Original Article

Dyspnea in patients with stage IV non-small cell lung cancer: a population-based analysis of disease burden and patterns of care

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Background: Patients with metastatic non-small cell lung cancer (NSCLC) experience significant morbidity with dyspnea being a common symptom with a prevalence of 70%. The objective of this study was to determine factors associated with a moderate-to-severe dyspnea score based on the Edmonton Symptom Assessment System (ESAS), as well as resultant patterns of intervention and factors correlated to intervention receipt.

Methods: Using health services administrative data, we conducted a population-based study of all patients diagnosed with metastatic NSCLC treated from January 2007 to September 2018 in the province of Ontario. The primary outcomes of interest are the prevalence of moderate-to-severe dyspnea scores, and the receipt of dyspnea-directed intervention. Differences in baseline characteristic between moderate-to-severe dyspnea and low dyspnea score cohorts were assessed by comparative statistics. Predictors of intervention receipt for patients with moderate-to-severe dyspnea scores were estimated using multivariable modified Poisson regression.

Results: The initial study cohort included 13,159 patients diagnosed with metastatic NSCLC and of these, 9,434 (71.7%) reported a moderate-to-severe dyspnea score. Compared to patients who did not report moderate-to-severe dyspnea scores, those who reported a moderate-to-severe dyspnea score were more likely to complete a greater number of ESAS surveys, be male, have a higher Elixhauser comorbidity index (ECI) score, and receive subsequent systemic therapy after diagnosis. Most patients with a moderate-to-severe dyspnea score received intervention (96%), of which the most common were palliative care management (87%), thoracic radiotherapy (56%) and thoracentesis (37%). Multivariable regression identified older patients to be less likely to undergo pleurodesis. Thoracentesis was less common for patients living in rural and non-major urban areas, lower income areas, and earlier year of diagnosis. Receipt of thoracic radiotherapy was less common for older patients, females, those with ECI ≥4, patients living in major urban areas, and those with later year of diagnosis. Finally, palliative care referrals were less frequent for patients with ECI ≥4, age 60–69, residence outside of major urban areas, earlier year of diagnosis, and lower income areas.

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Conclusions: Dyspnea is a prevalent symptom amongst patients with metastatic NSCLC. Subpopulations of patients with moderate-to-severe dyspnea scores were in which inequities may exist in access to care that require further attention and evaluation.

Keywords: Non-small cell lung cancer (NSCLC); dyspnea; Edmonton Symptom Assessment System (ESAS); population-base; metastatic

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Introduction

In 2020, lung cancer accounted for 11% of all new cancer globally (1). As most cases are locally advanced or metastatic at presentation (2), it remains the most common cause of cancer-related mortality, representing 18% of all cancer deaths worldwide. The morbidity of lung cancer is also significant; symptom burden commonly includes dyspnea, fatigue, distress, cough, pain, hemoptysis, and constipation (1,3). In particular, dyspnea has been characterized as a predominant symptom experienced by this patient population, with a reported prevalence of 70% in all lung cancer patients (4).

The use of patient reported outcomes (PROs) within the oncology community is becoming more prominent, with applications in routine clinical practice as well an expanding role as an endpoint within clinical studies (5,6). The Edmonton Symptom Assessment System (ESAS) is a validated PRO tool used ubiquitously throughout cancer centers in Ontario, Canada, typically conduced at each outpatient visit (7). Its use has been associated with increased referrals to palliative care services, as well as improved overall survival (8,9).

The provincial implementation of the ESAS tool allows for a unique opportunity to quantify and assess the symptom burden at the population level, and we have previously reported the overall symptom distribution of stage IV lung cancer patients, as measured through ESAS (10). In the current study, we focus on the subset of metastatic lung cancer patients reporting a moderate-to-severe dyspnea score, with the aim to establish factors associated with dyspnea, as well as characteristics associated with the use of interventions commonly used to treat dyspnea in lung cancer. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-919/rc).

Highlight box

Key findings

- 72% prevalence of moderate-severe dyspnea in stage IV lung cancer patients.
- Most patients with moderate-severe dyspnea receive intervention (96%), most commonly palliative care, radiotherapy, and thoracentesis.
- Patients with moderate-to-severe are less likely to receive intervention if living in rural areas, lower income neighborhoods, and neighborhoods with higher marginalization indices.

What is known and what is new?

- Dyspnea is a prevalent symptom in late stage lung cancer patients.
- The current study describes the magnitude of the problem, patterns of intervention, and identifies patient risk factors at risk for not receiving appropriate therapy.

What is the implication, and what should change now?

- Patients at risk of not receiving necessary dyspnea directed therapy require early identification and attention for appropriate management.

Methods

Study cohort and data sources

The details of our data sources and methods have been described previously (10). Briefly, we queried the provincial Institute for Clinical Evaluative Sciences (ICES) database for all eligible patients with available ESAS information. We included all patients diagnosed with stage IV lung cancer between January 2007 and September 2018 as identified in the 2020 Ontario Cancer Registry (OCR) using the International Classification of Disease for Oncology (ICD-O) topography codes ICD-O-3: C34.0-34.4, C34.8, and C34.9. Only non-small cell lung cancer (NSCLC) histologies were included in the current analysis. Patients were excluded if they were under the age of 18 or over 99, had less than 6 months of follow-up without death,

or had an additional diagnoses of cancer 5 years preceding their NSCLC diagnosis or up to the end of follow-up or death. This study conforms to the provisions of the Declaration of Helsinki (as revised in 2013). This study was approved by the Sunnybrook Health Sciences Centre research ethics board (REB # 2138-2019) and adhered to data confidentiality and privacy policies of the Institute for Clinical Evaluative Sciences (ICES). Individual consent for retrospective analysis was waived.

