

Management of dyspnea in advanced lung cancer: recent data and emerging concepts

Dong Xue^a and Amy P. Abernethy^b

^aKey Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Integrated Traditional Chinese and Western Medicine, Peking University School of Oncology, Beijing Cancer Hospital and Institute, Beijing, PR China and ^bDivision of Medical Oncology, Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA

Correspondence to Dong Xue, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Integrated Traditional Chinese and Western Medicine, Peking University School of Oncology, Beijing Cancer Hospital and Institute, Beijing 100142, PR China
Tel: +86 10 88196273; +86 13671133502;
fax: +86 10 88134037; xuedong123321@yahoo.cn

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Purpose of review

One of the most common symptoms for lung cancer patients, dyspnea, can seriously impact patients' quality of life.

Recent findings

Alongside conventional disease-focused approaches in lung cancer treatment, notably surgery, chemotherapy, and radiation therapy, physicians and researchers alike are increasingly attending to symptom control and seeking to evaluate the effectiveness of available interventions in mitigating symptoms.

Summary

This study reviews several interesting advances in the area of dyspnea with respect to symptom assessment and management.

Keywords

breathlessness, dyspnea, lung cancer, palliative care, quality of life

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Introduction

Lung cancer is still the leading cause of cancer death worldwide [1]. Over 70% of lung cancer patients are diagnosed in advanced stage [2]. Common symptoms include cough, dyspnea, weight loss, and chest pain [1]. Dyspnea is the most frequent distressing and burdensome symptom, with a prevalence of 55–90% [3–6]. New prevalence estimates confirm that distress due to dyspnea is still as common; for example, a 2008 Turkish study documented that 79% of female lung cancer patients suffered from dyspnea, second in frequency only to cough [7].

What is dyspnea and why treat it? The management of dyspnea in advanced cancer is strongly correlated with patient satisfaction with quality of life (QOL). In a 2007 study of 954 American cancer patients (16% lung cancer), dyspnea was measured using the European Organization for Research Treatment of Cancer QOL Questionnaire (EORTC QLQ-C30) dyspnea subscale and patient satisfaction with QOL was measured using the Ferrans and Powers Quality of Life Index (QLI). After controlling for the effects of age and treatment history, every 10-unit increase in dyspnea was significantly associated with degradation of QLI subscale scores for health/physical (0.81 units), social/economic (0.16 units), psychological/spiritual (0.47 units), and global functioning (0.47 units) [8]. Although our concern about dyspnea and its negative impact on QOL in the lung cancer setting is not new, recent research consolidates our understanding that the symptom is prominent and burdensome. It follows that

the management of dyspnea with a focus on improving QOL for lung cancer patients is a meaningful and practical topic.

We scanned the most recently published literature in PubMed and OVID to find some new ideas and interventions of dyspnea in advanced lung cancer. Keywords and synonyms included 'dyspnea', 'dyspnoea', and 'breathlessness'. As a starting point, it was interesting that the terms for breathlessness did not always correlate across languages and cultures. For example, in a 2007 qualitative study of Chinese palliative care patients in Hong Kong, 11 non-English speaking lung cancer participants who were clearly dyspneic and requiring oxygen therapy had no Chinese words to adequately define and describe their breathlessness. Instead, they relied on elaborate descriptions of the sensations they experienced during dyspneic episodes [9]. Review of English literature using strictly English terms may not encompass our full global understanding of the breadth and depth of the experience or interventions for it. Nonetheless, we have focused this current review on English articles identified in PubMed through November 2009.

Assessment and dyspnea patterns

Because of the subjective nature of the symptom, dyspnea assessment tools focus on patient self-report. The subjective intensity of dyspnea in lung cancer can be measured using standard single-item scales such as a visual analogue scale (VAS), numerical rating scale (NRS), or modified Borg scale [10]. A 2008 systematic

review of dyspnea assessment instruments for use in advanced illness identified four cancer-specific scales [the Cancer Dyspnea Scale (CDS), Breathlessness Assessment Guide, Dyspnea Exertion Scale, and Dyspnea Assessment Questionnaire] [11]. The authors noted that unidimensional scales like the VAS and NRS were most practical and applicable. The CDS had promise, especially because it blended sensation and impact of breathlessness on function, but it needs to be validated in English.

