival with 95% confidence intervals (CIs). The statistical analysis was stratified according to the subtype (limited-stage primary SCLC, extensive-stage primary SCLC, and stage-III NSCLC).

Results

The medical records of 45 patients were retrieved; five patients did not meet the eligibility criteria and were excluded. Thus, forty patients were included in the present analysis. Twenty-three patients had primary SCLC, with most of them (n=17;73.9%) having extensive-stage disease. The remaining patients had stage-III NSCLC (Figure 1).

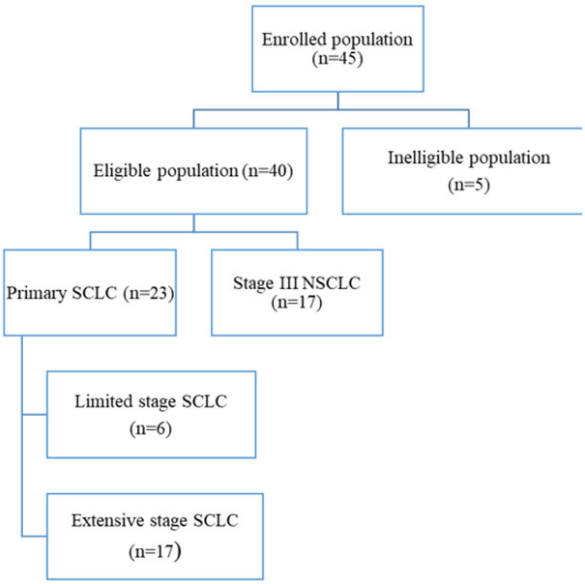

Figure 1 Study's flowchart.

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DOI: 10.15406/jcpcr.2025.16.00587

Demographic and clinical characteristics at diagnosis

Table 1 shows the demographic and clinical characteristics of the included patients at diagnosis. Tables 7 and 8 present demographic and clinical characteristics at the end of follow-up. Four patients with limited-stage SCLC progressed into extensive-stage SCLC at the end of follow-up.

Table 1 Demographic and clinical characteristics of the included patients

		Total	Limited stage SCLC	Extensive stage SCLC	Stage III NSCLC
		N=40	N=6	N=17	N=17
Age at diagnosis (years)	Mean ±SD	61.4±11.8	64.15±16.24	60.6±9.9	61.8±12.45
	Median (IQR)	61.4 (14.8)	68.5 (15.25)	61 (13.5)	61 (14)
Gender	Male	37 (92.5)	5 (83.3)	16 (94.1)	16 (94.1)
Ethnicity	Arab	39 (97.5)	6 (100)	17 (100)	16 (94.1)
	Not Available	1 (2.5)	0	0	1 (5.9)
BMI (Kg/m2)	Mean ±SD	26.3±5	25.58±4.47	27±6.25	25.98±4.29
Smoking History at Diagnosis	Never	4 (10)	0	2 (11.8)	2 (11.8)
	Current	26 (65)	5 (83.3)	14 (82.4)	7 (41.2)
	Ex-Smoker	9 (22.5)	1 (16.7)	1 (5.9)	7 (41.2)
	Not Available	1 (2.5)	0	0	1 (5.9)
Pack Years	Median (min-max)	30 (0.3-40)	30 (0.3-40)	30 (2-40)	2 (1-40)
Stage of NSCLC (7th Edition)	Stage IIIA	-	-	-	7 (41.17)
	Stage IIIB	-	-	-	4 (23.52)
	Not Available	-	-	-	6 (35.29)
Type of metastasis**	Non-visceral	-	-	8 (47)	-
	Lymph nodes	-	-	4 (23.5)	-
	Skin and soft tissue	-	-	0	-
	Bone	-	-	7 (41.1)	-
	Others	-	-	0	-
	Central Nervous System, "brain and spinal cord"	-	-	3 (17.6)	-
	Visceral	-	-	8 (47)	-
	Liver	-	-	6 (35)	-
	Adrenal	-	-	2 (11.7)	-
	Other	-	-	1 (5.8)	-
	Not available	-	-	1 (5.8)	-
Location of Tumour*	Right upper lobe	17 (42.5)	3 (50)	7 (41.1)	7 (41.2)
	Right middle lobe	1 (2.5)	0	0	1 (5.8)
	Right lower lobe	1 (2.5)	0	1 (5.8)	0
	Right lung, unspecified	0	0	0	0
	Left upper lobe	10 (25)	2 (33.3)	4 (23.5)	4 (23.5)
	Left lingual	0	0	0	0
	Left lower lobe	5 (12.5)	1 (16.7)	2 (11.7)	2 (11.8)
	Left lung, unspecified	1 (2.5)	0	1 (5.8)	0
	Right lung Pancoast tumour	2 (5)	0	1 (5.8)	1 (5.8)
	Left lung Pancoast tumour	0	0	0	0
	Not available	5 (12.5)	0	3 (17.9)	2 (11.8)
	Unknown	0	0	0	0
ECOG Performance Status	0	3 (7.5)	0	0	3 (17.6)
	1	20 (50)	4 (66.7)	8 (47.1)	8 (47.1)
	2	5 (12.5)	0	1 (5.8)	4 (23.5)
	3	7 (17.5)	1 (16.7)	4 (23.5)	2 (11.8)
	4	0	0	0	0
	Not available	5 (12.5)	1 (16.7)	4 (23.5)	0
Charlson Comorbidity Index	Low (0)	18 (45)	3 (50)	6 (35.3)	9 (52.9)
	Medium (1-2)	12 (30)	2 (33.3)	3 (17.6)	7 (41.1)
	High (>2)	10 (25)	1 (16.7)	8 (47)	1 (5.8)