Covariates and outcomes

All baseline covariates were measured at the time of diagnosis, including age and sex. Immigration status was defined as "immigrant" for patients who immigrated to or held refugee status in Canada. The Rurality Index scores a patient's primary place of residence on a scale of 0–100 depending on population size, density, and health care resource availability. An increasing score represents more rural inhabitation, with a score of 0–9, 10–44, and 45+ corresponding to "major urban", "non-major urban", and "rural" inhabitation, respectively. The neighborhood income quintiles were categorized according to the median income of a patient's postal code. Medical comorbidities were assessed using the Elixhauser comorbidity index (ECI) based on health service usage within 24 months of NSCLC diagnosis. The ECI was selected as it was an index specifically designed to be used with administrative databases and derived from International Classification of Diseases (ICD) codes (11). Low comorbidity burden was defined as 0–3, whereas greater values indicated a high burden (12,13). Quintiles were assigned for patients based on the four dimensions of the Ontario Marginalization Index: ethnic diversity, residential instability (home security and ownership), material deprivation (income, education, and single parent families), and dependency (workforce eligibility) (14). Interventions for dyspnea examined include airway stenting, pleurodesis, thoracentesis, thoracic radiotherapy, and palliative care referral.

The primary outcomes of interest were the receipt of interventions at any time from metastatic NSCLC diagnosis to the end of follow-up, as well as the receipt of dyspnea-directed interventions. Endpoints were stratified by the exposure variable of ESAS dyspnea score. A moderate-to-severe dyspnea score was defined as ≥4 out of 10 consistent with our initial report and literature cutoffs; otherwise, patients were considered to have a low score (7,10,15). Furthermore, we characterized the interventions received for patients reporting moderate-to-severe dyspnea score(s) and their association with baseline covariates in an exploratory manner.

Statistical analysis

Baseline characteristics were reported and stratified by patients who reported high and non-moderate-to-severe dyspnea scores. Continuous measures were summarized using means and standard deviations (SDs) or medians and interquartile range (IQR). Categorical variables were reported as frequencies and proportions. Comparisons of variables between the patient strata were performed using Student's *t*-test and chi square testing for continuous and categorical variables, respectively. Potential predictors of intervention receipt were analyzed using multivariable modified Poisson regression modelling with robust error variance. Relevant variables were included a priori based on clinical judgment. Relative risks (RRs) with 95% confidence intervals (CIs) were reported and P values for type-3 tests were used to determine the overall effect of each covariate in the model. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Study cohort

A total of 23,657 patients were diagnosed with stage IV NSCLC between January 2007 and September 2018. Of these, 13,159 patients (55.6%) met our inclusion criteria for this study. From the included patients, 9,434 (71.7%) patients reported a moderate-to-severe dyspnea score at any point in their ESAS evaluations. The median length of follow-up for the entire cohort was 9 months (IQR: 14), and the median number of ESAS surveys was 4 (IQR: 9). Those who reported a moderate-to-severe dyspnea score were more likely to complete more surveys (P<0.001).

Details of patients as stratified by ESAS dyspnea score reporting are summarized in *Table 1*. Compared to patients who did not report moderate-to-severe dyspnea scores, those who reported a moderate-to-severe dyspnea score were more likely to be male, have a higher ECI score, live in less ethnically diverse areas, and receive subsequent systemic therapy after diagnosis. Patients with moderate-to-severe dyspnea scores were also more likely to report comorbid high ESAS depression and pain scores. This cohort was more likely to die during the follow-up period of

Table 1 Baseline characteristics of all patients

Variable	Entire cohort (n=13,159)	Low dyspnea score (n=3,725)	Moderate-high dyspnea score (n=9,434)	P value
Number of ESAS survey completed, mean ± SD	9.09±12.14	6.62±10.39	10.07±12.63	<0.001
Age category (at diagnosis) (years), n (%)				0.139
18 to 59	3,020 (23.0)	847 (22.7)	2,173 (23.0)	
60 to 69	4,353 (33.1)	1,218 (32.7)	3,135 (33.2)	
70 to 79	4,051 (30.8)	1,128 (30.3)	2,923 (31.0)	
80+	1,735 (13.2)	532 (14.3)	1,203 (12.8)	
Sex, n (%)				<0.001
Female	6,426 (48.8)	1,937 (52.0)	4,489 (47.6)	
Male	6,733 (51.2)	1,788 (48.0)	4,945 (52.4)	
Rurality index, n (%)				0.082
Major urban	8,620 (65.5)	2,497 (67.0)	6,123 (64.9)	
Non-major urban	3,518 (26.7)	939 (25.2)	2,579 (27.3)	
Rural	974 (7.4)	274 (7.4)	700 (7.4)	
Missing	47 (0.4)	15 (0.4)	32 (0.3)	
Elixhauser comorbidity index, n (%)				<0.001
Less than 4	12,321 (93.6)	3,533 (94.8)	8,788 (93.2)	
4 or more	838 (6.4)	192 (5.2)	646 (6.8)	
Nearest census based neighbourhood income quintile, n (%)				0.79
Q1	2,817 (21.4)	773 (20.8)	2,044 (21.7)	
Q2	2,961 (22.5)	851 (22.8)	2,110 (22.4)	
Q3	2,573 (19.6)	734 (19.7)	1,839 (19.5)	
Q4	2,451 (18.6)	684 (18.4)	1,767 (18.7)	
Q5	2,317 (17.6)	673 (18.1)	1,644 (17.4)	
Missing	40 (0.3)	10 (0.3)	30 (0.3)	
Deprivation quintile, n (%)				0.549
Q1	2,285 (17.4)	611 (16.4)	1,674 (17.7)	
Q2	2,479 (18.8)	719 (19.3)	1,760 (18.7)	
Q3	2,649 (20.1)	760 (20.4)	1,889 (20.0)	
Q4	2,750 (20.9)	775 (20.8)	1,975 (20.9)	
Q5	2,905 (22.1)	832 (22.3)	2,073 (22.0)	
Missing	91 (0.7)	28 (0.8)	63 (0.7)	
Ethnic concentration quintile, n (%)				<0.001
Q1	2,944 (22.4)	793 (21.3)	2,151 (22.8)	
Q2	2,858 (21.7)	744 (20.0)	2,114 (22.4)	

