

Oncologic Emergencies in Lung Cancer Patients and the Effects of SARS-COV2 Pandemic

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Background: Lung cancer is one of the most frequent neoplasms and is associated with serious oncologic emergencies (OE). We performed a retrospective study to characterize OE in lung cancer patients admitted to the pulmonology department to determine the effects of the SARS-CoV2 pandemic.

Materials and Methods: A total number of 82 patients were admitted with an emergency, mostly brain metastasis (n=37; 45.1%), followed by superior vena cava syndrome (n=13; 15.9%), cardiac tamponade (n=7; 8.5%), large pleural effusion (n=7; 8.5%), severe pulmonary embolism (n=6; 7.3%), spinal cord syndrome (n=6; 7.3%), massive hemoptysis (n=3; 3.7%), stridor (n=2; 2.4%) and atelectasis (n=1; 1.2%). Clinical and pathological data were retrieved from clinical charts including demographic information, smoking status, cancer histology, clinical stage at diagnosis, anticancer treatment, time between LC diagnosis until the OE, outcomes of OE treatment, and overall survival after OE.

Results: The predominant histology was adenocarcinoma (n=59; 71.9%) and 86.8% of the patients (n=71) were in stage IV. OE was the disease presentation in 45.2% (n=37) and 6-month mortality was 75.6%. Neurologic emergencies were associated with a lower risk of 6-month mortality compared to cardiovascular and respiratory [OR 0.255 (CI 0.72-0.90), p=0.035]. Younger patients (p=0.011), metastatic disease (p=0.02), no cancer treatment (p<0.001), and small cell carcinoma (SCLC) (p=0.016) had a shorter time between cancer diagnosis and the event.

Conclusion: OE occurred mostly in men with metastatic adenocarcinomas. Younger patients, SCLC, metastatic disease, and no cancer treatment were associated with a shorter time between lung cancer diagnosis until the occurrence of an OE and brain metastasis with a better prognosis. There were no differences between patients admitted in 2019 and 2020 that could be related to the access to healthcare services during the SARS-COV2 pandemic.

Keywords: Lung cancer; Oncologic emergencies; SARS-COV2; Pandemic

INTRODUCTION

As the number of patients with cancer increases and improvements in overall survival are achieved, the diagnosis of oncologic emergencies (OE) becomes more frequent (1,2). Lung cancer (LC) is a common neoplasm

and the type of cancer associated with more OE, that can manifest at diagnosis or during the disease (3-5). An OE is an acute event that results directly or indirectly from the primary tumor or the metastases, including complications related to cancer treatments and paraneoplastic syndromes

(6). They are usually classified as metabolic, hematologic, structural, or treatment-related (7,8). Presentation can be subtle, during days or weeks, or manifest over a few hours, requiring early recognition, diagnosis, and timely management to avoid permanent damage or death (1,4,7). In LC, structural OE is caused by compression or invasion of thoracic structures by the primary tumor or metastasis and is the most frequent event (7). A partial or complete obstruction causes superior vena cava syndrome (SVCS) due to compression, invasion, or thrombosis of the vessel. Clinical symptoms include dyspnea, cough, facial edema, hoarseness, and collateral venous circulation. Lung cancer is the most prevalent malignant cause (3,4,7,8). Spinal cord syndrome can develop in about 10% of cancer patients and is characterized by back pain that worsens when lying down (8).

These symptoms are usually associated with motor, sensory, or autonomic neurological deficits, and paraplegia can occur if diagnosis and treatment are delayed (3-5,7). Regarding cardiac OE, malignant pericardial effusion is the main consequence of metastatic heart disease (9). It can be asymptomatic or present with dyspnea, chest pain, or palpitations, and the Beck triad might be seen in rapidly accumulating effusions, revealing muffled heart sounds, hypotension, or increased jugular venous pressure (3,4,7,8). Neurologic OE such as increased intracranial pressure or seizures is usually caused by brain metastasis that causes vasogenic oedema and can occur in 25% of cancers. Most common symptoms are headache, nausea, vomiting, focal deficits, or behavioral changes (4,8,10).

Literature also states that massive hemoptysis is an emergency that can lead to life-threatening situations due to airway obstruction, aspiration, respiratory failure, or hypovolemic shock, and is associated with a 60% mortality in LC patients (3,4,8). Concerning respiratory OE, stridor results from upper airway obstruction from intraluminal tumor growth or extrinsic compression (3,4,8). Large malignant pleural effusions and atelectasis are frequent in LC, representing a frequent cause of respiratory failure (3). Pulmonary embolism is also a common complication in all cancer patients and these events are the second cause of

death related to severe circulating obstruction causing respiratory failure and right ventricle dysfunction (3). Despite previous studies that found that cancer patients require frequently emergency care due to complications related to the disease (3), there is little data about OE in LC patients and even less regarding the prognosis and survival associated with each emergency. On the other hand, we currently lack significant data on the impact of the SARS-COV-2 pandemic on the diagnosis, treatment, and patient visits in pulmonology departments for all causes, including OE.

