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Symptom burden in lung cancer: management updates

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Practice points

- Lung cancer, the leading cause of cancer death worldwide, is recognized to carry a high symptom burden with associated lowered quality of life as compared with other cancers.
- Symptom burden combined with poorer prognosis in lung cancer inflicts harsh economic and social costs on patients and their families.
- Symptom severity and burden can be a prognostic indicator of poorer clinical outcomes and survival post anticancer treatment.
- Optimizing assessment and screening and incorporating symptom management and referrals for supportive care into the treatment plan are of high importance.
- Early initiation of palliative care in lung cancer is beneficial to promote best symptom management and seamless care over the survivorship trajectory.

Lung cancer is recognized to carry a high symptom burden with associated lowered quality of life as compared with other cancers. Research has shown that symptom severity can be a prognostic indicator of poorer clinical outcomes and survival post treatment. The purpose of this paper is to review current literature relative to symptom burden associated with diagnosis, medical and/or surgical intervention, assessment and management updates, and emerging initiatives that promote positive outcomes based on updated evidence. Discussion relative to interdisciplinary coordination of supportive services and palliative care initiation is provided.

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Lung cancer, the leading cause of cancer death worldwide, is recognized to carry a high symptom burden with associated lowered quality of life as compared with other cancers [1–3]. Symptom burden combined with poorer prognosis in lung cancer inflicts harsh economic and social costs on patients and their families [4]. Reducing symptom burden to enhance quality of life is a primary goal in clinical management [5] despite variation in stage of disease and treatment options. Research has shown that symptom severity can be a prognostic indicator of poorer clinical outcomes [6] and survival post medical treatment for lung cancer [7,8]. The purpose of this paper is to provide a current general overview about symptom burden in lung cancer associated with the diagnosis, medical and/or surgical intervention through the survivorship spectrum, management updates and emerging initiatives that promote positive outcomes.

KEYWORDS

- adaptation • distress
- illness perceptions • lung cancer • quality of life
- supportive management
- survivorship • symptoms
- symptom burden
- symptom distress

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Methods

A database search was conducted using the terms lung cancer and symptom burden with CINAHL, MEDLINE, Clinical Care, Health and Wellness Resource Center, psychINFO and PubMed search engines. Initially 36,982 citations were recovered. To narrow the search and maintain clinical and research currency in the context of a concise review, only papers published since 2010 were incorporated. Inclusion criteria included: focus on symptom burden in lung cancer; symptom management during treatment for lung cancer; therapeutic options for symptom burden and intervention strategies to promote quality of life. Exclusion criteria included articles that focused on symptom burden in other cancers. The paper includes a review of lung cancer symptom burden in the context of: points of care in the survivorship trajectory; clinical assessment; treatment modalities and management strategies; and research initiatives related to improving patient-reported outcomes and enhancing health-related quality of life.

Symptom burden relative to points of care in the survivorship trajectory

Patients newly diagnosed with lung cancer are confronted with an uncertain future and existential threats associated with the reality of death that can be highly distressing and negatively affect quality of life [9]. Psychological sequelae such as anxiety and depressive symptoms are thus common during this challenging early post-diagnostic period. A study that examined adjustment in lung cancer patients who had lived with lung cancer at least 6 months (average of 2.4 years) found that emotional symptoms were related to perceptions of illness ambiguity and to an intolerance of uncertainty [10]. Avoidance, a common response to traumatic circumstances that prevents cognitive processing of stressors, was a factor that mediated the relationship between intolerance of uncertainty and depressive symptoms [10]. Patients with lung cancer may also experience negative psychological symptoms secondary to perceptions of stigma relative to the disease association to smoking behaviors [11]. Psychosocial challenges may be predictive of higher distress and poorer quality of life as opposed to socio-demographic and clinical factors [12]. One study found patients reporting higher levels of hope to be associated with lower symptom burden including less pain, fatigue and psychological distress [13]. Other research

has shown that patients' perceptions of their illness may conflict with their actual prognosis [14]. Despite evident need, a recent study found that only 40% of a sample of lung cancer patients with psychological symptoms reported use of mental health resources at an academic cancer center with availability of such benefits [15].

In literature that examined symptom burden characteristics longitudinally in the same patients along the illness trajectory, fatigue, dyspnea and cough were a symptom cluster shown to persist over a 5-year trajectory post diagnosis [6,16]. In a longitudinal study that followed patients post diagnosis from the beginning of treatment to 12 months later, cough was the primary concern of a respiratory distress symptom cluster that exacerbated and interacted with other symptoms [17]. Another study compared symptoms and quality of life over the course of a year among patients with stage I to III disease who were on average 18 months since diagnosis. Findings emphasized the complexity of the patients who experienced little differences in symptom burden in relation to disease stage [18]. Even patients with early-stage disease experienced decrements in physical quality of life and fluctuating indices of function over the course of the study [18]. Another study found that lung cancer survivors who were sedentary had worse cough, fatigue, pain and shortness of breath when compared with survivors who remained physically active [19]. The onset of depressive symptoms are associated with the severity of symptom burden in patients with advanced disease over time [20]. Individualized patient perceptions about the meaning of symptoms such as their causes and consequences can also impact distress associated with symptom burden over time [2,21]. Furthermore, patients and their partners can similarly be impacted by high distress and depressive symptoms relative to the diagnosis [22].