Questionnaires to assess QOL supplement our understanding of dyspnea, including the EORTC QLQ-C30, its lung cancer subscale, QLQ-LC13, Edmonton Symptom Assessment Scale (ESAS), Functional Assessment of Cancer Therapies-Lung (FACT-L), general symptom assessment scores (SAS), CDS, and others [12,13*,14, 15]. A 2009 literature review about QOL measurement in cancer patients receiving palliative radiotherapy for symptomatic lung cancer identified 43 studies: 19 used a QOL tool and 24 examined symptom palliation without the use of a QOL instrument. The QLQ-C30 survey was the most commonly used QOL questionnaire (in 13 of 20 trials). Of those 13 studies, eight also incorporated the lung-specific EORTC QOL survey QLQ-LC13 (or the longer EORTC QLQ-LC17). A second lung-specific survey, FACT-L, was used in only two of the 20 trials. Only 10 of 43 trials (23%) used a lung-specific QOL tool, suggesting that QOL was of low priority as an endpoint and that measures created for lung cancer patients are underused [16].

In a 2008 study by Henoch *et al.* [17], lung cancer patients' experience of dyspnea and personal management strategies were explored through semi-structured interviews with 20 individuals. Participants described 'triggering factors' that contributed to dyspnea, comprising physical, psychosocial, and environmental triggers; 'bodily manifestations' that led to inability to breathe properly, strain, inability to bring in enough air, and descriptions of dyspnea frequency, severity, and longitudinal impact; 'immediate reactions' such as fatigue, weakness, and emotional responses; and 'long-term reactions', including limitations on activity, increased dependence, and existential concerns like hope, hopelessness, and thoughts of death. Although the study design was appropriate and carefully conducted, in order for the results to be persuasive, more participants are needed to facilitate subgroup analyses.

Another way of considering lung cancer patients' dyspnea experience is through symptom clusters. In a 2009 study, authors analyzed symptoms reported by 1366 cancer patients using the ESAS, 14% of whom had lung cancer. Principal component analysis was performed for the entire patient cohort to determine interrelationships of

nine ESAS symptoms. Two major symptom clusters were identified: cluster 1 included fatigue, drowsiness, nausea, decreased appetite, and dyspnea, which represented 45% of the total variance; cluster 2 included anxiety and depression, which represented 10% of the total variance. Internal reliability of the cluster analyses was high (Cronbach's α coefficient 0.80). Treatments directed at symptom clusters rather than individual symptoms may provide greater therapeutic benefit [18].

Another emerging concept in dyspnea assessment is that of 'breakthrough dyspnea'. In a prospective observational study among 70 patients with dyspnea referred to a palliative care service conducted in 2009, investigators monitored the character of dyspneic periods, including breakthrough events defined as 'a clinically significant aggravation of dyspnea in patients with continuous dyspnea or occurring intermittently.' Lung cancer was the most frequent cancer diagnosis (44%). Constant dyspnea occurred in 39% of patients, with 20% of these individuals also suffering breakthrough episodes. Breakthrough-only dyspnea occurred in 61%. The majority of patients with breakthrough episodes (68%) presented fewer than five episodes daily, most frequently lasting for less than 10 min (88%). Dyspnea intensity significantly interfered with activities (general activity, $P=0.01$; mood, $P=0.02$; walking ability, $P=0.04$; normal work $P=0.04$) and enjoyment of life ($P=0.01$) [3].

Assessment of dyspnea as presented in the published medical literature follows a pattern similar to that of pain, including unidimensional and global assessment scales, relationship to QOL, symptom clustering, and breakthrough symptomatology. Another emerging concept mimicking pain is that of 'total dyspnea'. First presented by Abernethy and Wheeler in 2008 [19], total dyspnea presents the compounding inputs from the physical, psychological, social, and existential domains. It follows that the complete assessment and management of dyspnea requires astute attention to all facets. Total dyspnea is a conceptual model and organizing principle for the management of breathlessness in the palliative care setting; it needs to be subjected to scientific study before being widely adopted.