Table 1 *(continued)*

Table 1 *(continued)*

Variable	Entire cohort (n=13,159)	Low dyspnea score (n=3,725)	Moderate-high dyspnea score (n=9,434)	P value
Q3	2,492 (18.9)	699 (18.8)	1,793 (19.0)	
Q4	2,395 (18.2)	690 (18.5)	1,705 (18.1)	
Q5	2,379 (18.1)	771 (20.7)	1,608 (17.0)	
Missing	91 (0.7)	28 (0.8)	63 (0.7)	
Dependency quintile, n (%)				0.808
Q1	2,058 (15.6)	571 (15.3)	1,487 (15.8)	
Q2	2,290 (17.4)	627 (16.8)	1,663 (17.6)	
Q3	2,437 (18.5)	695 (18.7)	1,742 (18.5)	
Q4	2,717 (20.6)	773 (20.8)	1,944 (20.6)	
Q5	3,566 (27.1)	1,031 (27.7)	2,535 (26.9)	
Missing	91 (0.7)	28 (0.8)	63 (0.7)	
Instability quintile, n (%)				0.326
Q1	1,925 (14.6)	572 (15.4)	1,353 (14.3)	
Q2	2,237 (17.0)	600 (16.1)	1,637 (17.4)	
Q3	2,569 (19.5)	734 (19.7)	1,835 (19.5)	
Q4	2,824 (21.5)	817 (21.9)	2,007 (21.3)	
Q5	3,513 (26.7)	974 (26.1)	2,539 (26.9)	
Missing	91 (0.7)	28 (0.8)	63 (0.7)	
Year of diagnosis, n (%)				0.235
2007 to 2012	5,154 (39.2)	1,429 (38.4)	3,725 (39.5)	
2013 to 2018	8,005 (60.8)	2,296 (61.6)	5,709 (60.5)	
Patients who received systemic therapy* after diagnosis, n (%)				<0.001
None	5,308 (40.3)	1,678 (45.0)	3,630 (38.5)	
Received therapy	7,851 (59.7)	2,047 (55.0)	5,804 (61.5)	
Follow-up time from diagnosis to end of study (months), median (IQR)	9 (4–18)	8 (4–17)	9 (5–18)	<0.001
Died after diagnosis until end of study, n (%)				<0.001
Alive	1,252 (9.5)	448 (12.0)	804 (8.5)	
Died during follow-up	11,907 (90.5)	3,277 (88.0)	8,630 (91.5)	
Time from diagnosis to death (months), median (IQR)	8 (4–15)	7 (4–14)	8 (4–16)	<0.001
Patients with High ESAS Depression score, n (%)				<0.001
No high ESAS score	3,762 (28.6)	1,781 (47.8)	1,981 (21.0)	
At least one high ESAS score	9,397 (71.4)	1,944 (52.2)	7,453 (79.0)	
Patients with High ESAS Pain score, n (%)				<0.001
No high ESAS score	4,151 (31.5)	1,850 (49.7)	2,301 (24.4)	
At least one high ESAS score	9,008 (68.5)	1,875 (50.3)	7,133 (75.6)	

*, systemic therapy refers to chemotherapy, targeted therapy, or immunotherapy. ESAS, Edmonton Symptom Assessment System; SD, standard deviation; IQR, interquartile range.

Table 2 Interventions for dyspnea

Variable	Low dyspnea (n=3,725)	Moderate-high dyspnea score (n=9,434)	Total (n=13,159)	P value
Airway stenting, n (%)				0.172
No	3,721 (99.9)	9,413 (99.8)	13,134 (99.8)	
Yes	4 (0.1)	21 (0.2)	25 (0.2)	
Pleurodesis, n (%)				<0.001
No	3,564 (95.7)	8,697 (92.2)	12,261 (93.2)	
Yes	161 (4.3)	737 (7.8)	898 (6.8)	
Thoracentesis, n (%)				<0.001
No	2,802 (75.2)	5,915 (62.7)	8,717 (66.2)	
Yes	923 (24.8)	3,519 (37.3)	4,442 (33.8)	
Thoracic radiation therapy, n (%)				<0.001
No	2,019 (54.2)	4,136 (43.8)	6,155 (46.8)	
Yes	1,706 (45.8)	5,298 (56.2)	7,004 (53.2)	
Palliative assessment, n (%)				<0.001
No	643 (17.3)	1,277 (13.5)	1,920 (14.6)	
Yes	3,082 (82.7)	8,157 (86.5)	11,239 (85.4)	
No intervention for shortness of breath, n (%)				<0.001
Received therapy	3,445 (92.5)	9,040 (95.8)	12,485 (94.9)	
No intervention	280 (7.5)	394 (4.2)	674 (5.1)	

this study, although the timeframe from diagnosis to death is longer for those with moderate-to-severe dyspnea scores who died compared to those who died and did not report a moderate-to-severe dyspnea score.

Interventions and association with dyspnea scores

Table 2 reports the distribution of interventions for dyspnea in patients stratified by high and low reported dyspnea ESAS scores. Overall, most stage IV patients received intervention at some point during their diagnosis (94.9%). Patients with moderate-to-severe dyspnea scores were more likely to receive interventions with the potential to improve dyspnea, including pleurodesis, thoracentesis, thoracic radiotherapy, and palliative care assessment compared to patients without a high score (P<0.001 for all). Airway stenting was not significantly different between the two groups however, and the overall incidence of its use was low (0.2%). Of the patients who reported a high ESAS dyspnea score, the most common interventions were palliative care referral (86.5%), thoracic radiotherapy (56.2%), and thoracentesis (37.3%).

Factors associated with receipt of therapy in moderate-to-severe dyspnea score patients

When looking at the proportion of patients with moderate-to-severe dyspnea scores who did not receive intervention, they completed fewer ESAS surveys (P<0.001), lived in rural areas (P<0.001), and were more likely to be from neighborhoods with lower income quintiles (P=0.004). There were differences in the distribution of patient quintiles amongst all four domains of the Ontario Marginalization Index, with those who did not receive intervention more likely to live in areas with higher deprivation (P=0.001), dependency (P<0.001), instability (P=0.007), and less ethnic diversity (P=0.004). Of patients who died, non-intervention patients had a shorter time to death from diagnosis, with a median time of 4 versus 8 months for patients who received intervention (Table S1).