Symptom burden in relation to types of treatment

• Surgery

Surgery remains the primary treatment modality with curative intent for patients with early-stage lung cancer. While early-stage lung cancer often is diagnosed in individuals who are asymptomatic, symptom burden may be present in patients even before surgery [23]. One study with a sample of 270 patients found that cough, low energy, worry and tiredness were prevalent preoperative symptoms, and over 40% of

patients reported less commonly identified symptoms such as reduced sexual interest and feeling bloated [23]. Given high levels of distress associated with a new cancer diagnosis, insomnia, anxiety and other emotional symptoms are also common prior to surgery [23]. While symptom burden was shown to decrease in the first few months following surgery, it continued to remain higher than preoperative levels following surgical intervention [24]. A review of 19 studies found that pain, fatigue, dyspnea and cough were most common following surgery, and patients may experience symptoms of dyspnea and fatigue 2 years post-operatively [25].

While management modalities have evolved, acute pain post surgery occurs in up to 90% of patients and chronic pain that persists over time may occur in 26–67% of patients [26]. Furthermore, patients may experience post-thoracotomy pain syndrome that aggravates symptom distress even with minimally invasive surgery [27]. One study found that acute procedural pain in the early postoperative course to be predictive of higher psychological distress and post-traumatic stress symptoms following surgery [28]. Use of opioids for pain management post-operatively are not comprehensively effective suggesting that a multifaceted approach that targets overall symptom burden may be needed [29].

Patients with early-stage (IA or IB) NSCLC who were treated 1–6 years ago with curative surgical resection persisted with fatigue (57%) with 17% reporting moderate to severe levels [30]. In this sample, higher fatigue levels were related to higher functional impairment, dyspnea, psychological distress and the presence of chronic obstructive pulmonary disease (COPD) [30]. Given high symptom burden and distress associated with breathing found in patients with COPD, patients with this comorbid condition are particularly vulnerable [31]. Many survivors are shown to persist with symptoms such as pain, fatigue, dyspnea, anxiety and depression for years following surgery [32]. **Table 1** documents findings relative to symptom burden in surgery.

• Chemotherapy

Given the poor prognosis associated with advanced lung cancer which is commonly treated with chemotherapeutic agents, the necessity to evaluate symptom burden and quality of life during treatment is imperative [33]. Most patients with lung cancer are diagnosed at an advanced stage and may already be negatively

impacted by symptoms and decrements in quality of life prior to the initiation of any anticancer treatments [5,34,35].

Symptom extent and severity are associated with decrements in quality of life for patients undergoing chemotherapy treatment for advanced cancer [1,36]. Symptoms such as fatigue, shortness of breath and cough, pain and diminished appetite at differing levels of severity were ubiquitous in a population-based study of European patients with advanced lung cancer who were undergoing first- or second-line chemotherapy regimens [36]. Symptom experience is compounded by co-occurring manifestation of generalized fatigue and low energy, respiratory symptoms such as cough, gastrointestinal symptoms such as nausea and low appetite, and pain [1]. Psychological symptoms that affect sleep quality, worry and sadness are also experienced and affect perceived quality of life [1]. Sleep pattern disturbances in particular are common, are associated with symptoms such as dyspnea and negatively impact daytime function and overall quality of life [37]. Research has also found that symptom severity during chemotherapy was higher in females [1], patients with lower income [1,38] and among those with lowered performance status [1].

Specific symptoms have also been implicated with overall prognosis and survival during chemotherapy. For example, severity of cough prior to the initiation of chemotherapy was independently predictive of lowered survival in patients with advanced NSCLC [7]. Furthermore, higher fatigue, lowered appetite and shortness of breath following the first cycle was also associated with poorer survival as compared with patients with lowered severity of these symptoms [7]. Another study found that poorer performance status and higher symptom interference were indicators of lowered survival in patients with advanced disease scheduled for first-line chemotherapy [8]. In a study that evaluated the impact of initiation of a palliative care model, patients with metastatic NSCLC undergoing treatment experienced high symptom burden and distress with greater severity associated with sexuality, energy, shortness of breath, skin and nail changes, neuropathy, lowered appetite and pain [39]. Such findings are in line with several other studies documenting symptom burden, high distress and lowered quality of life in this patient population [39]. Less commonly reported but challenging to manage symptoms are taste and smell alterations that can

Study (year)	Purpose	Disease stage: type of tx; ct; RT	Design/ methodology	Demographics	Instruments to examine symptom burden	Major findings	Ref.
Hopkins <i>et al.</i> (2015)	Examine symptoms and QoL of patients with and without PTPS	Stage I, II, or IIIa lung cancer without evidence of metastasis. 2–12 months post-surgery (standard thoracotomy or minimally invasive surgery)	Prospective cross-sectional	97 patients, age: 67.3 (SD: 9.7) years. Men: n = 47; women: n = 50. Primarily white	HHS: Charlson Comorbidity Index; MPQ assesses pain intensity (1–10 scale), including descriptors that characterize sensation, and figure to identify location. The SDS is a 13-item, self-report scale assesses distress associated with cancer-related symptoms (1 = least distress to 5 = most distress). NSQ examined neuropathic symptoms. HADS is a 14-item questionnaire designed to screen for anxiety/depression. FACT-L is a 44-item questionnaire that measures QoL: comprised of five subscales measuring symptoms; physical, social, functional, and emotional well-being	Despite new innovations in surgical techniques, PTPS remains common. About 50% of patients experienced PTPS. Thoracotomy (54.7%); thoracoscopic (45.3%) procedure. Patients with PTPS described discomfort as pain, neuropathic symptoms or both pain and neuropathic symptoms. Patients with PTPS had significantly more symptom distress, anxiety and depression, and poorer QoL, with higher distress associated with PTPS	[27]
Hung <i>et al.</i> (2011)	Examine the prevalence, severity and correlates of fatigue in early-stage NSCLC survivors	Received surgical tx with curative intent. Stage IA or IB NSCLC	Cross-sectional survey study of patients between 1 and 6 years post-treatment	350 patients; male (n = 128; 37%); female (n = 222; 63%); age 68.8 years (SD: 9.8); race: white (n = 324; 93%), black (n = 11; 3%), Asian (n = 4; 1%); Hispanic other (n = 8; 2%)	BFI – prevalence and severity of fatigue nine items; widely used; validated; evaluates current levels; past week and severity/interference with daily function. SR-KPS – measures current functional performance status from 1–7. HADS	Fatigue prevalence was 57%. About 17% of sample had moderate to severe levels of fatigue which was associated with functional impairment. Presurgical FEV1%; current dyspnea, comorbid pulmonary conditions, less physical activity, less than high school education, clinically significant depressive and anxious symptoms	[30]