Overview of management approaches to lung cancer-related dyspnea

Management of dyspnea in the advanced lung cancer setting is divided into two approaches: treatment of the underlying primary cancer using surgery, chemotherapy, and radiotherapy; and palliative care focused on relief of suffering and symptom control irrespective of disease modification. Frequently, care according to a more palliative pathway is called 'best supportive care (BSC)' in cancer clinical trials. Approach is guided by cancer stage,

performance status, prior treatment history, pathology, and the availability of anticancer treatments likely to change the illness. Palliative care and symptom control are not isolated to the end of life and should be a parallel focus throughout the care continuum.

Surgery

Surgical resection of tumor is the primary treatment of early stage lung cancer. With consideration of QOL, Demmy and Nwogu [20] compared video-assisted thoracic surgery (VATS) lobectomy and traditional open surgical approaches in a 2008 structured narrative review. The authors first presented a systematic review of the two approaches, demonstrating equivalent impact on survival and complication rates. Types of instruments used to measure QOL varied widely, but QOL was generally more favorable with VATS primarily due to reduced pain and dyspnea; better postoperative physical functioning and patient satisfaction also positively influenced QOL in favor of VATS. VATS-related QOL benefits were greater with advancing age (or other frailties) and reduced by advanced cancer stage or comorbid illness.

Chemotherapy

Most of the clinical trials focus on tumor response to chemotherapy, usually with other endpoints of overall survival (OS) and time to progression (TTP, or some variation on this endpoint). The tumor response evaluation standard is WHO or RECIST (Response Evaluation Criteria In Solid Tumors) criteria. Dyspnea may be measured as a common side effect, adverse event of chemotherapy, or secondary endpoint for symptom control. For a small number of chemotherapy clinical trials, symptom improvement is the main emphasis; these trials usually pay greater attention to QOL. A review of recent trials follows.

Recent trials demonstrating improvement in dyspnea with chemotherapy

A 2009 Norwegian multicenter phase III study of platinum-based chemotherapy for the QOL enrolled 432 advanced nonsmall cell lung cancer (NSCLC) patients. Of these, 123 had lower performance status (PS 2). The EORTC QLQ-C30 and QLQ-LC13 questionnaires were used to assess QOL. Poorly functioning patients (PS 2) had greater improvement in global QOL, dyspnea, fatigue, and other symptoms with platinum-based chemotherapy in comparison to the PS 0/1 group [21,22]. Similar findings have been noted for targeted anticancer agents such as erlotinib. First shown to positively impact OS and tumor response in a 2005 randomized controlled trial of previously treated lung cancer patients with metastatic illness [23], subsequent reports of erlotinib treatment has shown positive impact on

dyspnea, cough, and cancer-related pain. QOL improved in concert [24]. And, as a 2008 study notes, patients with advanced age have similar dyspnea and cough control as compared to younger cohorts, but the symptom control lasts longer [25]. These are not the only studies demonstrating benefit for chemotherapy and targeted agents; overall, this body of work presents a compelling rationale for the role of effective chemotherapy programs for the management of lung cancer-related dyspnea.

QOL can be considered a prognostic factor as well as an outcome. The relationship between QOL and OS was explored in the Radiation Therapy Oncology Group RTOG-9801 trial. Two hundred forty-three patients with stage II/III NSCLC were enrolled in a longitudinal treatment trial including chemotherapy (paclitaxel and carboplatin) and hyperfractionated radiation, with or without amifostine. In a 2009 'Epub ahead of print' manuscript, poor QOL scores (<66.7) predicted shorter survival ($P=0.004$); each 10-point increase in baseline QOL reduced the risk of death by 10%, and important symptoms like dyspnea predicted worsening survival ($P=0.012$) [11]. The relationship between cancer-related QOL and survival has been confirmed in a recent 2009 meta-analysis of EORTC trials; among 7417 participants (14% lung cancer), QOL parameters, including physical functioning ($P<0.0001$), pain ($P<0.0001$), and appetite loss ($P<0.0001$) influenced survival. In univariate analyses, dyspnea was also a predictor, though this did not hold up for the multivariable model; the analysis included all trials and all types of cancer [26].