ECOG, eastern cooperative oncology group; CNS, central nervous system, N, number of patients, IQR, interquartile range, NSCLC, non-small cell lung cancer, EGFR, epidermal growth factor receptor. *Patient may have more than one tumour location. **Patient may have more than one metastatic type/site.

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DOI: 10.15406/jcpcr.2025.16.00587

SCLC Cohort

The patients mean age at diagnosis in the SCLC group was 61.4±11.8 years, predominantly males, 37 patients (92.5%), with Arab ethnicity, 39 patients (97.5%). The mean BMI was 26.3±5Kg/m², with consistency across different SCLC stages. Current smokers' prevalence was highest in the extensive-stage SCLC group, 14 patients(82.4%), with a median pack-year of 30 years. Metastases were reported in most patients with extensive-stage SCLC (94%), with half having visceral metastases (mainly liver). The ECOG status at diagnosis time showed that most SCLC patients had a performance status of 1, 20 patients (50%). The comorbidity score indicated that the SCLC patients had a high comorbidity, with 8 patients (47%) of the extensive-stage SCLC group having a high comorbidity.

NSCLC Cohort

The mean patients age at diagnosis in the stage-III NSCLC group was 61.8 years predominantly males 16(94.1%) of Arab ethnicity 16 (94.1%). The mean BMI was 25.98±4.29 Kg/m². Current smokers' prevalence in this group was 7(41.2%), with a median pack year of 2years. Most NSCLC patients had stage-IIIA. Two (20%) out of 10-patients tested for epidermal growth factor receptor (EGFR) mutation were found positive. ECOG status at the time of diagnosis showed that 6(25%) of the NSCLC patients had a performance status of 2-4. The comorbidity score indicated that only 1(5.8%) of the NSCLC patients had a high burden of comorbidities.

Treatment characteristics

Table 2 shows the first-line treatment patterns, while Table 3 shows the chemotherapy treatment characteristics at first-line treatment. Table 9 presents the characteristics of the received treatments as the second and later lines of treatment.