BDI: Baseline Dyspnea Index; BFI: Brief Fatigue Inventory; BPI: Brief Pain Inventory; Ctx: Chemotherapy; EORTC: European Organization for Research and Treatment of Cancer; FACT-L: Functional Assessment of Cancer Therapy–Lung; FEV1: Forced expiratory volume 1 s; HADS: Hospital Anxiety and Depression Scale; HHS: Health History Survey; HRQoL: Health-related quality of life; IES-R: Impact of events scale-revised; MPQ: McGill Pain Questionnaire; NSQ: Neuropathic Symptom Questionnaire; PGWB: Psychological Well-Being Index; PTPS: Post-thoracotomy pain syndrome; PTSD: Post-traumatic stress disorder; QoL: Quality of life; QLQ-C30: Core Quality of Life Questionnaire 30; RT: Radiation therapy; SD: Standard deviation; SDS: Symptom Distress Scale; SR-KPS: Karnofsky Self-Reported Performance Rating Scale; Tx: Treatment; VAS: Visual Analog Scale; VATS: Video-assisted thoracoscopic surgery.

Table 1. Symptom burden in relation to types of treatment surgery (cont.).

Study (year)	Purpose	Disease stage: type of tx; ctx; RT	Design/ methodology	Demographics	Instruments to examine symptom burden	Major findings	Ref.
Jeantieu <i>et al.</i> (2014)	Examine the presence of PTSD symptoms in patients who receive lung cancer resection	Open thoracotomy (32 cases [68%]) minimally invasive resection (video-thoracoscopy; 15 [32%])	Single center observational study. Preoperative and 3-month assessments	47 patients; male (n = 26; 55%); female (n = 21; 45%); age 59 years (SD: 13); French patients	HADS (14 items [seven-item subscales]; 0–3 range for each item) widely used; validated IES-R – 22 items; 0–4 range (PTSD items of intrusion, avoidance and hyperarousal symptoms); validated PGWBI – 22 quality of life items. Pain VAS; widely used; validated	51% prevalence of PTSD-like symptoms at 3 months postsurgery; PTSD symptoms are associated with high preoperative anxiety and postoperative pain	[28]
Lowery <i>et al.</i> (2014)	Examine the impact of symptom burden on HRQoL and performance status in surgically treated NSCLC survivors	Received surgical tx with curative intent. Stage IA or IB NSCLC; mean of 2.9 ± 1.2 years since surgery; 2.4 ± 1.6 comorbid conditions; 15% had the VATS procedure. Most participants had lobectomy (n = 133; 73%)	Cross-sectional survey study of survivors 1–6 years postsurgical treatment	183 patients; female (n = 117; 64%); age (69 years [SD: 9.9]), white (n = 171; 93%); black (n = 5; 3%); Hispanic (n = 6; 3%); non-Hispanic other (n = 1; 0.6%)	BPI is a measure of pain severity and interference, used in other studies of cancer survivors; 0–10 scale; BFI. BDI is a measure of current dyspnea severity along three dimensions on a five-point (0–4) scale 'very severe' to 'no impairment'. HADS; SR-KPS; HRQoL was measured with the SF-36v2, a 36-item scale that has been validated in cancer survivors	About 80% of the sample had some degree of symptom burden with 31% having at least one clinically significant symptom. Physical HRQoL decreased as intensity of symptom burden increased. Two or more clinically significant symptoms are identified as increasing adverse effects on HRQoL and function. VATS procedure was associated with lowered symptom burden	[32]
Oksholm <i>et al.</i> (2015)	Examine the symptom experience of lung cancer patients before and following surgery for a 5-month period	Stage IA, n = 66 (33%); IB n = 63 (32%); II n = 39 (20%); IIIA n = 29 (14.5%); Preoperative tx n = 4 (2%); Postoperative tx: RT, n = 8 (17%); ctx n = 58 (27%); rehabilitation n = 32 (16%); physical therapy n = 66 (32%)	Longitudinal study. Patients completed symptom scale; pre- and 1-month, and 5-months postsurgery	264 patients completed preoperative assessment; 228 1-month; 212 5-month. males: n = 121 (57%); females: n = 91 (43%); age 66.1 years (SD: 8.3); Norwegian patients	Memorial Symptom Assessment Scale (list of 32 physical/ psychological symptoms rated on 1–4 Likert scale. Six physical and most frequent psychological symptom (worry) were used to examine change over time in occurrence and severity. widely used; validated. Study limited by only included seven of the 32 symptoms (most frequently reported)	Moderate to severe symptoms occurred at high rates but varied. Five symptoms (pain, low energy, shortness of breath, drowsiness, worry) were high pre- and 1-month post-surgery but were lower at the 5-month testing. Cough and insomnia were persistent. Postoperative neoadjuvant ctx was predictive of increased pain, low energy, insomnia, drowsiness before surgery. Females had higher worry and pain burden. Age was associated with lower symptom burden	[23]