What about nontraditional therapies? A 2007 study of Chinese herbal medicinal therapy combined with chemotherapy in treating patients with NSCLC of stage III or IV enrolled 116 patients assigned to treatment (Chinese herbal medicine and chemotherapy; $n=60$) or control (chemotherapy alone; $n=56$). The treatment group demonstrated longer OS and improvements in tumor-related symptoms such as fatigue and dyspnea ($P<0.05$) [27]. High-quality clinical trial designs, including double blinding are still finding their way to traditional Chinese treatment assessment, so it is difficult to know whether the results seen here are reliable and generalizable.

Recent trials demonstrating dyspnea-related adverse events with chemotherapy

Converse to the improvements described above, dyspnea is frequently reported as an adverse event in chemotherapy clinical trials. In a review of seven different recent phase II and III trials of chemotherapy for lung cancer published in major clinical journals, grade three or four adverse events due to dyspnea varied from 3 to 21% [28–35]. The trials reviewed represented a variety of treatment settings, including single and combination

chemotherapy, first-line and beyond, and occasionally combined with monoclonal antibody therapy or an endothelin A receptor antagonist.

The problem of worsening dyspnea due to chemotherapy highlights the need for thoughtful care toward balancing beneficial therapeutic effects against accompanying deleterious side effects. Because it may be difficult to determine in advance what any particular individual will experience, close monitoring is paramount. It is important to note that individuals with poorer performance status are most likely to develop adverse events and to carefully consider the patient's performance status when addressing dyspnea in the palliative care setting.

A frequent question is whether administrative or other nonpatient reported data can inform clinicians about adverse events – probably not. A 2008 study sought to understand whether the standard measures of chemotherapy-related toxicity used in clinical trials could be captured from observational Medicare claims. Medicare data were compared with clinical trials data for a cohort of 175 elderly clinical trial patients who were treated on two Cancer and Leukemia Group B (CALGB) trials. Vomiting was the only toxicity reliably identified by the Medicare-based algorithm. For such patient-centered concerns as dyspnea, administrative datasets are unlikely to be of value; we need to ask the patient [36].

Radiotherapy

Radiotherapy alone or concurrent with chemotherapy can help to control advanced lung cancer. For patients with locally advanced disease (stages IIIA and IIIB), concurrent chemotherapy and radiotherapy remain the standards of care. However, many patients cannot tolerate the regimen because of its toxicity. Sequential chemotherapy followed by radiotherapy is used in these situations. Radiation therapy alone is used for the rare patient who cannot tolerate the use of any chemotherapy because of comorbid conditions. Palliative external-beam radiotherapy is useful for patients with metastatic disease, causing symptoms such as dyspnea, cough, and so on [1,37].

Many articles relevant to radiotherapy, advanced lung cancer, and dyspnea have recently been published. Examples include the following. A 2009 study examined the effectiveness of two palliative radiotherapy treatment protocols to compare their impact on survival and breathing difficulty [38]. The study enrolled 648 patients with advanced lung cancer, who were allocated to two groups based on clinical stage and ECOG (Eastern Cooperative Oncology Group) score: 303 patients (47%) received a total dose of 22.5 Gy in three fractions once per week and 345 patients (53%) received a single fraction of 10 Gy. (Radiation can be delivered via single fraction

or multifraction external beam, brachytherapy, and other means.) The two treatment protocols achieved similar effect in improving participants' breathing. Another non-comparative prospective observational study examined 150 outpatient high-dose-rate endobronchial brachytherapy sessions, carried out on 35 consecutive lung cancer patients with symptoms due to central airway obstruction; after delivery of 2000 cGy, participants' dyspnea decreased significantly [39].

Another study compared three different schedules using endobronchial brachytherapy (EBBT) with or without external radiation (XRT). Forty-five patients were randomized to three treatment arms: arm A received XRT to a dose of 30 Gy/10 fr/2 weeks and two sessions of EBBT 8 Gy each; arm B received the same XRT and a single session of EBBT 10 Gy at 1 cm; and arm C received only a single fraction of brachytherapy to a dose of 15 Gy at 1 cm without XRT. Symptomatic response rates, duration of symptom palliation, obstruction scores, QOL outcomes, and complications were assessed and compared. The overall symptomatic response rate for dyspnea was 91%, median time to dyspnea symptom relapse was 7 months, and the median time to dyspnea symptom progression was 7 months. Dyspnea scores on the QLQ-C30 from pretreatment to posttreatment decreased from 55 to 21, with maximum benefit in arm A. These results suggest that EBBT is a safe and effective palliative tool in advanced NSCLC, either alone or in conjunction with XRT [40].