Table 2 Initial treatment patterns

		Total	Limited stage primary SCLC	Extensive stage primary SCLC	Stage III NSCLC
Treatment Pattern	**n**	40	6	17	17
	Chemotherapy	9 (22.5)	1 (16.7)	5 (29.4)	3 (17.6)
	Chemo-Radiotherapy	20 (50)	4 (66.7)	7 (41.2)	9 (52.9)
	Chemo-Radiotherapy with Surgery#	4 (10)	0	1 (5.9)	3 (17.6)
	Chemo-Radiotherapy with Targeted Therapy#	1 (2.5)	0	1 (5.9)	0
	Chemotherapy with Surgery	1 (2.5)	0	0	1 (5.9)
	Not available	3 (7.5)	0	2 (11.8)	1 (5.9)
	Radiotherapy	2 (5)	1 (16.7)	1 (5.9)	0

*n is the number of frequencies of the treatment event; #including sequential and concurrent regimens.

Table 3 Chemotherapy treatment characteristics at first-line treatment

		Total	Limited stage primary SCLC	Extensive stage primary SCLC	Stage III NSCLC
Number of cycles	Mean/Standard deviation	4.88 ± 1.94	5.75 ± 0.46	5.42 ± 1.93	4.18 ± 2
	Median/IQR	5 (2)	6 (0.5)	6 (1.5)	4.5 (1.5)
Duration of Treatment Regimens (months)	Mean/Standard deviation	3.85 ± 5.72	3.25 ± 1.49	5.87 ± 8.09	2.29 ± 2.98
	Median/IQR	3 (3)	4 (2)	4 (2.5)	2 (2)
Reason(s) for stopping	Adverse Event	1 (1.7)	0 (0)	1 (4.2)	0 (0)
	Progression	13 (21.7)	3 (37.5)	7 (29.2)	3 (10.7)
	Other	24 (40)	2 (25)	9 (37.5)	13 (46.4)
	Not Available	22 (36.7)	3 (37.5)	7 (29.2)	12 (42.9)

SCLC cohort

Two-thirds of limited-stage SCLC patients received chemoradiotherapy, while 1(16.7%) received chemotherapy only (Table 2). Regarding chemotherapy treatment, the mean cycles number was 5.75±0.46, with a median of 6 (IQR:0.5) cycles. The treatment regimens' median duration was 3 months (IQR:3). About 37.5% of patients discontinued first-line treatment due to disease progression (Table 3). The second-line treatment was chemotherapy 6 (100%), with a median duration of treatment of 2-months (IQR:2).

For extensive-stage primary SCLC, chemoradiotherapy was administered in 8(53%) of the patients, while 5(29.4%) received chemotherapy only (Table 2). Regarding chemotherapy treatment, the mean number of cycles was 5.42±1.93, and the mean duration of treatment regimens was 5.87±8.09months. 7(29.2%) of treatments were discontinued due to disease progression, and 1(4.2%) were discontinued due to adverse-events (Table 3). Second-line treatment also predominantly involved chemotherapy (77.8%), with a mean treatment duration of 3±1.94 months. All treatment discontinuation

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DOI: 10.15406/jcpcr.2025.16.00587

reasons were due to disease progression (100%). Regarding surgical procedures, only one patient underwent metastasis resection; however, its outcome was not determined.

NSCLC cohort

First-line treatment pattern for stage-III NSCLC patients predominantly involved chemoradiotherapy 12(70.5%) and chemotherapy 3(17.6%) (Table 2). Regarding chemotherapy treatment, treatment cycles mean number was 4.18±2, and the mean duration of treatment regimens was 2.29±2.98 months. Treatment discontinuation was recorded in 3(10.7%) of treatments due to progression (Table 3). Four out of 17 patients were eligible for surgery. One (5.9%) of the 17 patients underwent a pneumonectomy, and 3(17.6%) underwent lobectomy, where complete resection was recorded in 3 patients. Second-line treatment predominantly involved systemic therapy (75%), including atezolizumab, docetaxel, and pembrolizumab. The mean duration of second-line treatment was 1.5±2.38months. For subsequent lines of therapy, all treatments were systemic chemotherapy (100%).