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Study (year)	Purpose	Disease stage: type of tx; ctx; RT	Design/ methodology	Demographics	Instruments to examine symptom burden	Major findings	Ref.
Poghosyan <i>et al.</i> (2013)	Review the literature on HRQoL in surgically treated NSCLC patients	Stage I, II, or III NSCLC. Postoperative frame ranged broadly (12 studies included measures within immediate to 1-year postsurgery) and seven studies were 2 or more years. 11 studies had longitudinal assessments	Evaluation of 19 studies that assessed HRQoL after surgical treatment	Studies ranged from 22 to 422 participants; most were prospective longitudinal studies. There were four cross-sectional studies. Only two studies provided race/ethnicity information	Included studies that used the SF-36 and the EORTC QLQ-C30 with the lung cancer module (QLQLC13)	Pain, fatigue, dyspnea and coughing were most prevalent symptoms. In the first-month following surgery, pain, fatigue, cough and dyspnea were primary. Five studies that measured symptoms at 3–4 months after surgery identified that pain and dyspnea was significantly worse compared with baseline but varied by type of surgery and patient's age. More extensive surgery (e.g., pneumonectomy) was comparatively related to higher dyspnea and pain. Three studies found that dyspnea was common 2–3 years after surgery. Dyspnea following surgery did not improve overtime (in one study 53% of patients free of disease recurrence persisted with increased dyspnea and 40% had worse fatigue compared with baseline. Other research found that patients had significant anxiety and 10–20% and depression symptoms)	[25]

BDI: Baseline Dyspnea Index; BFI: Brief Fatigue Inventory; BPI: Brief Pain Inventory; Ctx: Chemotherapy; EORTC: European Organization for Research and Treatment of Cancer; FACT-L: Functional Assessment of Cancer Therapy–Lung; FEV1: Forced expiratory volume 1 s; HADS: Hospital Anxiety and Depression Scale; HHS: Health History Survey; HRQoL: Health-related quality of life; IES-R: Impact of events scale-revised; MPQ: McGill Pain Questionnaire; NSQ: Neuropathic Symptom Questionnaire; PGWB: Psychological Well-Being Index; PTPS: Post-thoracotomy pain syndrome; PTSD: Post-traumatic stress disorder; QoL: Quality of life; QLQ-C30: Core Quality of Life Questionnaire 30; RT: Radiation therapy; SD: Standard deviation; SR-KPS: Karnofsky Self-Reported Performance Rating Scale; Tx: Treatment; VAS: Visual Analog Scale; VATS: Video-assisted thoracoscopic surgery.

affect nutritional status in patients undergoing treatment for advanced lung cancer [40,41]. Such symptoms result in lowered food enjoyment, food aversions, reduced energy intake and weight loss [41]. Unique symptom challenges have also been identified to occur among patients with brain metastasis from NSCLC or small cell carcinoma [42]. Such patients may incur cognitive sequelae such as delirium, consciousness deterioration, and even seizure activity [42]. **Table 2** presents study findings of symptom burden in chemotherapy.

• Radiation therapy

Patients may receive radiation therapy (RT) as a primary treatment or in combination with chemotherapy for advanced lung cancer [43]. There have been chemoradiation advances for treating locally advanced NSCLC including proton-beam therapy, 3D conformal RT and intensity-modulated RT that can be associated with treatment symptom burden [44]. Another advance for early-stage lung cancer treatment in patients who are ineligible for surgery is stereotactic body radiation (SBRT) which involves administering a high dose of RT with high accuracy to the targeted tumor [45]. Quality of life during RT can be complicated by psychological and physical symptoms that occur concomitantly, necessitating the need for management strategies that are holistic in approach [46,47]. Patients receiving radiation to the mediastinal area may also develop esophagitis, dysphagia and vocal impairment [43]. Patients may receive radiation as palliation of disease-related symptoms such as dyspnea, thoracic pain, cough and hemoptysis [48]. **Table 3** documents types of symptoms associated with RT.

• Targeted therapies

An increasing number of patients with advanced NSCLC are receiving oral chemotherapeutic agents that retard growth and spread of disease by interfering with targeted molecular signals that are associated with tumor growth and progression [49,50]. Agents such as the oral EGFR-TKI gefitinib that is used to treat tumors that are molecularly *EGFR*-mutation positive, are associated with long term progression-free survival [51,52]. Immunotherapies are also used to reduce NSCLC relapse rates are designed to directed an immune response against tumor-related antigens or the use of antibodies to block signaling pathways involved in

tumor response [53]. **Table 4** documents types of symptoms associated with targeted therapies.

• Supportive care

The burden from symptoms such as fatigue, shortness of breath and pain have significant negative impact on quality of life for patients with advanced lung cancer [36]. In particular, dyspnea is a common symptom that may be accompanied by high distress [54]. At the end of life, effective management of physical and psychological symptoms and avoidance of suffering are primary treatment goals [26]. Depressive symptoms may increase particularly in individuals who are of younger age, and/or with history of lower self esteem, higher hopelessness, attachment insecurity and lower spiritual well-being [20]. Unmet supportive care needs were associated with higher distress and more symptoms indicating the critical need for adequate assessment and resources [55].

Clinical assessment

Given research that has found predictive relationships between higher symptom burden and lowered survival for patients in treatment, [7] it is apparent that optimizing assessment and incorporating symptom management in the treatment plan is of high import. Mental health referrals for patients with high distress following diagnosis are imperative. In addition, ongoing evaluation of mental health over the course of the illness trajectory and into survivorship is integral. The American College of Chest Physicians have developed evidence-based guidelines to assist providers in their evaluation of patient symptoms [56]. Routine screening for distress among lung cancer patients followed by triage was found to reduce symptom reports at a 3-month follow-up as compared with patients with minimal screening [57]. Other research has shown that symptom management can be improved by comprehensive assessment of needs and discharge planning when patients with lung cancer are hospitalized [58]. Such findings emphasize the importance of proactive screening, management of symptoms and referral for supportive resources [55]. It is recognized that detailed ongoing symptom tracking can be made possible with use of electronic patient care monitoring systems which can be used to tailor individualized care [59].