The results of the multivariable modified Poisson regressions are reported in *Table 3*. In general, interventions

Table 3 Multivariable modified poisson regression of intervention receipt and baseline characteristics

Variable	Pleurodesis (95% CI)	Thoracentesis (95% CI)	Thoracic radiotherapy (95% CI)	Palliative assessment (95% CI)
Age group (years)				
60–69	0.762 (0.635–0.914)*	0.933 (0.87–1.002)*	0.994 (0.95–1.041)**	0.977 (0.957–0.998)
70–79	0.812 (0.676–0.975)	0.942 (0.877–1.013)	0.925 (0.881–0.971)	0.987 (0.966–1.009)
80 and older	0.762 (0.597–0.973)	1.038 (0.952–1.132)	0.895 (0.839–0.956)	0.976 (0.95–1.004)
18–59 (ref)				
Sex				
Female	0.904 (0.786–1.04)	1.001 (0.95–1.055)	0.944 (0.911–0.978)*	1.012 (0.996–1.028)
Male (ref)				
Elixhauser comorbidity index				
4 or more	1.01 (0.765–1.335)	0.936 (0.839–1.044)	0.869 (0.801–0.943)**	0.96 (0.926–0.996)*
Less than 4 (ref)				
Rural residence				
Non-major urban	0.867 (0.734–1.025)	0.778 (0.729–0.83)**	1.01 (0.969–1.052)**	0.953 (0.935–0.971)**
Rural	1.107 (0.858–1.428)	0.748 (0.665–0.842)	1.145 (1.077–1.217)	0.869 (0.833–0.906)
Major urban (ref)				
Income quintile				
Q1	1.054 (0.841–1.321)	0.849 (0.782–0.921)**	0.967 (0.914–1.024)	0.973 (0.949–0.998)*
Q2	0.944 (0.75–1.187)	0.846 (0.78–0.918)	0.986 (0.933–1.043)	0.964 (0.94–0.989)
Q3	0.943 (0.744–1.195)	0.892 (0.821–0.969)	0.966 (0.911–1.024)	0.996 (0.972–1.021)
Q4	1.191 (0.951–1.493)	0.943 (0.869–1.023)	0.987 (0.931–1.045)	0.985 (0.96–1.011)
Q5 (ref)				
Diagnosis year				
2007–2018	0.983 (0.963–1.004)	1.021 (1.012–1.029)**	0.968 (0.962–0.973)**	1.004 (1.002–1.007)*

*, P value for the overall effect of the variable (type 3 effects) <0.05; **, P value for the overall effect of the variable (type 3 effects) <0.001. CI, confidence interval; ref, reference.

were less likely to be given to older patients, although the use of thoracentesis was not significantly different based on age. Female sex was associated with a lower chance of receiving thoracic radiotherapy [RR =0.944; 95% CI: 0.911–0.978]. Patients with an ECI of ≥4 were also less likely to receive thoracic radiotherapy (RR =0.869; 95% CI: 0.801–0.943) or a palliative care assessment (RR =0.96; 95% CI: 0.926–0.996). Patients living in rural areas were more likely to receive thoracic RT, but less likely to receive thoracentesis or palliative care assessment than patients living in major urban settings. Similarly, patients living in non-major urban areas were less likely to receive thoracentesis than those living in major urban centres. Patients in lower income quintiles were less likely to receive thoracentesis and palliative care assessment, while other interventions had no association with income. The use of thoracentesis and palliative care assessment increased with year of diagnosis, while the use of thoracic radiotherapy decreased.

Discussion

Moderate to severe dyspnea was prevalent in patients with metastatic NSCLC, with 71.7% of patients reporting at least one ESAS dyspnea score ≥4 throughout the course of their follow-up. Several factors may explain this observation.

First, a patient's dyspnea may relate to anatomic factors from lung cancer, including primary disease burden, presence of pleural effusion, and lung obstruction or even collapse. Second, many patients with lung cancer have co-existing pulmonary and/or cardiac morbidities, often as a consequence from a common risk factor, smoking. It has been reported that smokers with chronic obstructive pulmonary disease (COPD) are five times more likely to develop lung cancer than smokers who do not have obstructive airways (16,17). Third, certain side effects from lung cancer therapies manifest as dyspnea, including pneumonitis (radiation/systemic therapy), and pneumonia (chemotherapy). Nevertheless, regardless of etiology, the prevalence of dyspnea in this cohort underscores the importance of intervention for potentially reversible causes.

We observed several factors associated with non-receipt of any intervention in patients who reported a moderate-to-severe dyspnea score. Some of these factors are intuitive, such as ECI score. Patients with more comorbidities may not tolerate or be too frail to benefit from certain interventions, including thoracentesis or pleurodesis. Others however, present more of a concern. In general, more marginalized patients were less likely to receive intervention for their dyspnea despite reporting a high score. Disparity in cancer care in Canada is not a novel concept and is well described in the literature (18,19). Patients with lower socioeconomic status or from marginalized communities are less likely to access necessary care, both due to intrinsic factors, such as lower health literacy to make informed decisions for care, as well as extrinsic factors such as physical access to services. Thus, patients living in areas with higher marginalization scores have greater odds of mortality compared to those living in areas with better scores (20). This inequity has been highlighted in a recent publication by the Canadian Partnership Against Cancer, in which rural and remote inhabitants experienced inequities in lung cancer risk, access to care, and outcomes. Patients in lower income brackets are significantly more likely to smoke, to be diagnosed with stage III or IV disease, and less likely to receive curative surgeries. Native populations in particular have been identified as a high-risk marginalized group (21). Healthcare providers and policymakers should be cognizant of these disparities. Further efforts are required to identify and address barriers to access, ideally with the input of the marginalized cancer population (18).