Treatment response and survival outcomes

Table 4 shows the treatment response and survival outcomes.

Table 4 Best response to line therapies.

	Level	Total	Limited stage SCLC	Extensive stage SCLC	Stage III NSCLC
The best response to first-line chemotherapy	n	35	5	14	16
	CR	1 (2.9)	0 (0)	0 (0)	1 (6.3)
	PR	11 (31.4)	1 (20)	5 (35.7)	5 (31.1)
	SD	5 (14.3)	1 (20)	1 (7.1)	3 (18.8)
	PD	12 (34.3)	3 (60)	6 (42.9)	3 (18.8)
	Unknown	6 (17.1%)	0	2 (14.3)	4 (25)
Best response to second-line chemotherapy	n	2	4	4	10
	CR	0	0	0	0
	PR	0	0	0	0
	SD	0	0	0	0
	PD	1 (50)	4 (100)	3 (75)	8 (80)
	Unknown	1 (50)	0	1 (25)	2 (20)
Best response to subsequent line chemotherapy	n	6	1	2	3
	CR	0	0	0	0
	PR	2 (33.3)	0	0	2 (66.7)
	SD	1 (16.7)	0	1 (50)	0
	PD	2 (33.3)	0	2 (50)	1 (33.3)
	Unknown	1 (16.7)	1 (100)	0	0
Patients' status at the end of follow-up	Alive	16 (40)	4 (66.6)	3 (17.6)	9 (52.9)
	Dead	24 (60)	2 (33.3)	14 (82.3)	8 (47)
Cause of Death (n=24)	Cancer-related	23 (96)	2 (100)	14 (100)	7 (87.5)
	Not Available	1 (4)	0	0	1 (12.5)

CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease

SCLC cohort

The investigator-assessed response rate to first-line chemotherapy (with or without radiotherapy) were 1(20%) and 5(35.7%) for limited-stage and extensive-stage SCLC, respectively. PR was observed as the best response to first-line chemotherapy in 1(20%) of the limited-stage SCLC patients and 5(35.7%) of the extensive-stage SCLC patients (Table 4). All patients with available data had PD as the best response in the second and later lines of treatment. Regarding survival outcomes, the median first-line PFS was six months (95% CI 1.19 -10.8) in extensive-stage SCLC and non-estimable for limited-stage SCLC patients (Figure 2a). On the other hand, 22 SCLC patients died at the end of the follow-up period. Most of them were from the extensive-stage SCLC group 14(82.3%). The median OS was 38 months (95%CI 0 –84.51) and 11 months (95% CI 0.93-21.06) in limited-stage SCLC and extensive-stage SCLC (Figure 2 b). Distant metastasis was present in 18 SCLC patients (86%) at the end of follow-up, mainly affecting visceral sites, followed by non-visceral and CNS equally (Table 5).

Table 5 Metastasis at the end of follow-up for patients with SCLC

	Level	Limited stage SCLC	Extensive stage SCLC
		N=6	N=17
Presence of distant metastasis for patients at the end of follow-up (n=21)#	Yes	4 (66.6)	14 (82.3)
	No	0	1 (6)
	Not available	0	2 (12)
Type of Metastasis*	Non-visceral	0	3 (17.6)
	Lymph nodes	0	1 (6)

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Table 5 Continued....

Bone	0	2
Central Nervous System (brain and spinal cord)	3 (50)	3 (17.6)
Visceral	0	8
Liver	0	4
Adrenal	0	1 (23.5)
Other	0	3 (17.6)
Not available	1 (16.6)	1 (6)

*Patient may have more than one metastatic type/site; #Data regarding progression were not collected for stage III NSCLC patients

NSCLC cohort

Response rate of the received first-line chemotherapy (with or without radiotherapy) was 6(37.4%) (CR =6.3%). In terms of survival outcomes, the median PFS was six months (95%CI 1.84-6.15; Figure 2a). Alternatively, eight stage-III NSCLC patients 8(47%) died at the end of the follow-up period. The median OS was 20-months in stage-III NSCLC patients (Figure 2b).