MATERIALS AND METHODS

We performed a retrospective study to characterize OE in patients with LC admitted to the Pulmonology Department of Hospital de Braga from January 2019 to December 2020 and to determine the effects of the SARS-COV2 pandemic on these patients. In this study, we included all patients admitted with the following OE: symptomatic brain metastasis, SVCS, spinal cord syndrome, cardiac tamponade, stridor, massive hemoptysis, atelectasis, severe pulmonary embolism, and large pleural effusion.

Data collection

Clinical and pathological data were retrieved from clinical charts including demographic information, smoking status, cancer histology, clinical stage at diagnosis, anticancer treatment, time between LC diagnosis until the OE, outcomes of OE treatment, and overall survival after OE.

Ethics

The study received approval from the Ethical Commission and the Confidentiality of Health Information Commission of Hospital de Braga.

Statistical analyses

Statistical analyses were performed with SPSS® software. The T-test or Mann-Whitney test was used to compare independent continuous variables and the Chi-square for comparison between proportions in categorical variables. The univariate and multivariable conditional logistic regression model was used to estimate the

association between relevant clinical variables and 6-month mortality and results were presented as odds ratios (OR) and 95% confidence intervals. Two-sided *P*-values <0.05 were considered statistically significant.

RESULTS

From January 2019 to December 2020, eighty-two patients were admitted with an OE to the Pulmonology Department of Braga Hospital, that corresponded to 45% of all LC patients. The patient's demographic and oncological data are depicted in Table 1. In this study cohort median age was 66 years old (IQR 58.5-71.0), 73.1% (n=60) of the population were male and 80.5% (n=66) had a smoking history. Regarding OE, the most frequent were neurologic, including patients admitted with acute motor or sensitive deficits or seizures caused by brain metastases (n=37; 45.1%). They were followed by SVCS (n=13; 15.9%), cardiac tamponade (n=7; 8.5%), large pleural effusion (n=7; 8.5%), severe pulmonary embolism (central, bilateral, hemodynamic instability) (n=6; 7.3%), spinal cord syndrome (n=6; 7.3%), massive hemoptysis (n=3; 3.7%), stridor (n=2; 2.4%) and pulmonary atelectasis (n=1; 1.2%). Concerning LC histology, the most frequent was adenocarcinoma (n=59; 71.9%), followed by SCLC (n=11; 13.4%), squamous cell carcinoma (n=7; 8.5%), adenosquamous carcinoma (n=2; 2.4%), solitary fibrous tumor (n=1; 1.2%) and poorly differentiated neuroendocrine tumor (n=1; 1.2%). The majority of patients (n=71; 86.8%) were diagnosed at stage IV, followed by IIIB (n=7; 8.5%), IIC (n=2; 2.4%), IA (n=1; 1.2%) and IIA (n=1; 1.2%).

Specifically about OE, they were the first manifestation of LC in 45.2% (n=37) of cases, and in the remaining (n=45; 54.8%) median time from LC diagnosis until OE was 12 months. In this group, concerning LC treatment, 28% (n=23) of the patients had an OE during first-line treatment, 11% (n=9) in second-line, 9.8% (n=8) had not started any treatment, 3.7% (n=3) during third-line and 2.4% (n=2) in a fifth-line. Regarding OE treatment outcomes, the majority of patients (n=54, 65.9%) achieved a clinical improvement, while 17.1% (n=14) remained the same, 2.4% (n=2) became worse than admission and 14.6% (n=12) died during hospitalization. In this cohort,

observing the survival data after the OE, only 47% of the patients were alive 3 months after the event and 24.4% at 6 months.