We also observed a significant association between moderate-to-severe dyspnea scores and patients that live in less ethnically diverse areas. Several studies in the literature support racial disparities that exist in health-related quality of life (QoL), including dyspnea, in the management of lung cancer patients and oncology patients in general (22-24). Vogel *et al.* reported worse intervention related QoL outcomes for African American patients who underwent chemoradiotherapy for stage IIIB lung cancer (22). In a population-level analysis of NSCLC patients who underwent surgery, Poghosyan *et al.* reported worse mental health QoL scores in black patients versus white patients (24). Clinicians must be cognizant of internal biases that may compromise the equity of patient care, such as age or sex, so that the principle of medical justice may be upheld.

Our analysis found that those reporting a moderate-to-severe dyspnea score had a greater number of ESAS surveys completed in a cancer centre, likely related to more outpatient visits to manage their disease and symptoms. Furthermore, pain and depression were comorbid symptoms in this patient cohort, which may all be manifestations of the significant symptom burden and generally poor prognosis that these patients are afflicted with. Andersen *et al.* reported a 36% incidence of moderate and severe depressive symptoms in a prospective observational study of stage IV lung cancer patients (25). Pain can manifest from many etiologies, including bone metastases, chest pain from the primary tumor, pleural effusions, and visceral metastases to organs such as the liver or adrenal glands (26). A previous analysis implementing statistical grouping methods identified clusters of comorbid symptoms in patients with advanced malignancies. Specifically, patients with depression were clustered with anxiety. Pain was clustered with nausea, dyspnea, as well as tiredness, anorexia, and decreased well-being (27). Specific to lung cancer, Choi *et al.* identified three specific clusters, grouping them into intervention-related, lung cancer-related, and psychological, with the latter two clusters having a negative impact on QoL on regression analysis (28). Lou *et al.* observed the clustering of respiratory symptoms with poor sleep and lower QoL (29). Symptom burden and QoL have been shown to have a direct impact on survival. Sloan *et al.* investigated 2,442 NSCLC patients in which a QoL score from 0–100 was measured at least once in the first 6-months of diagnosis. They observed a significant association between decreased survival [hazard ratio (HR) =1.55, P<0.001] with worsening QoL score (30). Similarly, a multi-institutional observational study of 1,790 NSCLC patients revealed that depression symptoms were associated with increased mortality at follow-up for patients with late-stage disease (HR =1.32, P=0.025) (31). Clinicians caring

for patients with advanced lung cancer must stay vigilant of symptomatology beyond the primary complaint and ensure that any additional symptoms are addressed. PRO instruments such as ESAS allow clinicians to systemically assess patients and facilitates holistic patient care.

Interestingly, we also observed an association between moderate-to-severe dyspnea scores and male sex. The association of dyspnea and sex is inconsistent in the literature. A European cross-sectional study of 200 lung cancer patients using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-LC30 questionnaire did not show a significant difference in dyspnea scores between male and female respondents, although numerically, the mean score for males was higher than females (44.7 *vs.* 38.9) (32). Similarly, Lövgren *et al.* did not observe a significant difference in dyspnea scores between men and women with inoperable lung cancer (33). However, other experiences in the general advanced cancer population reported a higher proportion of male patients experiencing dyspnea (34), whereas conversely, our previous analysis of cancer patients in Ontario suggested that dyspnea was more prevalent in female patients (35). One possible explanation for this observation lies in the preponderance of non-smoking females to develop endothelial growth factor receptor (EGFR) mutated lung cancer, which accounts for about 24% of all NSCLC in North and South America, and 50% of never smokers (36). With a negligible smoking history, these patients likely have better baseline pulmonary function and less susceptible to dyspnea because of NSCLC. This is speculative however, given that specific biomarker data is not available from our data sources, and correlative analyses cannot be conducted.

In our multivariable regression analyses, we observed a reduction in the receipt of intervention with increasing patient age, except for palliative care referral and thoracic radiotherapy. Specific to radiotherapy, we observed a lower utilization rate in those with an ECI ≥4 compared to those with a lower score. This presents a point of concern however, because thoracic radiotherapy should not be limited to the most robust patients and may benefit even those with poorer performance statuses. Palliative thoracic radiotherapy has been recommended as an effective, generally well tolerated intervention for symptom control in advanced lung cancer patients. Shorter radiotherapy courses have been associated with less toxicity. Protracted, higher dose courses may be considered in patients with good performance status as evidence suggests potential improvements in survival (37). The optimal radiotherapy utilization rate (ORUR) in lung cancer patients has been an area of active investigation and debate. Population based studies out of Canada (38) and Australia (39) have observed lower than ORURs for lung cancer patients. A systematic review has suggested that the lifetime ORUR for all lung cancer patients is between 61–82%, and that most studies consistently show underutilization. Actuarial utilization rates of radiotherapy in patients with metastatic disease ranged from 17–47% (40). Our results fortunately report a higher utilization rate for palliative thoracic radiotherapy, in that 53.1% of all metastatic NSCLC patients, and 56.1% of those reporting a moderate-to-severe dyspnea score received therapy. However, the results of our regression analysis point towards a decline in thoracic radiotherapy use with later year of diagnosis, even in patients with significant dyspnea. This has been observed by a Surveillance, Epidemiology, and End Results (SEER) analysis of lung cancer patients treated in the United States from the 1970s to 2015 revealed a similar downward trend in radiotherapy utilization in metastatic lung cancer patients overtime (41). The introduction of novel systemic agents such as targeted therapy (TT) or immunotherapy (IO), may in part explain these observations. Given the improved outcomes, tolerability, and efficacy observed with these agents over traditional chemotherapy, clinicians may not feel that thoracic radiotherapy is as necessary (42,43). More importantly however, the risk of toxicity with concomitant administration of radiation and targeted agents has been shown to be increased (44,45). Because of these reasons, we surmise that clinicians may be less inclined to offer thoracic radiotherapy compared to the pre-TT and IO era. Nevertheless, with the advent of stereotactic body radiotherapy (SBRT) techniques and its potential synergy with systemic therapies, this presents the opportunity to provide further benefit for metastatic NSCLC patients with radiotherapy. In particular, the subset of patients with limited, oligometastatic disease could benefit and survive longer and free of disease progression (46,47).