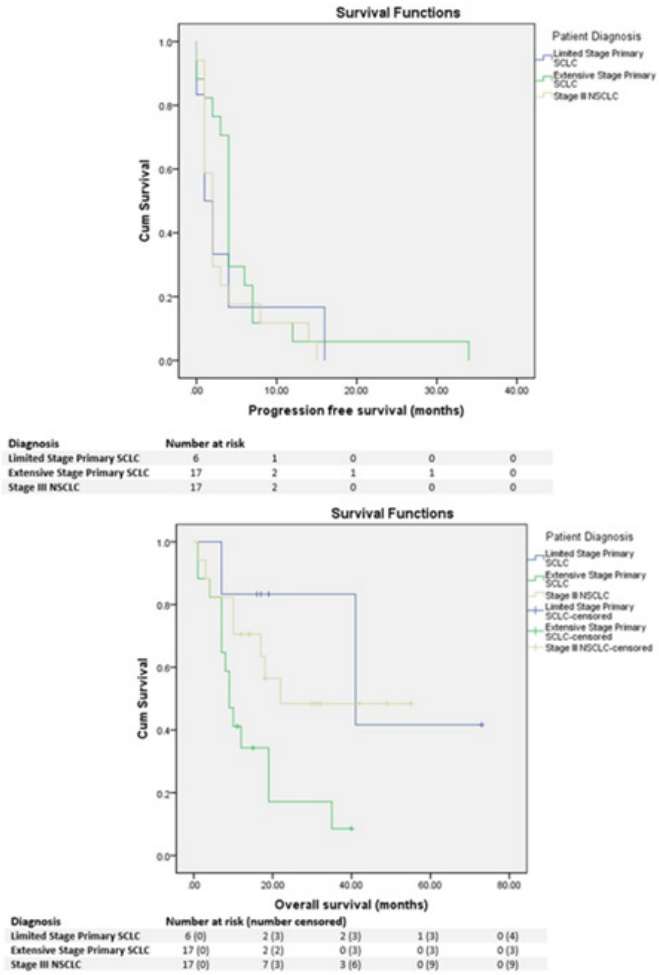

Figure 2 Kaplan Meier curves showing (a) progression-free survival and (b) overall survival.

Health care resource utilization

Thirty-two (80%) patients were hospitalized during the study period, with a median hospitalization number of 2(IRQ:2). The highest hospitalization rate was observed in the extensive-stage SCLC group 15 (88%), and the limited-stage SCLC patients had a median hospitalization number of 3(50%). The median hospital stays length varied, with the longest in stage-III NSCLC (6 days). Most visits were at the hospital care level for all groups 55 (74.3%), and the reasons for admission were mainly respiratory symptoms in the form of dyspnoea, cough, pyrexia, and haemoptysis. ICU admissions were for 11(14.9%), with the highest percentage in stage-III NSCLC 7

(41.17%). Most patients had outpatient visits 35 (87.5%), particularly in limited-stage SCLC 6 (100%) and stage-III NSCLC 16(94%). The median visits number was similar across groups, ranging from 29 to 30. Thirty (75%) patients were admitted to the emergency department (ED) with a median of 3 (IQR:3) visits. Most patients underwent one or more imaging modalities during their hospital visits like chest X-ray, computed tomography (CT) scan, positron emission tomography–CT (PET-CT), and magnetic resonance imaging (MRI) in 90.0%, 95.0%, 62.5%, and 40.0%, respectively. Nine patients (22.5%) underwent other procedures during their visits (Table 6).