While health providers were found to agree that assessment of sexuality and intimacy is important, this is an area that is neglected in

Table 2. Symptom burden in relation to types of treatment chemotherapy.							
Study (year)	Purpose	Disease stage: type of tx; ctx; RT	Design/ methodology	Demographics	Instruments to examine symptom burden	Major findings	Ref.
Akin <i>et al.</i> (2010)	Examine quality of life and symptom burden in lung cancer patients receiving ctx	Stage II–IV NSCLC; patients treated with: veveside and cisplatin; docetaxel and cisplatin/carboplatin; vinorelbine and cisplatin/carboplatin; vinorelbine and cisplatin/carboplatin; paclitaxel and cisplatin/carboplatin; vinorelbine and gemcitabine	Cross-sectional study	154 patients; 68% age range 40–59 years; males: n =130 (84%); females: n = 24 (16%); Turkish	The MSAS is a Likert-type scale assessing 32 physical and psychological symptoms. The QLI was used to measure QoL in four domains: health and functioning, psychological/spiritual, social/economic, family	Most common physical symptoms were fatigue, cough, pain, lack of appetite and nausea; psychological symptoms were anxiety, insomnia, worry and sadness. Symptom burden associated with decrements in QoL	[1]
Cleeland <i>et al.</i> (2011)	Examine symptom burden in underserved patients receiving ctx at a public hospital versus patients at a cancer center	Stage IIIB–IV NSCLC. Received either intravenous ctx (platinum, paclitaxel or docetaxel, n = 89; platinum + other n = 45; single agent n = 28; or the oral tyrosine kinase inhibitor, erlotinib; n = 12)	Symptom assessment was conducted prior to initiation of ctx; and weekly for 15 weeks following initiation of treatment.	Total sample was 181; 80 underserved patients (males: n = 49 [61%]; age 58 years [SD: 8.3]; whites: n = 18 [23%]; blacks: n = 36 [45%]; Hispanic: n = 25 [31%]; Asian: n = 1 [1%]; 101 patients from tertiary cancer center (males: n = 49, [61%]; age 61.6 years [SD: 9.0]; whites: n = 93 [92%]; blacks: n = 7 [7%]; Hispanic: n = 1 [1%])	MDASI assesses 13 common cancer-related symptoms (cough added) and six items measuring symptom interference. ECOG PS	Overall, 70% of patients had low symptom burden (severity) that decreased over time. 30% had severe symptoms. Patients with good functional status but higher symptom burden were more likely to be treated at public hospital (nine-times more likely). Risk factors for higher symptom burden included being medically underserved (no insurance, less education, being non white). Pain management was less adequate among medically underserved	[38]

Ctx: Chemotherapy; ECOG PS: Eastern Cooperative Oncology Group performance status; EQ-SD: EuroQol five-dimensional questionnaire; FACT-L: Functional Assessment of Cancer Therapy–Lung; HADS: Hospital Anxiety and Depression Scale; HRQoL: Health-related quality of life; LCSS: Lung cancer symptom scale; MDASI: M. D. Anderson Symptom Inventory; MSAS: Memorial Symptom Assessment Scale; PSQI: Pittsburgh Sleep Quality Index; QoL: Quality of life; RT: Radiation therapy; SD: Standard deviation; Tx: Treatment; VAS: Visual Analogue Scale

Ctx: Chemotherapy; ECOG PS: Eastern Cooperative Oncology Group performance status; EQ-5D: EuroQol five-dimensional questionnaire; FACT-L: Functional Assessment of Cancer Therapy–Lung; HADS: Hospital Anxiety and Depression Scale; HRQoL: Health-related quality of life; LCSS: Lung cancer symptom scale; MDASI: M. D. Anderson Symptom Inventory; MSAS: Memorial Symptom Assessment Scale; PSQ: Pittsburgh Sleep Quality Index; QLI: Quality of Life Index; QoL: Quality of life; RT: Radiation therapy; SD: Standard deviation; Tx: Treatment; VAS: Visual Analog Scale.

Table 2. Symptom burden in relation to types of treatment chemotherapy (cont.).

Study (year)	Purpose	Disease stage; type of tx; ctx; RT	Design/ methodology	Demographics	Instruments to examine symptom burden	Major findings	Ref.
Dean <i>et al.</i> (2013)	Examine sleep, mood, QoL in patients receiving ctx for lung cancer.	NSCLC n = 21 (60%); small cell n = 12 (34%); missing n = 2 (6%). Stage IIIa–IV n = 28 (80%). Ctx regimen: carboplatin and paclitaxel n = 15; carboplatin and gemcitabine n = 3; carboplatin and etoposide n = 2; cisplatin and etoposide n = 12; missing n = 3	Cross-sectional descriptive design. Patients were recruited after completing one cycle of ctx	Total sample was 35 patients; 34 males (97%); age 63.5 years (SD: 9.7) years; white: n = 23 (66%); black: n = 12 (34%)	FACT-L; 36-items measure of lung cancer specific QoL. HADS; motion logger actigraph to measure sleep efficiency, onset latency, sleep time and waking after sleep onset. PSQI	28% had anxiety and 18% had depressive symptoms high enough for referral. Poor sleep highly significant symptom. Sleep disturbance associated with lung cancer symptoms such as dyspnea, and to lowered QoL	[37]
Iyer <i>et al.</i> (2013)	Examine patient reported symptom burden and impact on disease specific HRQoL in advanced NSCLC patients	Stage IIIB–IV NSCLC; 52% receiving first-line treatment; 48% second line	A multicenter, patient record-based cross-sectional study	517 patients Germany; 320 patients France; average age 63 years; males (67%); white (93%)	FACT-L scale. FACT-L is a validated questionnaire containing five subscales. QoL and general health status were assessed using the EQ-5D; LCSS; nine items on 100 mm VAS	Over 90% of the patients reported fatigue, appetite loss, shortness of breath, cough and pain	[36]
Wang <i>et al.</i> (2010)	To evaluate prognostic value of symptom burden on survival in patients receiving ctx for advanced NSCLC	Stage IIIB or IV NSCLC; scheduled for first-line ctx; 53 (56%) patients had previous cancer therapy	Pre-post design; patients with advanced NSCLC; ECOG PS of 0 to 2 rated symptom severity pre- and post-first cycle of ctx	94 patients; 63 males (67%); 31 females (33%); men aged 61.2 years (SD: 9.5); white: n = 86 (92%); black: n = 7 (7%); Hispanic: n = 1 (1%)	MDASI was used to assess multiple symptoms	Risk for lowered survival was indicated by moderate to severe coughing at baseline, increased fatigue, shortness of breath during the first ctx cycle	[7]