Pulmonary interventions, that is thoracentesis, pleurodesis, and endobronchial stenting were used in less than half of all patients, regardless of dyspnea score. We observed decreased receipt of thoracentesis for patients living in rural areas, as well as those within lower income quintiles. The former may be likely attributed to decreased access to a tertiary center with technical expertise and equipment to perform the procedure. Thoracentesis is a specialized procedure in which operator dependent outcomes may be variable in terms of complications such

as bleeding or pneumothorax. Physician comfort level and resource availability are required for thoracentesis to be performed. Procedures performed in centers located in wealthier, metropolitan areas in the United States were associated with better guideline compliance and survival outcomes (48,49). This may reflect our observations in which patients living in lower income quintiles were less likely to receive thoracentesis. Notably, the use of endobronchial stenting was low amongst the entire cohort at 0.2%. The reason for this is likely multifactorial. Firstly, the indication for stenting applies to just a subset of dyspneic patients with malignant airway obstruction (MAO) which is thought to occur infrequently, with only 80,000 cases a year occurring in the United States (50). Furthermore, *in situ* stents present with a host of complications after prolonged deployment, including stent migration, infection, fracture, and perforation amongst others (51). Lastly, endobronchial stenting is a technically challenging procedure, requiring a high level of training and experience as endorsed by the European Respiratory and American Thoracic Societies (52). As a result, stenting comfort and expertise may be limited to select centres.

Limitations of our study include the risk of selection bias introduced by the nearly 40% ESAS non-completion rate of our initial patient cohort. As observed in our previous report, non-respondents were more likely to be older, have higher ECI scores, and not receive active oncologic therapy (10). This limits the generalizability of the findings of the current study and suggests that the non-ESAS respondents may have not received care at a cancer center in Ontario, where implementation of the ESAS questionnaire was standard. Furthermore, the use of administrative data precludes granular description of interventions. It would be informative to differentiate outcomes stratified by different types of systemic therapy (i.e., IO, chemotherapy, or TT), and radiotherapy techniques and doses. Given that the dates of inclusion of this study precedes the widespread utilization of targeted and immunotherapies, many patients may have received chemotherapy and as such, our observations may not be reflective of a contemporary cohort of metastatic NSCLC patients. Our data also captures a single snapshot of any patient reporting a moderate-to-severe dyspnea score at one time point and does not report on the effects of any interventions received. The differential diagnosis for dyspnea is multifactorial, ranging from cancer progression to pulmonary embolism to panic attacks. Our study, limited by the data source, does not discern etiology, and only captures interventions used to address direct oncologic-related causes of dyspnea such as disease progression or malignant pleural effusion. Furthermore, it is difficult to characterize possible discordance between patient and clinician reported cases of dyspnea which is inherent in using PRO instruments such as ESAS. Lastly, due to the large sample size of our dataset, statistical significance is not necessarily indicative of clinical significance (53). Spurious associations may be observed, such as that between dyspnea and sex or race. Readers should interpret these results within the context of a population-based analysis.

Conclusions

This population-based analysis demonstrates that nearly three quarters of patients with metastatic NSCLC in Ontario report significant dyspnea. Most patients with moderate-to-severe dyspnea scores receive intervention, although disparities exist based on patient and social factors. These data of symptom burden and patterns of care can help inform policymaking and guide the astute clinician in identifying patient populations at risk of suboptimal care.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study conforms to the provisions of the Declaration of Helsinki (as revised in 2013). This study was approved by the Sunnybrook Health Sciences Centre research ethics board (REB # 2138-2019) and adhered to data confidentiality and privacy policies of the Institute for Clinical Evaluative Sciences (ICES). Individual consent for retrospective analysis was waived.

References

1. Whisenant MS, Williams LA, Garcia Gonzalez A, et al. What Do Patients With Non-Small-Cell Lung Cancer Experience? Content Domain for the MD Anderson Symptom Inventory for Lung Cancer. JCO Oncol Pract 2020;16:e1151-60.
2. Morgensztern D, Ng SH, Gao F, et al. Trends in stage distribution for patients with non-small cell lung cancer: a National Cancer Database survey. J Thorac Oncol 2010;5:29-33.
3. Iyer S, Roughley A, Rider A, et al. The symptom burden of non-small cell lung cancer in the USA: a real-world cross-sectional study. Support Care Cancer 2014;22:181-7.
4. Kathiresan G, Clement RF, Sankaranarayanan MT. Dyspnea in lung cancer patients: a systematic review. Lung Cancer (Auckl) 2010;1:141-50.
5. Nic Giolla Easpaig B, Tran Y, Bierbaum M, et al. What are the attitudes of health professionals regarding patient reported outcome measures (PROMs) in oncology practice? A mixed-method synthesis of the qualitative evidence. BMC Health Serv Res 2020;20:102.
6. Brundage MD, Smith KC, Little EA, et al. Communicating patient-reported outcome scores using graphic formats: results from a mixed-methods evaluation. Qual Life Res 2015;24:2457-72.
7. Hui D, Bruera E. The Edmonton Symptom Assessment System 25 Years Later: Past, Present, and Future Developments. J Pain Symptom Manage 2017;53:630-43.
8. Barbera L, Sutradhar R, Earle CC, et al. The impact of routine Edmonton symptom assessment system use on receiving palliative care services: results of a population-based retrospective-matched cohort analysis. BMJ Support Palliat Care 2020;bmjspcare-2020-002220.
9. Barbera L, Sutradhar R, Seow H, et al. The impact of routine Edmonton Symptom Assessment System (ESAS) use on overall survival in cancer patients: Results of a population-based retrospective matched cohort analysis. Cancer Med 2020;9:7107-15.
10. Tjong MC, Doherty M, Tan H, et al. Province-Wide Analysis of Patient-Reported Outcomes for Stage IV Non-Small Cell Lung Cancer. Oncologist 2021;26:e1800-11.
11. Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. Med Care 1998;36:8-27.
12. Jawitz OK, Wang Z, Boffa DJ, et al. The differential impact of preoperative comorbidity on perioperative outcomes following thoracoscopic and open lobectomies. Eur J Cardiothorac Surg 2017;51:169-74.
13. Azzalini L, Chabot-Blanchet M, Southern DA, et al. A disease-specific comorbidity index for predicting mortality in patients admitted to hospital with a cardiac condition. CMAJ 2019;191:E299-307.
14. Matheson FI, Dunn JR, Smith KL, et al. Development of the Canadian Marginalization Index: a new tool for the study of inequality. Can J Public Health 2012;103:S12-6.
15. Oldenmenger WH, de Raaf PJ, de Klerk C, et al. Cut points on 0-10 numeric rating scales for symptoms