Table 1. Clinical and oncologic variables of lung cancer patients admitted with an oncologic emergency

Variables		
Age, median (IQR), years, at LC diagnosis	66	(58.5-71.0)
Gender, n (%)		
Male	60	(73.1%)
Female	22	(26.9%)
Smoking habits, n (%)		
Former smoker	47	(57.3%)
Smoker	19	(23.2%)
Non-smoker	16	(19.4%)
Oncologic emergency, n (%)		
Brain neurologic	37	(45.1%)
SVCS	13	(15.9%)
Cardiac tamponade	7	(8.5%)
Large pleural effusion	7	(8.5%)
Severe pulmonary embolism	6	(7.3%)
Acute spinal cord syndrome	6	(7.3%)
Massive hemoptysis	3	(3.7%)
Stridor	2	(2.4%)
Pulmonary atelectasis	1	(1.2%)
Histology, n (%)		
Adenocarcinoma	59	(71.9%)
Small cell lung carcinoma	11	(13.4%)
Squamous cell carcinoma	7	(8.5%)
Adenosquamous carcinoma	2	(2.4%)
Solitary fibrous tumor	1	(1.2%)
Poorly differentiated neuroendocrine tumor	1	(1.2%)
Stage at lung cancer diagnosis, n (%)		
Stage IV	71	(86.8%)
Stage IIB	7	(8.5%)
Stage IIC	2	(2.4%)
Stage IA	1	(1.2%)
Stage IIA	1	(1.2%)
Moment of the OE, n (%)		
At LC diagnosis	37	(45.2%)
During the disease	45	(54.8%)
LC treatment		
1 st line	23	(28.0%)
2 nd line	9	(11.0%)
No treatment	8	(9.8%)
3 rd line	3	(3.7%)
5 th line	2	(2.4%)
Outcome of OE treatment, n (%)		
Clinical improvement	54	(65.9%)
Same condition	14	(17.2%)
Died	12	(14.7%)
Worse	2	(2.4%)
Survival after OE, n (%)		
At 3 months	38	(47.0%)
At 6 months	20	(24.4%)

Abbreviations: IQR, interquartile range; SVCS, superior vena cava syndrome;

In a multivariate Cox regression analysis, we found that neurologic OE, which included mainly symptomatic brain metastases, was associated with a lower risk of 6-months mortality compared to cardiovascular and respiratory OE, regardless of gender, age, stage, histology, smoking status, and cancer treatment [OR 0.255 (CI 0.72-0.90), $p=0.035$], as seen in table 2.

Table 2. Binary logistic regression analysis for 6-month mortality in lung cancer patients with an OE

Variables	6-months mortality		
	N	OR (95% CI)	P*
Age			
<66	39	Referent	
≥66	43	0.72 (0.2-2.4)	0.600
Gender			
Male	60	Referent	
Female	22	1.53 (0.2-10.4)	0.659
Histology			
NSCLC	68	Referent	
SCLC	11	0.28 (0.0-1.9)	0.190
Others	3	-	-
Smoking			
Non smoker	16	Referent	
Smoker/ex	66	0.62 (0.1-5.8)	0.680
Stage at LC diagnosis			
Non metastatic	12	Referent	
Metastatic	70	0.35 (0.1-2.1)	0.258
Treatment at OE			
No	45	Referent	
Yes	37	0.41 (0.1-1.5)	0.172
Type of OE			
Cardiovascular	26	Referent	
Neurologic	43	0.25 (0.1-0.9)	0.035
Respiratory	13	0.49 (0.0-2.8)	0.421
Year			
2019	36	Referent	
2020	46	2.07 (0.6-6.7)	0.228

Abbreviations: OE, oncologic emergency; OR, odd-ratio; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer *Multivariate logistic regression

Further data analysis also revealed that younger patients had a shorter time between LC diagnosis and the occurrence of an OE compared with older patients

($p=0.011$), as well as in SCLC compared to NSCLC ($p=0.016$), metastatic disease compared to local disease ($p=0.02$) and in those without previous cancer treatment ($p<0.001$), as described in Table 3.

Table 3. Analysis of relevant clinical variables and time since lung cancer diagnosis until OE

	Time until OE (months)		
Variables	N	Mean (95% CI)	P
Age			
<66	39	3.95 (1.93-5.96)	0.011*
≥66	43	9.18 (4.45-13.91)	
Gender			
Male	60	7.63 (4.1-11.1)	0.429*
Female	22	3.95 (0.8-7.09)	
Histology			
NSCLC	68	7.65 (4.5-10.8)	0.016*
SCLC	11	1.36 (0.0-3.5)	
Stage at LC diagnosis			
Non metastatic	12	13.67 (7.8-19.5)	0.002*
Metastatic	70	5.44 (2.5-8.4)	
Treatment at OE			
No treatment	45	0.38 (0.1-0.7)	<0.001**
Systemic Therapy	35	13.86 (8.6-19.1)	
SBRT	2	21.50 (0.0-53.3)	
Type of OE			
Cardiovascular	26	5.6 (1.8-9.3)	0.551**
Neurologic	43	8.0 (3.4-12.6)	
Respiratory	13	4.3 (1.9-6.7)	
Year			
2019	36	1.0 (0.1-8.3)	0.670*
2020	46	1.5 (0.1-10.3)	