Ctx: Chemotherapy; ECOG PS: Eastern Cooperative Oncology Group performance status; EQ-5D: EuroQol five-dimensional questionnaire; FACT-L: Functional Assessment of Cancer Therapy–Lung; HADS: Hospital Anxiety and Depression Scale; HRQoL: Health-related quality of life; LCSS: Lung cancer symptom scale; MDASI: M. D. Anderson Symptom Inventory; MSAS: Memorial Symptom Assessment Scale; PSQI: Pittsburgh Sleep Quality Index; QoL: Quality of Life Index; QoL: Quality of life; RT: Radiation therapy; SD: Standard deviation; Tx: Treatment; VAS: Visual Analog Scale.

Table 3. Symptom burden in relation to types of treatment radiation therapy.							
Study (year)	Purpose	Disease stage: type of tx; ctx; RT	Design/ methodology	Demographics	Instruments to examine symptom burden	Major findings	Ref.
Chan <i>et al.</i> (2011)	Examine effectiveness of psycho-education intervention for symptom management during RT	Stage III or IV lung cancer; scheduled to receive palliative RT of an average of 4.3 Gy/fraction	Pre-/post-test, two-group, randomized, controlled trial that compared a psycho-education intervention for management of symptom cluster (anxiety, fatigue, breathlessness) assessed at baseline, weeks 3, 6 and 12	Total sample was 140; adults (age not reported); 83% male; Asian sample was from Hong Kong	Breathlessness was measured with a 100 mm VAS. Chinese version of the Piper Fatigue Scale (23 items). Chinese version of the A-state scale of the State-Trait Anxiety Inventory (20 items). Reliability and validity of instruments identified as established	Evidence demonstrated for symptom cluster of breathlessness, fatigue and anxiety during palliative RT	[46]
Petri <i>et al.</i> (2015)	Examine the lived experience of patients undergoing RT	Stage of NSCLC not reported; it is stated that the RT was curative in intent	Qualitative phenomenology study	Three patients; one female; two males; age 65–72 years; Danish	Interviews	Debilitating symptom experience affected functioning on all levels	[47]
Ricardi <i>et al.</i> (2015)	Review SBRT for early-stage NSCLC	Stage I disease	Literature review of clinical trials involving SBRT	Studies included 40–70 patients	Clinical trial data	Very limited discussion. States few studies examine QoL issues but report that those reporting had patients who were less fit at baseline. Symptoms are primarily respiratory; neuropathic pain, motor weakness	[45]

3DCRT: 3D conformal radiation therapy; Ctx: Chemotherapy; IMRT: Intensity-modulated radiation therapy; MDASI: M. D. Anderson Symptom Inventory; PBT: Proton-beam therapy; QoL: Quality of life; RT: Radiation therapy; SBRT: Stereotactic body radiation therapy; VAS: Visual Analogue Scale.

3DCRT: 3D conformal radiation therapy; Ctx: Chemotherapy; IMRT: Intensity-modulated radiation therapy; MDASI: M. D. Anderson Symptom Inventory; PBT: Proton-beam therapy; QoL: Quality of life; RT: Radiation therapy; SBRT: Stereotactic body radiotherapy; SD: Standard deviation; Tx: Treatment; VAS: Visual Analog Scale.

Study (year)	Purpose	Disease stage: type of tx; ctx; RT	Design/ methodology	Demographics	Instruments to examine symptom burden	Major findings	Ref.
Wang <i>et al.</i> (2016)	To examine symptom burden in patients with NSCLC receiving proton or photon chemoradiation therapy	Unresectable primary or recurrent NSCLC. IMRT, (stage I–II n = 10 [29%]; III n = 24 [71%]), 3DCRT (stage I–II n = 2 [9%]; III n = 20 [91%]), and PBT (stage I–II n = 8 [35%]; III n = 15 [65%])	Longitudinal observational study	22 patients age 63.6 years (SD: 9.0); males: n = 10 (45%); 12 females (55%); white: n = 19 (86%); in 3DCRT; 34 patients, aged 65.7 (SD: 6.7) years; males: n = 17 (50%); females: n = 17 (50%); white: n = 28 (82%); in IMRT, 26 patients, aged 65.0 (SD: 9.2) years; males: n = 14 (54%); females: n = 12 (46%); whites: n = 22 (85%) in PBT	Symptom severity measured with MDASI; 13 common cancer-related symptoms (pain, fatigue, nausea, vomiting, dry mouth, shortness of breath, lack of appetite, difficulty remembering, drowsiness, disturbed sleep, sadness, distress, numbness/tingling) assessed on 0–10 rating scale. The symptoms 'coughing' and 'sore throat' were added to the MDASI in the 3DCRT/IMRT protocol, and 'mouth or throat sores' were added in the PBT protocol. Six items that evaluate symptoms interference with general activity, mood, walking, work, relations with others, and enjoyment of life assessed on 0–10 scale. MDASI was administered before the start of treatment (baseline) and then weekly during and after therapy for up to 12 weeks	Fatigue was the most severe symptom in all three groups over time. Other common severe symptoms included drowsiness, pain, sleep disturbances, lack of appetite, sore throat. PBT group reported significantly less severe symptoms than did patients receiving IMRT or 3DCRT. Esophagitis-related pain increased more during therapy and decreased more after therapy in the 3DCRT and IMRT groups than in the PBT group. The 3DCRT and IMRT groups reported greater decrease in symptoms of fatigue, drowsiness, lack of appetite, disturbed sleep after therapy	[44]

