A Study on the Correlation of Emotional Distress and Symptom Burden With Brain Metastasis Status in Patients With Advanced Lung Cancer Based on Electronic Patient-reported Outcomes

Version: V1.1

Date:November 3, 2025

Institution: Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Background:

According to the latest national cancer statistics released by the National Cancer Center, lung cancer ranks first in both morbidity and mortality of malignant tumors among males and females worldwide. In 2022, there were 1.0606 million new cases of lung cancer, accounting for 22.0% of all malignant tumors, and 733,300 deaths, accounting for 28.5% of all cancer-related deaths [1]. Brain metastasis is the most common form of intracranial malignant tumor in adults and is associated with a poor prognosis, with a median survival of 3 to 6 months. Lung cancer is the most common primary tumor leading to brain metastasis, accounting for approximately 40%–50% of all brain metastases globally. Up to 22%–57% of patients with non-small-cell lung cancer (NSCLC) will develop brain metastasis at some point during the disease course. For patients with small-cell lung cancer (SCLC), brain metastasis is present at diagnosis in an estimated 10%–20% of cases, and up to 50%–80% of patients will develop brain metastasis throughout their illness.The mechanisms underlying brain metastasis are extremely complex. Among them, local invasion, intravasation, survival in the circulation, extravasation, and tissue colonization represent the core pathological processes [2,3]. Accumulating evidence supports the potential significance of host-related factors (e.g., psychological factors) in malignant tumor management. Emotional distress (ED) refers to a negative psychological state or unpleasant feelings induced by stressors, which can be quantitatively assessed using standardized scales [4,5]. The effects of psychological stress on malignancies are mainly mediated by the neuroendocrine-immune system, with the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis serving as the critical regulatory pathways. Studies have demonstrated that ED facilitates tumorigenesis, disease progression and metastasis, and impairs the efficacy of anti-tumor therapies [6]. Preclinical studies have revealed that chronic stress promotes cancer metastasis via neutrophils, suggesting that stress reduction should be regarded as an essential component of comprehensive cancer treatment and prevention strategies [7]. Additional clinical research has indicated that ED is closely associated with immunotherapy resistance in lung cancer. Exploratory analyses have further shown that patients with elevated ED present increased serum cortisol levels, which are correlated with adverse survival outcomes [8].Current preclinical models fail to simulate the complex and unpredictable stress status of cancer patients. Moreover, high-quality prospective clinical cohorts are still lacking to clarify the impact of ED on brain metastasis risk and long-term prognosis in lung cancer patients. To address this research gap, we plan to conduct a prospective observational study focusing on emotional distress, symptom severity, and symptom

interference with daily activities. Accurate longitudinal monitoring and comprehensive assessment can enable clinicians to better recognize symptom burden and symptom cluster characteristics, optimize psychological intervention and symptom management strategies, further improve functional outcomes and health- related quality of life, and ultimately bring substantial clinical benefits to lung cancer patients.

Patient-reported outcome (PRO) refers to any report directly provided by patients regarding their own health status, functional performance, and treatment experience, without interpretation from clinicians or any other third parties. PRO encompasses a broad range of concepts and includes all health-related information directly reported by patients, such as physical symptoms, functional status, health-related quality of life, perceptions and feelings toward treatment, doctor–patient satisfaction, economic benefits, and treatment adherence. Compared with information obtained through observation or medical staff evaluation, PRO data are more authentic, reliable, and capable of reflecting patients' real conditions in a comprehensive and dynamic manner [9]. Patient-reported outcome measurements (PROMs) are primarily used to assess patients' current health status and health-related quality of life at specific time points, mostly in the form of concise self-administered questionnaires. Their measurement domains cover physical symptoms (e.g., pain, fatigue, cough), functional interference (e.g., daily activities, work performance), psychological functioning (e.g., sadness, fear of death), social functioning (e.g., family relationships, social support), and overall quality of life [10-13]. PROMs are mainly delivered via paper-based or electronic questionnaires. Electronic collection of PRO data through smartphones, computers and other digital devices is defined as electronic patient-reported outcome (ePRO) [9].