Abbreviations: OE, oncologic emergency; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SBRT, stereotactic body radiation therapy; * Mann-Whitney U test ** One-way Anova

To answer to another aim of this study we performed a comparative analysis between the two groups, patients admitted in 2019 and 2020. We found no differences in the following variables: age ($p=0.712$), gender ($p=0.269$), past smoking history ($p=0.584$), histology ($p=0.057$), OE as first manifestation of LC ($p=0.913$), time between diagnosis and OE ($p=0.670$), stage ($p=0.276$), type of OE ($p=0.733$), and 6-months mortality ($p=0.741$), as depicted in Table 4.

Table 4. Comparison between lung cancer patients admitted in 2019 and 2020

Variables	Patients 2019 (N=36)	Patients 2020 (N=46)	P
Age at LC diagnosis, median (IQR), years	65.0 (54.8-71.8)	66.5 (59.8-71.0)	0.712*
Gender, n (%)			0.269**
Male	26 (72)	34 (74)	
Female	10 (28)	12 (26)	
Smoking history, n (%)			0.584**
Yes	28 (78)	38 (83)	
No	8 (22)	8 (17)	
Histology, n (%)			0.057**
NSCLC	34 (94)	37 (80)	
SCLC	2 (6)	9 (20)	
OE as presentation of lung cancer, n (%)	16 (44)	21 (46)	0.913**
Time between diagnosis and OE, median (IQR), months	1.0 (0.1-8.3)	1.5 (0.1-10.3)	0.670*
Stage, n (%)			0.276**
Metastatic	29 (81)	41 (89)	
Non-metastatic	7 (19)	5 (11)	
Type of oncologic emergency, n (%)			0.733**
Neurologic	18 (50)	25 (54)	
Respiratory	5 (14)	8 (17)	
Cardiovascular	13 (36)	13 (28)	
Mortality at 6 months (alive), n (%)	9 (25)	13 (28)	0.741**

Abbreviations: IQR: interquartile range; OE, oncologic emergency; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

* T-test; ** Chi-square test

DISCUSSION

OE are frequent and unfavorable events in cancer patients (3). There are few studies about this subject and most of the literature reports very heterogeneity, including patients with all cancer types and all admission motives. This study describes clinical and oncological characteristics and outcomes in LC patients admitted with an OE for two years. Our results are in agreement with previous data as we demonstrated that they are a common cause of hospital admission in this population. Outcomes are consistent with former findings: OE was the third cause of admission in emergency services in cancer patients and included mainly spinal cord compression, symptomatic brain metastases, and SVCS, right after uncontrolled symptoms and side effects related to treatments (11). Furthermore, in a prospective study, Yates and Barret (12) found that LC patients corresponded to the majority of emergency admissions (25%), and Wallace et al. (13) confirmed the same results. Later, Kim et al. (2), showed that LC was the

most prevalent neoplasm requiring emergency admission for any reason, with an increased 2-fold higher odds of in-hospital mortality than other types of cancer.

In a retrospective study performed exclusively on lung cancer (LC) patients in 2014, Kotajima et al. (5) demonstrated that most of the hospital admissions were related to direct invasion or distant metastases. These included intrathoracic invasion, airway obstruction, massive hemoptysis, pleuritis or carcinomatous pericarditis, respiratory failure, as well as brain and bone metastases.

Regarding patient characteristics, Leak et al. (14) analyzed all cancer patients who died in an emergency department. They found a majority of males (62,5%), a median age of 66 years old, and a predominance of LC (36.7%). Tanriverdi et al. also showed that OE represented 55% of the admissions and occurred mostly in men (65%), those over 65 years old (52%), and a clear predominance of LC (32%) or lung metastasis (30%). This retrospective

study also revealed that most common OE were complications related to local compression by malignant masses, including spinal cord syndrome and symptomatic brain metastasis, the majority of patients had metastatic disease (53%) and were under palliative chemotherapy (25%) (15). This information is in concordance with our results.

We observed that neurologic OE, which included patients with focal neurologic deficits or seizures resulting from brain metastases, was the most common cause of admission. These findings are in agreement with literature that reports this is one of the most common sites of LC metastases, that can be present at diagnosis or during the disease (16). Moreover, LC is responsible for approximately 50% of all brain metastasis cases which are very difficult to manage, contributing to high rates of mortality in LC (17).