3DCRT: 3D conformal radiation therapy; Ctx: Chemotherapy; IMRT: Intensity-modulated radiation therapy; MDASI: M. D. Anderson Symptom Inventory; PBT: Proton-beam therapy; QoL: Quality of life; RT: Radiation therapy; SBRT: Stereotactic body radiotherapy; SD: Standard deviation; Tx: Treatment; VAS: Visual Analog Scale.

Table 4. Symptom burden in relation to types of treatment-targeted therapies.						
Study (year)	Purpose	Disease stage: type of tx; ctx; RT	Design/methodology	Demographics	Instruments to examine symptom burden	Major findings
Wang <i>et al.</i> (2014)	Examine symptom severity in advanced NSCLC patients receiving gefitinib treatment	All patients had advanced NSCLC diagnosed within the previous year, and prescribed daily gefitinib	Longitudinal analysis; symptom severity assessed before and at 1-, 3-, and 6-month intervals after starting treatment	n = 57; age 62.3 years (SD: 12.6) years; males: n = 24 (42%); females: n = 33 (58%); Taiwanese	Taiwanese version of the M.D. Anderson Symptom Inventory	Primary symptoms that were increased at 1 month included nausea, lack of appetite, vomiting, cognitive difficulties and sadness. Shortness of breath, fatigue and pain were increased at 3 months and sleep difficulties, drowsiness and numbness increased after 6 months. Distress decreased over time
Minguet <i>et al.</i> (2016)	Review the types of targeted therapies used in NSCLC	Evaluates key clinical trials that examined progressive-free survival and response rates (not focused on symptoms but some are reported)	Literature review	Clinical trials ranged from 24 patients to 1314	Clinical data	Gefitinib: skin reactions, rash, diarrhea. Afatinib: skin reactions, diarrhea. Crizotinib: nausea, diarrhea, gastrointestinal symptoms. Ceritinib: diarrhea, vomiting, nausea. Meretinib: skin reactions, diarrhea. Nivolumab: fatigue, diminished appetite most common. Less common were rash, diarrhea. Ipilimumab: alopecia, nausea
Quoix & Limacher (2014)	Review new developments in lung cancer immunotherapy	Evaluates updates relative to peptide-based; cell-based; vector-based vaccines and nonspecific immunotherapies (not focused on symptoms but some are reported)	Review of current clinical trials	Sample size not reported	Clinical data	Fatigue, diarrhea, arthralgias, rash, itching, headache, nausea

Ctx: Chemotherapy; RT: Radiation therapy; SD: Standard deviation; Tx: Treatment.

lung cancer [60]. Interpersonal communication between the patient and their family or friend caregivers should also be assessed. For example, patients who are concerned about being a burden on their family members may conceal or under report pain [61]. Furthermore, evaluating vulnerable lung cancer patients early in the illness trajectory who may need targeted resources such as patients who are medically underserved with lowered income and education and from underrepresented groups is essential [38].

One cross-comparison study found many instruments did not target highly distressing concerns of an emotional and existential nature experienced by patients with inoperable lung cancer during their first year following diagnosis [62]. In this study patients reported distress brought on by interaction with the health-care system [62]. The National Comprehensive Cancer Network NCCN-FACT-Lung Symptom Index-17 is a brief validated measure that was developed with patient and provider input to evaluate symptoms in advanced lung cancer [63]. The National Comprehensive Cancer Network NCCN-FACT-Lung Symptom Index-17 is composed of treatment, disease and functional wellbeing items and was developed primarily to assess symptoms in patients undergoing chemotherapy [63]. Visual analog or numerical rating scales are also options for evaluating the severity of specific symptoms such as dyspnea [64]. The Patient Health Questionnaires (PHQ-2) can be used to evaluate depressive symptoms in the clinic environment to determine needs for mental health referral [65]. Distress, pain and fatigue thermometers, Psychological Screen for Cancer Part C and use of problem checklists may help standardize the process of symptom screening [57].

Treatment modalities & management strategies

Palliative care is an interdisciplinary-treatment approach that targets symptom burden management with the provision of comprehensive and holistic resources [26,66–68]. Research and clinical evidence are demonstrating increasing support that the early initiation of palliative care in lung cancer is beneficial to promote best symptom management and seamless care over the survivorship trajectory [18,39,67,69]. Given many lung cancer patients experience disease recurrence and ongoing symptom burden following successful surgical resection, there are recommendations

for such care for patients across all stages of disease [26]. Currently, the American College of Chest Physicians evidence-based practice guidelines recommend the discussion of palliative care for patients with stage IV disease [66]. Furthermore, these guidelines indicate that lung cancer providers initiate discussions about care goals and prognosis at the time of diagnosis and to continue this dialogue throughout the course of illness [66].