Table 6 Healthcare resources utilization

		Total	Limited stage SCLC n=6 (%)	Extensive stage SCLC n=17(%)	Stage III NSCLC n=17(%)
Hospitalization	Number of patients admitted to hospital	32 (80)	3 (50)	15 (88)	14 (82)
Number of hospitalizations	Median (IQR)	2 (2)	3 (2)	2 (1)	2 (2)
Length of Stay	Median/IQR	5 (9)	3 (4)	4.5 (12.5)	6 (13)
Care Level*	Primary Care	2 (2.7)	0	2 (6.4)	0
	Specialty Physician Care	7 (9.5)	0	5 (16)	2 (6)
	Hospital care	55 (74.3)	9 (100)	14 (45)	32 (94)
	Specialty Hospital care	4 (5.4)	0	4 (13)	0
	Not available	6 (8.1)	0	6 (19.3)	0
ICU Admission	Yes	11 (14.9)	1 (16.6)	3 (17.6)	7 (41.17)
Outpatient Visit	Yes	35 (87.5)	6 (100)	13 (76.4)	16(94)
	No	4 (10)	0	4 (23.5)	0
	Not available	1 (2.5)	0	0	1 (6)
Number of Outpatient Visits	Median/IQR	29 (37)	30 (42)	29 (36)	29.5 (38)
Emergency department (ER) admission	Yes	30 (75)	4 (66.6)	14 (82.3)	12 (70.5)
	No	9 (22.5)	2 (33.3)	3 (17.6)	4 (23.5)
	Not available	1 (2.5)	0	0	1 (5.8)
Number of ER visits	Median/IQR	3 (3)	4 (3)	2 (5)	3 (4)
Imaging Tests	Yes	39 (97.5)	6 (100)	17 (100)	16 (94)
	No	0	0	0	0
	Not available	1 (2.5)	0	0	1 (6)
Number of imaging tests***	Radiograph	8.6±7.7	3.16±1.9	7.9±8.3	11.18±7
		5.5 (11.5)	2.5 (4)	4 (8)	11 (13)
Mean/SD	CT	9.4±6.2	15.5±1.94	8.2±5.3	8.62±4.8
Median/IQR		8 (10)	2.5 (0)	8 (10)	8 (16)
	PET	3.6±4.1 2 (3)	6±5.56	3.8±5.7	3.18±2
			5	2 (2)	3 (3)
	MRI	2.1±1.9 1 (2)	2.25±1.89	2.4±2.5	1.8±1.3
			1.5 (3)	1 (3)	1 (2)
	Other imaging number	1.7±2.3 (0) 1	1±0	2±3	1.5±0.5
			1	1 (0)	1.5 (1)
Other procedures	Yes	9 (22.5)	2 (33.3)	6 (35.3)	1 (5.8)
	No	30 (75)	4 (66.6)	11 (64.7)	15 (88.2)
	Not available	1 (2.5)	0	0	1 (5.8)

IQR, interquartile range; ICU, intensive care unit; ER, emergency room; CT, computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging; *Per admission; **One patient can perform more than one imaging type/test.

Discussion

Over the years, LC incidence and mortality in KSA have shown a concerning increase, with a more than 3% increase in less than two decades highlighted in one report.[24] In a broader timeframe between 1990 and 2016, there was a significant rise in LC incidence from 350 to 1,200 cases, illustrating a 3.5-fold increase in KSA[6] This alarming increase highlights the urgent need for real-world data regarding the presentation and outcomes of different histological subtypes and stages of LC in the Saudi population or robust healthcare policies. The REVEAL study aimed to reflect the real-world clinical characteristics, treatment patterns, clinical outcomes, survival, and HCRU for patients diagnosed with primary SCLC and stage-III NSCLC.