To enable cancer patients to master home-based self-care after discharge and reduce disease-related symptom burden, understanding patients' subjective experiences serves as the starting point of clinical practice. With the advancement of evidence-based medicine, patient-reported outcomes (PROs) provide indispensable information for clinical assessment and offer more comprehensive evidence for clinical practice. At present, electronic patient-reported outcomes (ePROs) have been widely adopted in Western countries for clinical efficacy evaluation, drug review and approval, medical service quality assessment, and health technology assessment. As PROs are increasingly integrated into clinical oncology practice, symptom monitoring based on PROs has demonstrated vital roles in optimizing symptom management, improving treatment adherence, and prolonging patient survival. Considering that certain treatment outcomes can only be truly reflected by patients themselves, as well as the reliability, sensitivity and convenience of PROs in the evaluation of daily function and symptoms, the U.S. Food and Drug Administration (FDA) recommends PROs as novel endpoints for clinical research.Professor Jennifer R. from the Memorial Sloan Kettering Cancer Center analyzed ePRO data from 12,433 postoperative outpatient cancer patients, clarified detailed postoperative symptom burden, and provided valuable evidence for the implementation and long-term maintenance of remote symptom monitoring programs among oncological surgical patients. Such data facilitates patient education, clinical expectation management, and relevant research, enabling iterative optimization of clinical care based on real-world patient experiences after hospital discharge [14].

Professor Nadia Harbeck adopted ePROs to evaluate the impacts of palbociclib combined with endocrine therapy on the quality of life of patients with HR+/HER2- advanced breast cancer. This exploratory safety analysis firstly confirmed that ePRO application significantly reduces the risk of severe adverse events in advanced HR+/HER2- breast cancer patients receiving oral anti-tumor therapy [15]. Li et al. investigated the incidence, severity, and temporal trajectories of exacerbation and relief of perioperative symptoms in lung cancer patients. Three stable symptom clusters (lung cancer-specific symptom cluster, sleep disturbance symptom cluster, and neurological symptom cluster) were identified and remained stable from postoperative days 2–4 to one month after surgery [16].

To enable cancer patients to master home self-management after discharge and alleviate disease-related symptom burden, understanding patients' subjective perceptions is the cornerstone of clinical practice. With the development of evidence-based medicine,PROs provide indispensable information for clinical evaluation and furnish robust evidence to support clinical decision-making.Currently, ePROs have been widely applied in Western countries in multiple scenarios, including clinical efficacy evaluation, drug review and approval, medical service quality assessment, and health technology assessment. With the gradual integration of PROs into routine oncological care, PRO-based symptom monitoring has proven critical in strengthening symptom management, enhancing treatment adherence, and prolonging patient survival. Given that several treatment-related outcomes can only be truly reported by patients themselves, together with the high reliability, sensitivity and feasibility of PROs in assessing daily function and symptoms, the U.S. Food and Drug Administration (FDA) has recommended PROs as key indicators for novel clinical trial endpoints.Professor Jennifer R. at Memorial Sloan Kettering Cancer Center analyzed ePRO data from 12,433 ambulatory patients undergoing cancer surgery, systematically clarified their postoperative symptom burden, and delivered valuable evidence for the implementation and sustained operation of remote symptom monitoring programs in surgical oncology populations. These data help optimize patient education, rationalize clinical expectations, and promote translational research, thereby facilitating the continuous improvement of post-discharge clinical care according to real patient-reported experiences [14].Professor Nadia Harbeck utilized ePROs to assess the effects of palbociclib combined with endocrine therapy on quality of life among patients with HR+/HER2- advanced breast cancer. This exploratory safety analysis first validated that ePRO implementation markedly reduces the risk of severe adverse events in patients with HR+/HER2- advanced breast cancer receiving oral antitumor agents [15].Li et al. explored the incidence, severity, and dynamic trajectories of fluctuation and relief of perioperative symptoms in lung cancer patients. Three stable symptom clusters, namely lung cancer-specific symptoms, sleep disturbances and neurological symptoms, were identified and remained stable from postoperative days 2 to 4 until one month after surgery [16].

With the in-depth development of the concept of "focusing on patient perceptions and improving patient experience", increasing attention has been paid to ePROs in China. Patients' evaluations of symptom burden and quality of life are considered to be more clinically significant than treatment response. However, research on PROs in China lags behind that in foreign countries and has developed slowly. Currently, domestic studies related to ePROs and tumors are mostly focused on

postoperative symptom assessment, rehabilitation prediction, and efficacy evaluation of traditional Chinese medicine in preventing and treating symptoms induced by tumor treatment.The research team led by Professor Shi Qiuling conducted a multi-center randomized controlled clinical study on perioperative symptom monitoring of lung cancer based on electronic patient-reported outcomes, and established an active postoperative symptom management model centered on the ePRO symptom "monitoring-early warning-feedback" cycle. Through this model, patients can actively report their symptoms, functional status, and quality of life electronically after surgery. The electronic data platform automatically monitors patients' conditions, judges the severity of symptoms, detects and automatically warns of abnormalities, and transmits the information to doctors, supporting doctors' subsequent active intervention. This model accelerates patients' postoperative rehabilitation, reduces their symptom burden at discharge, significantly decreases the incidence of postoperative complications, and greatly improves patient satisfaction [17].