included in the Edmonton Symptom Assessment Scale in cancer patients: a systematic review. J Pain Symptom Manage 2013;45:1083-93.
16. Durham AL, Adcock IM. The relationship between COPD and lung cancer. Lung Cancer 2015;90:121-7.
17. Leduc C, Antoni D, Charloux A, et al. Comorbidities in the management of patients with lung cancer. Eur Respir J 2017;49:1601721.
18. Ahmed S, Shahid RK. Disparity in cancer care: a Canadian perspective. Curr Oncol 2012;19:e376-82.
19. Horrill T, Lavoie J, Martin D, et al. Places & Spaces: A Critical Analysis of Cancer Disparities and Access to Cancer Care Among First Nations Peoples in Canada. Witness: The Canadian Journal of Critical Nursing Discourse 2020;2:104-23.
20. Zygmunt A, Tanuseputro P, James P, et al. Neighbourhood-level marginalization and avoidable mortality in Ontario, Canada: a population-based study. Can J Public Health 2020;111:169-81.
21. Cancer CPA. Lung cancer and equity: a focus on income and geography. 2020.
22. Vogel J, Wang X, Troxel AB, et al. Prospective assessment of demographic characteristics associated with worse health related quality of life measures following definitive chemoradiation in patients with locally advanced non-small cell lung cancer. Transl Lung Cancer Res 2019;8:332-9.
23. Han X, Robinson LA, Jensen RE, et al. Factors Associated With Health-Related Quality of Life Among Cancer Survivors in the United States. JNCI Cancer Spectr 2021;5:pkaa123.
24. Poghosyan H, Stock S, Kennedy Sheldon L, et al. Racial Disparities in Health-Related Quality of Life After Lung Cancer Surgery: Findings From the Cancer Care Outcomes Research and Surveillance Consortium. J Thorac Oncol 2015;10:1404-12.
25. Andersen BL, Valentine TR, Lo SB, et al. Newly diagnosed patients with advanced non-small cell lung cancer: A clinical description of those with moderate to severe depressive symptoms. Lung Cancer 2020;145:195-204.
26. Simmons CP, Macleod N, Laird BJ. Clinical management of pain in advanced lung cancer. Clin Med Insights Oncol 2012;6:331-46.
27. McKenzie E, Zhang L, Zaki P, et al. Re-analysis of symptom clusters in advanced cancer patients attending a palliative outpatient radiotherapy clinic. Ann Palliat Med 2019;8:140-9.
28. Choi S, Ryu E. Effects of symptom clusters and depression on the quality of life in patients with advanced lung cancer. Eur J Cancer Care (Engl) 2018;27:10.1111/ecc.12508.
29. Lou VW, Chen EJ, Jian H, et al. Respiratory Symptoms, Sleep, and Quality of Life in Patients With Advanced Lung Cancer. J Pain Symptom Manage 2017;53:250-6.e1.
30. Sloan JA, Zhao X, Novotny PJ, et al. Relationship between deficits in overall quality of life and non-small-cell lung cancer survival. J Clin Oncol 2012;30:1498-504.
31. Sullivan DR, Forsberg CW, Ganzini L, et al. Longitudinal Changes in Depression Symptoms and Survival Among Patients With Lung Cancer: A National Cohort Assessment. J Clin Oncol 2016;34:3984-91.
32. Koch M, Hjermstad MJ, Tomaszewski K, et al. Gender effects on quality of life and symptom burden in patients with lung cancer: results from a prospective, cross-cultural, multi-center study. J Thorac Dis 2020;12:4253-61.
33. Lövgren M, Tishelman C, Sprangers M, et al. Symptoms and problems with functioning among women and men with inoperable lung cancer—a longitudinal study. Lung Cancer 2008;60:113-24.
34. Heedman PA, Strang P. Symptom assessment in advanced palliative home care for cancer patients using the ESAS: clinical aspects. Anticancer Res 2001;21:4077-82.
35. Bubis LD, Davis L, Mahar A, et al. Symptom Burden in the First Year After Cancer Diagnosis: An Analysis of Patient-Reported Outcomes. J Clin Oncol 2018;36:1103-11.
36. Zhang YL, Yuan JQ, Wang KF, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget 2016;7:78985-93.
37. Rodrigues G, Videtic GM, Sur R, et al. Palliative thoracic radiotherapy in lung cancer: An American Society for Radiation Oncology evidence-based clinical practice guideline. Pract Radiat Oncol 2011;1:60-71.
38. Chan J, Brown E, Dennis K, et al. Provincial variations in radiotherapy utilization as a measure of access: A pan-Canadian study. Radiother Oncol 2022;167:122-6.
39. Yap ML, O'Connell DL, Goldsbury DE, et al. Actual Versus Optimal Radiotherapy Utilisation for Metastatic Cancer Patients in the 45 and Up Study Cohort, New South Wales. Clin Oncol (R Coll Radiol) 2021;33:650-60.
40. Liu W, Liu A, Chan J, et al. What is the optimal radiotherapy utilization rate for lung cancer?-a systematic review. Transl Lung Cancer Res 2019;8:S163-71.
41. Lu T, Yang X, Huang Y, et al. Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. Cancer Manag Res 2019;11:943-53.
42. Shields MD, Marin-Acevedo JA, Pellini B. Immunotherapy for Advanced Non-Small Cell Lung Cancer: A Decade of