Population-based studies demonstrated that the median age at the presentation of LC was 66, with a male predominance[5] For stage-III NSCLC, previous reports suggested that the median age at diagnosis ranged from 65 to 79years[14]. In this study, relatively younger age at LC diagnosis (median age=61.4years) was found, and mostly males. This relatively younger age is explained by the fact that the majority of the patients in our cohort were SCLC, which tends to present at

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DOI: 10.15406/jcpcr.2025.16.00587

a younger age.[25,26] In a single-center study, the median age at SCLC diagnosis was 62years, and mostly males.[26] Males also comprised a larger proportion in similar studies.[27,28]

As discussed, SCLC is a highly aggressive malignancy with a poor prognosis and typical metastatic disease (70%) at presentation. A cumulative body of evidence shows that patients with SCLC usually present with extensive disease and poor performance status, negatively impacting their prognosis[29] In line with these findings, we found that 17(73.9%) of the SCLC patients had extensive-stage disease; of them, 16(94%) of patients had either visceral or non-visceral metastasis. Moreover, one-fourth of the patients had a high comorbidity burden. In a single institutional data review by Ganguly et al., 85% of the SCLC patients had extensive disease, and 45% had a high comorbidity index[26] In another report from the United States (US), nearly 70% of SCLC patients had extensive disease[30] Notably, studies from East Asian countries showed a higher prevalence of limited disease in the SCLC cohort than our report, which may be attributed to different population characteristics or screening protocols[31,32] Overall, our results indicate that SCLC typically presents with extensive metastatic disease in KSA at the present time. These indicators are vital for developing effective diagnostic, management, and potentially preventive strategies to improve patient outcomes. Through a better understanding of the regional disease behavior and response to treatments, healthcare providers can tailor management plans, fostering a more personalized approach to LC care in KSA.

The management of SCLC and NSCLC is multifaceted and entails tailored treatment plans. For limited-stage SCLC, concurrent chemoradiotherapy is the standard care, while extensive-stage SCLC predominantly necessitates chemotherapy. However, with the recent advances in ICIs, ICIs plus chemotherapy have become the standard of care for first-line management of extensive-stage SCLC[17,18] On the other hand, the management of stage-III NSCLC often involves a combination of chemotherapy, radiation, and surgical intervention, with the recent integration of ICIs, like PD-L1 inhibitors, showing promise in improving survival outcomes[10] Targeted therapies, particularly for patients with identifiable genetic mutations such as EGFR or ALK, have become a cornerstone in the management of NSCLC with driver mutations[33] In KSA, the Saudi LC Association (SLCA) and the Saudi National Cancer Centre have formulated local guidelines for KSA's unique patient demographics, disease biology, and practice settings. Standard chemotherapy agents are accessible to all LC patients in KSA. Targeted therapies are available for those identified with driver mutations, while others with wild-type tumors are managed with either ICIs (if PD-L1 expression is at least 50%) or systemic chemotherapy for NSCLC. In KSA, tertiary centers provide access to at least one EGFR TKI, primarily erlotinib.

According to our findings, the current practice of stage-III NSCLC treatment in KSA runs in line with international and local guidelines. On the contrary, the practice regarding limited-stage SCLC significantly differs from the standard care protocols, particularly chemoradiation therapy. We found that only 4(66.7%) of the limited-stage SCLC received this recommended treatment at first-line, highlighting that a significant proportion did not undergo the standard of care treatment. The observed underutilization of chemoradiation therapy could plausibly be attributed to the patient's poor general health status and the presence of comorbid conditions, which potentially limit their eligibility for or tolerance to chemotherapy. This insight necessitates a deeper investigation into the decision-making processes in clinical practice, emphasizing the need to balance guideline-directed treatments with individual patient factors, including their overall health condition and concurrent diseases, to optimize care outcomes.