To date, no ePRO studies have focused on the correlation between emotional distress, symptom burden and brain metastasis status in patients with advanced lung cancer. This study aims to collect symptom data using internationally recognized ePRO tools and explore the associations between emotional distress, symptom burden and brain metastasis status in patients with advanced lung cancer. A longitudinal study will be adopted to analyze the correlation between emotional distress and brain metastasis during the treatment period in all patients with advanced lung cancer and lung cancer with brain metastasis, as well as the developmental trajectories and influencing factors of relevant symptoms or symptom clusters during treatment. This study will help clinicians obtain more important information about patients' own health status, providing a strong reference for delivering timely and effective psychological and symptom management, and formulating individualized diagnosis and treatment plans.

Objectives:

This study will adopt a prospective longitudinal design to assess patients' emotional distress, symptom burden, and their associations with brain metastasis, so as to deepen the understanding of symptom expression characteristics and their relationship with brain metastasis. Patients will be divided into three cohorts based on the presence, absence, or progression of brain metastasis to compare differences in emotional distress and symptom burden.

Significance:

1.To provide guidance for the accurate emotional and symptom management of advanced lung cancer patients after treatment.

2.To offer a reference for the correlation between emotions, symptoms and brain metastasis in advanced lung cancer patients based on PRO full-course symptom management.

3.To provide a theoretical basis for improving the survival period and quality of life of lung cancer patients through PRO full-course symptom management.

4.To conduct an exploratory analysis of emotional, blood, microbial and other related biomarkers that affect the diagnosis and treatment of lung cancer patients with brain metastasis.

Study Design:

Based on a prospective longitudinal study design, this study intends to recruit outpatients and inpatients diagnosed with advanced lung cancer and lung cancer with brain metastasis from the Department of Thoracic Oncology of Tongji Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology, Xiangyang Central Hospital, and Xiangyang No.1 People's Hospital. All subjects will sign a written informed consent form and participate in structured follow-up based on electronic Patient-Reported Outcomes (ePRO).

Primary Outcomes:

To clarify the number of symptom clusters, changes in emotional stress, the composition of symptoms within each cluster, and their dynamic temporal trends during treatment.

Secondary Outcomes:

1. Questionnaire response rate.

2. The correlations of patients' emotional stress status and symptom severity scores with brain metastasis and PFS.

3. changes in quality of life over time.

Eligibility Criteria:

Inclusion Criteria:

1. Non-brain metastasis cohort: patients with stage IV non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) confirmed by pathology and imaging, without brain metastasis;Brain metastasis cohort: patients with pathologically and radiologically confirmed stage IV NSCLC and SCLC accompanied by brain metastasis;

2. Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2;

3. Age ≥ 18 years old;

4. Estimated survival time ≥ 3 months;

5. Capable and willing to repeatedly complete electronic questionnaires via smartphones or tablets;

6. All enrolled patients signed the hospital-approved informed consent form.

Exclusion Criteria:

1. Prior receipt of anti-tumor treatment;
2. Complicated with severe chronic diseases of the heart, liver, kidney and other vital organs;
3. Abnormal consciousness or mental status;
4. Inability to understand the research content and requirements;
5. A previous medical history of other malignant tumors.

Sample Size:

There are 16 symptom variables in total; therefore, the theoretical sample size should be ≥ 80 cases, with at least 80 cases in each cohort, 160 cases in the two cohorts, and a maximum sample size of 200 cases.

Study Procedures:

Patients enrolled in this study completed the MDASI-LC and EQ-5D questionnaires via WeChat mini-programs on mobile phones, tablets or computers at 1–2 days before treatment initiation (baseline), every 4 weeks within the first six months of treatment, and every 8 weeks thereafter until disease progression. Specifically, for the non-brain metastasis cohort, the endpoint was the development of brain metastasis; for the brain metastasis cohort, the endpoint was disease progression. The assessment frequency was once every 4 weeks in the first six months and once every 8 weeks after six months.

Data Sources:

1. EMR: Demographics, tumor characteristics, comorbidities, treatment details, labs, and costs Clinical research data platform: Survival tracking.

2. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale.

3. CTCAE 5.0: The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, developed by the National Cancer Institute (NCI) of the United States, is a descriptive terminology. It can be used to evaluate adverse events in patients during clinical trials and clinical practice, with strong practicality.

4. Emotional stress assessment tools: Based on the PHQ-9 and GAD-7 scales, patients with a score ＜5 on either scale were classified into the no emotional stress group; those with a score ≥5 were classified into the emotional stress group.