Progress. Am Soc Clin Oncol Educ Book 2021;41:1-23.
43. Howlader N, Forjaz G, Mooradian MJ, et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. N Engl J Med 2020;383:640-9.
44. Zheng L, Wang Y, Xu Z, et al. Concurrent EGFR-TKI and Thoracic Radiotherapy as First-Line Treatment for Stage IV Non-Small Cell Lung Cancer Harboring EGFR Active Mutations. Oncologist 2019;24:1031-e612.
45. Jia W, Guo H, Jing W, et al. An especially high rate of radiation pneumonitis observed in patients treated with thoracic radiotherapy and simultaneous simertinib. Radiother Oncol 2020;152:96-100.
46. Jumeau R, Vilotte F, Durham AD, et al. Current landscape of palliative radiotherapy for non-small-cell lung cancer. Transl Lung Cancer Res 2019;8:S192-201.
47. Gomez DR, Tang C, Zhang J, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. J Clin Oncol 2019;37:1558-65.
48. Behera M, Steuer CE, Kim S, et al. Management approaches and outcomes of lung cancer patients hospitalized for malignant pleural effusions. J Clin Oncol 2014;32:abstr9646.
49. Ost DE, Niu J, Zhao H, et al. Quality Gaps and Comparative Effectiveness of Management Strategies for Recurrent Malignant Pleural Effusions. Chest 2018;153:438-52.
50. Oberg C, Folch E, Santacruz JF. Management of malignant airway obstruction. AME Med J 2018;3:115.
51. Mudambi L, Miller R, Eapen GA. Malignant central airway obstruction. J Thorac Dis 2017;9:S1087-110.
52. Bolliger CT, Mathur PN, Beamis JF, et al. ERS/ATS statement on interventional pulmonology. European Respiratory Society/American Thoracic Society. Eur Respir J 2002;19:356-73.
53. Armstrong RA. Is there a large sample size problem? Ophthalmic Physiol Opt 2019;39:129-30.

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Supplementary

Table S1 Baseline characteristics and receipt of intervention in patients with moderate-high dyspnea scores

Variable	Treatment for dyspnea		
	Treatment received (n=9,040)	No treatment (n=394)	P value
Number of ESAS survey completed, mean ± SD	10.14±12.67	8.29±11.38	0.004
Age category (at diagnosis) (years), n (%)			0.812
18 to 49	436 (4.8)	14 (3.6)	
50 to 59	1,648 (18.2)	75 (19.0)	
60 to 69	3,000 (33.2)	135 (34.3)	
70 to 79	2,803 (31.0)	120 (30.5)	
80+	1,153 (12.8)	50 (12.7)	
Sex, n (%)			0.72
Female	4,305 (47.6)	184 (46.7)	
Male	4,735 (52.4)	210 (53.3)	
Rural residence (Rurality Index for Ontario 40+), n (%)			<0.001
Major urban	5,897 (65.2)	226 (57.4)	
Non-major urban	2,459 (27.2)	120 (30.5)	
Rural	653 (7.2)	47 (11.9)	
Missing	31 (0.3)	≤5 (0.3)	
Elixhauser comorbidity score (categorical), n (%)			0.102
Less than 4	8,429 (93.2)	359 (91.1)	
4 or more	611 (6.8)	35 (8.9)	
Nearest Census Based Neighbourhood Income Quintile, n (%)			0.004
Q1	1,955 (21.6)	89 (22.6)	
Q2	2,000 (22.1)	110 (27.9)	
Q3	1,773 (19.6)	66 (16.8)	
Q4	1,695 (18.8)	72 (18.3)	
Q5	1,591 (17.6)	53 (13.5)	
Missing	26 (0.3)	≤5 (1.0)	
Deprivation Quintile, n (%)			0.001
Q1	1,616 (17.9)	58 (14.7)	
Q2	1,699 (18.8)	61 (15.5)	
Q3	1,816 (20.1)	73 (18.5)	
Q4	1,878 (20.8)	97 (24.6)	
Q5	1,976 (21.9)	97 (24.6)	
Missing	55 (0.6)	8 (2.0)	
Ethnic Diversity Quintile, n (%)			0.004
Q1	2,045 (22.6)	106 (26.9)	

Table S1 *(continued)*

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Table S1 *(continued)*

Variable	Treatment for dyspnea		
	Treatment received (n=9,040)	No treatment (n=394)	P value
Q2	2,025 (22.4)	89 (22.6)	
Q3	1,728 (19.1)	65 (16.5)	
Q4	1,638 (18.1)	67 (17.0)	
Q5	1,549 (17.1)	59 (15.0)	
Missing	55 (0.6)	8 (2.0)	
Dependency Quintile, n (%)			<0.001
Q1	1,446 (16.0)	41 (10.4)	
Q2	1,601 (17.7)	62 (15.7)	
Q3	1,666 (18.4)	76 (19.3)	
Q4	1,847 (20.4)	97 (24.6)	
Q5	2,425 (26.8)	110 (27.9)	
Missing	55 (0.6)	8 (2.0)	
Instability Quintile, n (%)			0.007
Q1	1,299 (14.4)	54 (13.7)	
Q2	1,568 (17.3)	69 (17.5)	
Q3	1,765 (19.5)	70 (17.8)	
Q4	1,909 (21.1)	98 (24.9)	
Q5	2,444 (27.0)	95 (24.1)	
Missing	55 (0.6)	8 (2.0)	
Year of diagnosis (categorical) , n (%)			0.718
2007 to 2012	3,566 (39.4)	159 (40.4)	
2013 to 2018	5,474 (60.6)	235 (59.6)	
Patients who received systemic therapy after diagnosis, n (%)			0.228
None	3,467 (38.4)	163 (41.4)	
Received therapy	5,573 (61.6)	231 (58.6)	
Died after diagnosis until end of study, n (%)			<0.001
Alive	691 (7.6)	113 (28.7)	
Died during follow-up	8,349 (92.4)	281 (71.3)	
Time from diagnosis to death (months), median (IQR)	8 (4–16)	4 (2–8)	<0.001

ESAS, Edmonton Symptom Assessment System; SD, standard deviation; IQR, interquartile range.

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