Like chemotherapy, radiotherapy can cause radiation-induced lung toxicity (RILT). One letter to the editor and response addressed the question of how to predict and describe RILT [41,42]. Although these discourses do not express agreement, their publication provides evidence of concern for the dyspnea induced by radiotherapy.

Best supportive care

Over 30 studies comparing chemotherapy interventions to BSC have been published; studies most commonly include patients with NSCLC, pancreatic cancer, and gastrointestinal cancer. It could be presumed that BSC is a separate cancer treatment program appropriate for symptom management for people with advanced lung cancer. However, a 2009 systematic review of clinical trials with a BSC comparator arm demonstrated that the BSC arm was really synonymous with 'usual care,' which was frequently haphazard at the end of life after anticancer treatments stopped [43]. Hence, a more rational approach to managing dyspnea and QOL concerns in people with advanced lung cancer is to seek interventions defined within current best palliative care practice, provided there is evidence that they are effective and safe. We review potential symptomatic interventions below.

Overview for symptom control and palliative care for refractory dyspnea

For those advanced lung cancer patients who have poor performance status and very short estimated life expectancy and who cannot tolerate further treatment, relief of dyspnea symptoms becomes the most important medical service. Dyspnea treatment can follow either a pharmacological or nonpharmacological approach or can draw from both types of intervention.

Pharmacological treatment

Opioids, bronchodilators, diuretics, and benzodiazepines have been used for the anxiety, agitation, and air hunger accompanying dyspnea; physicians can prescribe as needed, but should be aware that the evidence is variable and, for certain interventions, weak [44–47].

An observational case series of oral transmucosal fentanyl citrate (OTFC) for dyspnea in terminally ill patients reported on only four patients, two of whom had end-stage lung cancer. At the onset of dyspnea, patients were instructed to slowly dissolve the OTFC lozenge and to rate their dyspnea on a 10-point VAS at 15-min intervals for 60 min. Patients were observed for approximately 48 h and reported experiencing rapid relief of dyspnea as soon as 5 min after OTFC began [48]. Though extremely limited in size, this small observational study yielded intriguing initial findings.

A double-blinded, randomized, placebo-controlled trial of nebulized furosemide for breathlessness in cancer patients was conducted in the United Kingdom. Patients with primary or secondary lung cancer and a Dyspnea Exertion Scale score of more than 3 were recruited [49]. Following familiarization, patients were randomized to receive either 40 mg nebulized furosemide, nebulized 0.9% saline, or no treatment, on 3 consecutive days. The 15 participating patients underwent number reading and arm exercise tests to assess breathlessness and its impact and reported subjective benefit and any preference between nebulized treatments. The study's results did not support a beneficial effect from nebulized furosemide in patients with cancer-related breathlessness; however, the lack of detailed demographic information and the design and method of this trial make it difficult to draw definitive conclusions about this pharmacological approach to dyspnea management in advanced lung cancer.

Nonpharmacological management for dyspnea

A literature review evaluating nonpharmacological interventions for breathlessness in advanced stages of malig-

nant and nonmalignant disease was published in 2008 in the Cochrane database of systematic reviews [50]. Included studies were controlled clinical trials assessing the effects of nonpharmacological and noninvasive interventions to relieve breathlessness in participants suffering from breathlessness due to advanced stages of cancer, chronic obstructive pulmonary disease (COPD), and other late-stage diseases. Heterogeneity across studies prevented meta-analysis. The authors concluded that training in breathing techniques, walking aids, neuroelectrical muscle stimulation, and chest wall vibration appear to be effective nonpharmacological interventions for relieving breathlessness in advanced stages of disease. Most studies were conducted on COPD patients; only a few studies included participants with other conditions, including lung cancer. Another literature review retrieved five studies of nonpharmacological interventions for breathlessness management in patients with lung cancer; the report highlighted evidence that tailored instructions delivered by nurses with sufficient training and supervision may have some benefits over other delivery approaches [51].