5. PRO Tool:The M. D. Anderson Symptom Inventory-Lung Cancer (MDASI-LC): Symptom assessment was conducted using the MD Anderson Symptom Inventory (MDASI), a symptom scale developed by the University of Texas MD Anderson Cancer Center.European Quality of Life-5 Dimension Health Outcome Survey (EQ-5D): The EQ-5D health descriptive system includes five dimensions.

Data Collection Platform:

WeChat mini-program with automated reminders. Trained thoracic oncology clinicians will support data entry and follow-up.

Risk and Ethical Considerations:

As a non-interventional study, risks are minimal. No identifiable personal data will be collected. Study adheres to the Declaration of Helsinki.

Statistical Analysis:

Mixed-effects models to analyze symptom trajectories

Descriptive statistics for symptom frequency/severity

Cox models for associations with PFS and OS

PCA, EFA, and hierarchical clustering to identify symptom clusters

Multivariate regression and nomogram development for prediction modeling

References

[1] Zheng RS, Chen R, Han BF, et al. [Cancer incidence and mortality in China, 2022]. Zhonghua Zhong Liu Za Zhi. 2024. 46(3): 221-231.

[2] Amin S, Baine MJ, Meza JL, Lin C. Association of immunotherapy with survival among patients with brain metastases whose cancer was managed with definitive surgery of the primary tumor. JAMA Netw Open (2020) 3:e2015444. doi: 10.1001/ jama net work open. 2020.15444.

[3] Wood DE, Kazerooni EA, Aberle DR, Brown LM, Eapen GA, Ettinger DS, et al.NCCN clinical practice guidelines in oncology (NCCN guidelines®). Lung cancer screening. Version 1.2024.

[4] Daly, M. & Macchia, L. Global trends in emotional distress. Proc. Natl Acad. Sci. USA 120, e2216207120 (2023).

[5] Deshields, T. L. et al. Addressing distress management challenges:recommendations from the consensus panel of the American Psychosocial Oncology Society and the Association of Oncology Social Work. CA Cancer J. Clin. 71, 407–436 (2021).

[6] Yuanjun Wu, Laiyan Zhou, Xuanwei Zhang,et al.Psychological distress and eustress in cancer and cancer treatment: Advances and perspectives.Sci Adv. 2022 Nov 25.8(47): eabq7982.

[7] Xue-Yan He 1, Yuan Gao 1, David Ng,et al. Chronic stress increases metastasis via neutrophil-mediated changes to the microenvironment[J].Cancer cell,2024 Mar 11; 42(3): 474-486.e12.

[8] Yue Zeng,Chun-Hong Hu,Yi-Zheng Li,Fang Wu,et al.Association between pretreatment emotional distress and immune checkpoint inhibitor response in non-small-cell lung cancer Nat Med. 2024 Jun;30(6):1680-1688.

[9] Bennett AV, Jensen RE, Basch E. Electronic patient-reported outcome systems in oncology clinical practice. CA Cancer J Clin. 2012. 62(5): 337-47.

[10] Hollen PJ, Gralla RJ, Liepa AM, Symanowski JT, Rusthoven JJ. Adapting the Lung Cancer Symptom Scale (LCSS) to mesothelioma: using the LCSS-Meso conceptual model for validation. Cancer. 2004. 101(3): 587-95.

[11] Pompili C, Koller M, Velikova G, et al. EORTC QLQ-C30 summary score reliably detects changes in QoL three months after anatomic lung resection for Non-Small Cell Lung Cancer (NSCLC). Lung Cancer. 2018. 123: 149-154.

[12] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010. 363(8): 733-42.

[13] Mendoza TR, Wang XS, Lu C, et al. Measuring the symptom burden of lung cancer: the validity and utility of the lung cancer module of the M. D. Anderson Symptom Inventory. Oncologist. 2011. 16(2): 217-27.

[14] Cracchiolo JR, Tin AL, Assel M, et al. Electronic Patient-Reported Symptoms After Ambulatory Cancer Surgery. JAMA Surg. 2024 .

[15] Kalinsky K, Accordino MK, Chiuzan C, et al. Randomized Phase II Trial of Endocrine Therapy With or Without Ribociclib After Progression on Cyclin-Dependent Kinase 4/6 Inhibition in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: MAINTAIN Trial. J Clin Oncol. 2023. 41(24): 4004-4013.

[16] Li JJ, Li JR, Wu JM, et al. Change in symptom clusters perioperatively in patients with lung cancer. Eur J Oncol Nurs. 2021. 55: 102046.

[17] Dai W, Feng W, Zhang Y, et al. Patient-Reported Outcome-Based Symptom Management Versus Usual Care After Lung Cancer Surgery: A Multicenter Randomized Controlled Trial. J Clin Oncol. 2022. 40(9): 988-996.