Concerning the second most frequent OE, SVCS, LC is the most common cancer, and SCLC the histologic type more often associated, due to the presence of central thoracic masses with a high growth rate (7-18). This is in agreement with our data which revealed that 38% of the patients admitted with this OE had SCLC, rising to 50% when SVCS was the first manifestation of cancer (62% of the cases), with a predominance of metastatic stage (92%). Despite clinical improvement achieved in 85% of the patients with OE treatment, only 30% were alive 6 months after the event.

In our cohort cardiac tamponade corresponded to 8.5% of the OE and occurred mostly as the first manifestation of cancer (71.4%) in non-smokers (42.9%), and females (57%) with a median age of 51 years old. The histologic type was adenocarcinoma (100%), 71.4% had molecular mutations, and all patients presented clinical improvement with OE treatment. Although they were all in stage IV, 71.5% were alive 6 months after the event. There is little scientific literature regarding specifically cardiac tamponade in LC patients. However, previous studies described a predominance of LC (52.4%) as the main cause of malignant pericardial disease compared to breast,

melanoma, or hematologic malignancies (9,19). Other authors reported that metastatic pericardial disease was detected in up to 20% of cancer autopsies (9). Moreover, malignant pericardial effusion can occur in 20% to 34% of cancer patients, and cardiac tamponade can be related to the direct involvement of the disease, radiation, or chemotherapy treatments (7). Nevertheless, in thoracic tumors like breast, lung, or mediastinal lymphoma, infections related to immunosuppression or autoimmune diseases can also lead to pericardial effusion (19). Regarding survival, previous findings revealed that one-third of the patients died as a consequence of such involvement, and the overall prognosis was poor, with a median survival time of 130-140 days (7-9). However, this data is in disagreement with our results.

Information available in the literature concerning clinical outcomes in different OEs is very sparse, especially about which patient's characteristics are associated with better or worse outcomes. In our study, in a multivariate analysis, neurologic emergencies were identified as an independent predictor factor for longer survival after the OE, reflecting a better prognosis compared to cardiovascular or respiratory emergencies. Fortunately, they represented most of the admissions. This result might be explained by the fact that the majority of these patients (65%) were treated with dexamethasone and brain radiotherapy and presented significant clinical improvement (60%) after treatment. Another relevant factor was that most of the tumors were adenocarcinomas (86.5%) with molecular mutations (43.8%). This allowed the treatment with tyrosine kinase inhibitors, capable to pass the blood-brain barrier and reduce or eliminate brain metastasis, improving neurological symptoms and survival.

On the other hand, our data revealed that younger age, SCLC, metastatic disease, and no previous cancer treatment were associated with less time between LC diagnosis and OE occurrence. Considering the low survival after OE in this cohort, these patients seemed to have the worst prognosis. These findings can probably be

corroborated by the fact that these conditions are commonly associated with a more aggressive disease. Therefore, careful attention should be given at the time of LC diagnosis, especially in patients with these conditions such as in SCLC, metastatic disease as well as tumor relation with anatomic structures. This is an attempt to predict possible complications and anticipate adverse events, without forgetting to educate patients and families about warning signs and red flags. We found no statistical differences in relevant clinical variables between patients admitted before and during the SARS-COV2 pandemic, despite constraints felt worldwide in accessing healthcare services, so we can suppose that patients with these serious conditions continued to seek medical help.

We recognize some limitations in our study as this was a single-center, retrospective, observational study with a limited sample size and included mostly structural OE. However, data available in the literature concerning this matter is very sparse, so we consider that our results are useful as far as they highlight the frequency of OE in pulmonology practice, are probably representative of this type of OE in LC patients, and demonstrate the importance of proper medical care to enhance patient outcomes.

CONCLUSION

As the cancer burden increases, OE in LC patients is more frequent and can occur in previously unknown malignancies or as complications during the disease. Due to improvements in LC diagnosis and treatment in recent years, nowadays patients have longer overall survival. However, in this study, the occurrence of an OE was associated with low survival. Despite this, our results showed that neurologic emergencies were associated with a better prognosis compared to cardiovascular or respiratory, but younger age, SCLC, metastatic disease, and no previous cancer treatment were associated with less time between LC diagnosis until the OE. Moreover, we compared a non-pandemic and a pandemic year and found no differences in relevant clinical variables that could be related to the access of LC patients to healthcare services

during the SARS-COV2 pandemic. Nevertheless, we consider that prompt recognition of an OE and its management requires experience and often a multidisciplinary evaluation in specialized centers, in an early, timely way. The implementation of the correct treatment as well as proper palliative care can change the course of the disease in LC patients.

Declaration of Conflicting Interests

All authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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