One well designed negative clinical trial deserves mention. Vickers *et al.* [52] enrolled a study sample of 47 lung or breast cancer patients presenting with dyspnea. Patients were randomized to receive a single session of true or placebo acupuncture in addition to their regular treatment for dyspnea. Thereafter, semi-permanent acupuncture 'studs' were inserted, and participants stimulated the acupuncture points by pressing these studs twice daily. Immediately before and after acupuncture treatment and daily for the subsequent week, patients rated their subjective sensation of dyspnea on a 0–10 NRS. Patients receiving true acupuncture had slightly higher dyspnea scores than did those receiving placebo acupuncture, for both the period immediately following acupuncture treatment and for the 1 week of follow-up [mean differences, respectively: 0.34, 95% confidence interval (CI) –0.33–1.02; 0.56, 95% CI –0.39–1.51]. Despite the pilot nature of this study, the small CI and small magnitude of effect led the authors to conclude that the acupuncture intervention had no effect on the sensation of dyspnea.

Malignant pleural effusions commonly cause dyspnea among advanced lung cancer patients [53,54]. Neragi-Miandoab [53,54] reviewed surgical and other invasive options for the management of recurrent malignant pleural effusions and found no universally established, standard approach. Among the multiple surgical and nonsurgical options, including thoracentesis, chest tube drainage, thoracoscopy followed by chemical and mechanical pleurodesis, Pleur-X catheter drainage, and pleuroctomy, chemical pleurodesis remains the most common treatment for patients with recurrent pleural effusion.

A consecutive cohort study conducted by Currow *et al.* in Australia [13^{*}] examined the potential benefit of palliative home oxygen for alleviating dyspnea. The study enrolled 5862 patients, 92% of whom had cancer diagnoses. Using the dyspnea subscales of the SAS (0–10 NRS), the investigators compared baseline breathlessness before oxygen therapy with breathlessness at 1 and 2 weeks after the introduction of oxygen. The mean breathlessness score before home oxygen therapy began was 5.3 (SD 2.5; median 5; range 0–10). There were no significant differences overall between baseline and 1 or 2 weeks ($P=0.28$), nor between any diagnostic subgroups, including primary lung cancer. In multifactor analysis, neither the underlying diagnosis causing breathlessness nor demographic variables predicted responders to oxygen at 1 week. The investigators concluded that oxygen therapy, when prescribed on the basis of breathlessness alone across a large, predominantly cancer population, does not improve breathlessness for the majority of people. Results of a more definitive randomized trial are outstanding and will greatly inform our thinking in this area.

Several case reports offer interesting perspectives on the sometimes perplexing phenomenon of dyspnea. Das *et al.* [55] suggested that the ‘point of peaceful surrender to death without futile bargaining to live’ relieves the air hunger and anguish attending dyspnea in terminal illness. Lee *et al.* [56] found that Qi therapy (external Qigong) had a beneficial impact on an end-stage lung cancer patient’s symptoms of dyspnea. Glennon and Seskevich [57] reported that a relaxation technique serves as a useful tool by which oncology nurses can help ease dyspnea.

Conclusion

One of the most common symptoms for lung cancer patients, dyspnea, can seriously impact patients’ QOL. Alongside conventional disease-focused approaches in lung cancer treatment, notably, surgery, chemotherapy, and radiation therapy, physicians and researchers alike are increasingly attending to symptom control and seeking to evaluate the effectiveness of available interventions in mitigating symptoms. We have reviewed, above, several interesting advances in the area of dyspnea with respect to symptom assessment and management. Most studies were carried out in populations of NSCLC patients, perhaps because SCLC accounts for only 14% [58] of all lung cancer cases. Overall, there are relatively few pragmatic randomized controlled trials to provide definitive data regarding the effectiveness of available interventions for relieving dyspnea in this population. Clinical practice would benefit greatly from further randomized controlled trials studying approaches to dyspnea management in advanced lung cancer; the end

result of a more robust body of evidence on dyspnea management would be a higher QOL for advanced lung cancer patients.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 113–114).

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