Access to targeted rehabilitation services across the disease and treatment trajectory such as physical and pulmonary therapy, social work services, nutritional counseling and information support have been found lacking or unevenly available [70]. Such services can ease symptoms such as dyspnea and fatigue while strengthening functional status [70,71]. For specific respiratory symptoms such as breathlessness and dyspnea, a comprehensive management approach that includes both pharmacological and a broad range of supportive strategies may be optimal [64,68]. Pulmonary rehabilitation has shown benefits in improving exercise capacity and dyspnea symptoms [71]. In addition, access to psychological counseling and psychiatric care as needed for mental health symptoms are essential. Recent research has examined the acceptability and feasibility of a multimodal non-pharmacologic intervention to address respiratory symptom clusters [72]. A comprehensive systematic review of the literature on social support and quality of life indices indicated that perceived support from healthcare providers was associated with both physical and emotional aspects of quality of life [73]. However, many patients with lung cancer do not use supportive care resources regularly [74]. The use of technologies such as telehealth to enhance symptom monitoring and management for patients in their home environments may reduce barriers to care for patients with limited access [75].

Complementary modalities such as alternative medicine (e.g., acupuncture) and mind-body therapies (e.g., massage, meditation and yoga) have received increasing attention over the past two decades [76]. Many cancer centers now offer integrative health options to interested patients for wellness and symptom management. The American College of Chest Physicians has developed evidence-based guidelines regarding the use of complementary therapies for symptom management in lung cancer that are based on an extensive evaluation of the state of the science [76]. In a study that queried use of supportive services, about 27% of patients who were not

using such modalities expressed interest [15]. In two studies that evaluated use of complementary modalities, 22 to 33% of patients were using integrative therapies, mainly mind–body types such as breathing and relaxation, with more patients deriving support from personal religious and spiritual resources [15,77].

It has also been shown that patients may experience varying severity of symptom burden in relation to the treatment environment [38]. One study found that patients who received chemotherapy at public hospitals reported higher symptom burden compared with patients deriving such care at a tertiary cancer center [38]. A comprehensive cancer center that provided symptom referrals for supportive care demonstrated that such services can result in significant reductions in depressive symptoms, fatigue and pain levels [78]. The same study determined that disparities in symptom burden outcomes existed for non-Hispanic blacks [78]. The presence of research targeting symptom burden experience and management among less represented groups remains a gap in the literature.

Physical activity has been associated with improved symptom control and better quality of life in lung cancer survivors [19,79]. A 12-week home-based walking program that incorporated exercise counseling was demonstrated to improve anxiety and depressive symptoms over time in Taiwanese patients with lung cancer [80]. Research has been increasing to evaluate the role of physical activity such as walking to alleviate problematic symptoms [80]. For example, a protocol has been developed to evaluate the benefits of aerobic and resistance training for symptom, performance and quality of life parameters for patients receiving palliative radiation and chemotherapy [81]. Another randomized control trial also conducted in patients with advanced lung cancer is determining the effects of cardiovascular, strength and relaxation training to alleviate symptom burden and improve function [82]. Importantly, review papers that evaluated feasibility and the benefits of exercise toward alleviating symptoms such as cancer-related fatigue identified potential benefit but cautioned that the quality of the evidence was limited [83,84].

Research initiatives to improve patient-reported outcomes & enhance quality of life

There has been increasing interest in the examination of genetic factors such as the presence

of single nucleotide polymorphisms (SNPs) in cytokine genes that may increase susceptibility to symptom burden severity and perceptions of lowered quality of life in lung cancer. In a large cohort study conducted by the Mayo clinic, after controlling for disease and demographic factors, 21 SNPs were associated with heightened symptoms and poorer quality of life outcomes [85]. In a study of 1149 long-term lung cancer survivors, three inflammatory gene SNPs were associated with pain severity [86]. Another study with a sample of 599 newly diagnosed patients found evidence for a symptom cluster of high pain, fatigue and depressed mood (19% of sample) [87]. These studies examining genetic polymorphisms are promising toward targeting symptom management, identifying high risk patients and enhancing quality of life for lung cancer survivors who may have genetic vulnerability to specific symptomatology [86,87].

Sexual concerns are common and related to both emotional and physical symptoms and function in lung cancer [88]. Only limited research has examined the impact of symptom burden on lung cancer patients' sexuality [60,88]. However, there has been increasing recognition of the interdependence between patient and caregiver mental health and quality of life indices [89]. Given the importance of healthy communication and intimacy to quality of life, this is an area where further inquiry is warranted.

Conclusion & future perspective

Much of the research on symptom burden in lung cancer is cross-sectional in nature and relies primarily on self-report. More prospective longitudinal studies are needed that follow patients over time with careful attention to the illness trajectory. It is problematic to compare patients even at the same stage of disease when some might be experiencing recurrence with a past history of surgery and others are in varying points in treatment. While factors such as age have not been strong predictors of the extent of symptom burden [23], functional performance and the number and severity of comorbid conditions at the time of diagnosis are likely powerful contributors to variation in the symptom burden experience. Given the subjective nature of symptom reports and perceived burden, more research that examines the supportive role of healthcare providers in the context of an interdisciplinary team is needed. Furthermore, since studies suggest illness perceptions may vary

among patients from a cross-cultural perspective, more research that examines multicultural symptom presentation is essential [21]. In addition, patients' perceptions about their illness and associated prognosis may conflict with the viewpoints of their health providers [14]. As more patients receive oral chemotherapy agents, the impact of polypharmacy on symptom burden needs to be evaluated [49]. There is increasing recognition of the need for evidence-based standards for supportive care delivery [90]. Expanding symptom management to incorporate a holistic approach that addresses co-occurring problems such as pain and depression [29] and the impact from co-morbid health conditions remain a challenge.

Symptom burden and associated distress in lung cancer is well documented. Patients with lung cancer rarely experience symptoms in isolation demonstrating the importance of

a multifaceted approach to symptom management. For example, patients with physical symptoms of fatigue may also have underlying depression [65]. Given more patient care and symptom management is delivered by home caregivers who may also experience social and financial stressors, comprehensive palliative care that incorporates an interdisciplinary approach is imperative.

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