In the present study, the treatment response and survival outcomes of SCLC and stage-III NSCLC were suboptimal, aligning with both entities' aggressive behavior. We found that only 1(20%), 5(35.7%), and 1(31,1%) of the limited-stage, extensive-stage SCLC, and stage-III NSCLC patients achieved PR as the best response at the first line of chemotherapy, respectively. Comparatively, pivotal trials showed that durvalumab plus chemotherapy was associated with 51.5% and 85.2-90.5% response rates in extensive-stage SCLC and stage-III NSCLC, highlighting the better responses that our patients might have had if they were offered immunotherapy[34–36] The median first-line PFS was 6(95% CI 1.19 -10.8) and 6(95% CI 1.84 -6.15) months in extensive-stage SCLC and stage-III NSCLC patients, respectively. The median OS was 38(95%CI 0 – 84.51), 11(95% CI 0.93-21.06), and 20-months in limited-stage SCLC, extensive-stage SCLC, and stage-III NSCLC patients, respectively. A single-center study showed that the median PFS and OS in extensive-stage SCLC were six and 14.9 months, respectively[37] In the setting of stage-III NSCLC, data from the US showed a median OS of 13.2-21 and 14.8-18months in patients receiving chemotherapy and chemoradiotherapy, respectively [38,39] Data from Turkey and Brazil showed 3-year OS rates of 27% and 45.5%, respectively.[40,41]

The economic burden of SCLC and NSCLC is substantial. The costs associated with both entities include diagnostic procedures, treatment (including surgery, chemotherapy, radiation therapy, and targeted therapies), follow-up care, and palliative care[42] These costs can exert enormous economic strains on the patients and their families. Moreover, the HCRU of patients with LC is a significant burden, particularly in advanced-stage cases, due to hospital admissions, ED visits, and long-term medical care[43] The complexity and long-term nature of LC care also exacerbate the financial burden due to the need for specialized cancer centers and the high cost of novel therapies[44] The economic impact extends beyond the direct costs of medical care to include indirect costs such as lost productivity due to illness or premature death[45] To our knowledge, few studies have described the HCRU for the SCLC and NSCLC and showed a substantial economic burden[42,43] In line with these studies, we showed that SCLC and NSCLC exerted a substantial economic burden on KSA regarding direct treatment costs, medical procedures, and hospital admission.

The current study is one of the few reports that describe the clinical characteristics and management of LC in KSA. However, we acknowledge the existence of certain limitations. The small sample size in the present study significantly limits the statistical power of the findings and the generalizability to the broader population of LC patients in KSA. Additionally, the small sample size may not capture the inherent variability within the larger population or represent different subgroups, yielding less precise estimates of survival outcomes. Due to the small and imbalanced number of patients with SCLC compared to NSCLC and the descriptive nature of the REVEAL study, formal or exploratory comparisons of treatment responses between the two groups were not performed. Although the study was multicentre, data were collected from two centres, which only further impacted the generalizability of the findings. The retrospective nature of the study might have increased the risk of selection or misclassification bias. Hence, the findings of this study should be interpreted with caution, and larger prospective studies are needed to validate our findings.

Conclusion

The REVEAL study provides novel insights into the clinical characteristics and management landscape of primary SCLC or stage-III NSCLC in KSA. Our data indicates that the survival outcomes of the patients in KSA remain suboptimal, which calls for improved

availability and accessibility of novel therapies. Further studies with a larger sample size are recommended.

Disclosures

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

None.

Ethics statement

Ethical approval was obtained from the two participating centers' Institutional Review Boards (IRBs) (NGH-Riyadh IRB approval no. SRC21R-010-10 and KFMC-Riyadh IRB approval no. 21-427. As this was a retrospective observational study, informed consent from individual patients was waived by the IRBs**.**

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Citation: Jazieh AR, Bakhribah HM, Elashry H,et al. Presentation, management patterns and outcome of small cell lung cancer and stage III non-small cell lung cancer in Saudi Arabia: a multicentre retrospective observational study (REVEAL Study). *J Cancer Prev Curr Res.* 2025;16(4):107–116.
DOI: 10.15406/jcpcr.2025.16.00587