Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (2) : 245–250

OPEN ACCESS

Case Report

Palliative Care Case Report: A Man with End Stage Lung Cancer with Brain Metastases

Yanuar Ardani[1], Hamzah Shatri[1], Rudi Putranto[1], Rendi Faris Anggono[2]

[1]Psychosomatic and Palliative Division, Department of Internal Medicine Faculty of Medicine, University of Indonesia/Cipto Mangunkusumo National General Hospital Jakarta, Indonesia
[2]Department of Internal Medicine Faculty of Medicine, University of Diponegoro/ Doctor Kariadi General Hospital Semarang, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i2.901

Accepted: April 02nd, 2023
Approved: July13th, 2023

Author Affiliation:
Psychosomatic and Palliative Division, Department of Internal Medicine Faculty of Medicine, University of Indonesia/ Cipto Mangunkusumo National General Hospital Jakarta, Indonesia

Author Correspondence:
Yanuar Ardani
Pangeran Diponegoro Street No. 71
Jakarta, DKI Jakarta 10430,
Indonesia

E-mail:
dr.yanuardani@gmail.com

Abstract

Background : Lung cancer accounts for 13% of malignancies in the world and the most common type of cancer suffered by men in Indonesia. The 5-year survival rate for patients with lung cancer is only 18.1%. About 25–30% will develop brain metastases. Overall palliative care is needed including biologically targeted therapy, chemotherapy, stereotactic radiosurgery (SRS), surgery in selected cases, and whole brain radiotherapy treatment (WBRT). Rare studies that take into account surgical palliation in advanced NSCLC. It has been demonstrated that metastaticectomy generally improves survival and, in some patients, even long-term survival.
Case Report : A 65-year-old male patient with Non-Small Cell Carcinoma favor Lung Adenocarcinoma and cerebellum metastases. The patient underwent surgery to remove a brain tumor. The patient received 8 radiotherapies and Erlotinib chemotherapy for 4 cycles for 6 months. The dose of Erlotinib 150g/24 hours was used in the first month. The dose was reduced in the 2nd to 6th month to 100g/24 hours. Assessment of palliative care was carried out using the Karnopsky Questionnaire, Fatigue Severity Scale (FSS), and Palliative Performance Scale (PPS).
Conclusion : Despite major improvements in the way lung cancer patients are treated in recent years, morbidity and death rates are still high. Palliative care (PC) is an approach to treating patients with life-threatening diseases, one of which is lung cancer.

Keywords : Brain Metastases, Lung Cancer, Palliative Care

INTRODUCTION

Lung cancer is one of the most common malignancies worldwide, accounting for 13% of all cancer cases. Lung cancer also causes 1/3 of all cancer-related deaths in men. By 2030, there will be an estimated 26 million deaths from lung cancer.[1] In the United States, lung cancer was the leading cause of cancer-related deaths, with a prevalence of 25.9% of all cancer-related deaths in 2017.[2]

According to data from the World Health Organization (WHO), the most common type of cancer found in men in Indonesia is lung cancer, which is the fifth most common cancer in women.[1] Based to the 2018 Riskesdas, the prevalence of cancer in Indonesia increased from 1.40% in 2013 to 1.79% in 2018. Indonesia experienced an increase in the number of cancer cases from 2013–2018, namely from 1.4–1.8 per mil. The province with the most cases of permil is the province of the Special Region of Yogyakarta, namely 4.9 permil in 2018.[3]

Lung cancer can take many forms, ranging from asymptomatic or minimally symptomatic disease with a mild burden and/or moderate progression to aggressive and rapidly progressing disease with severe symptoms. Survival rates and quality of life tend to be worse in patients with advanced lung cancer who experience more severe symptoms.[4] Symptoms of lung cancer include pain, nausea, dyspnea, fatigue, anorexia/cachexia, depression, and confusion/delirium.[5] Due to the high prevalence and symptom burden of the disease, the impact of palliative care on lung cancer patients has attracted a great deal of research attention in recent years.[6]

Currently, the anticipated 5-year survival rate of patients with lung cancer is only 18.1%. Even for patients with stage 1 Non-Small Cell Lung Cancer (NSCLC), the 5-year overall survival rate is 73–90%, whereas for patients with stage 4 NSCLC, it is only 0–10%.[7] A meta-analysis involving more than 5,000 patients with lung cancer showed that the median survival time of patients not receiving antineoplastic treatment was approximately 7 months.[8] Although the incidence and mortality of lung cancer are declining, the prevalence remains high, with more than 500,000 patients in the United States currently suffering from this disease. For patients with advanced lung cancer, disease burden, consequences, and side effects of treatment can dramatically reduce quality of life.[9]

Among several types of lung cancer, approximately 7.4% of patients with Non-Small Cell Lung Cancer (NSCLC) will have brain metastases (BM) at the time of first diagnosis and 25–30% will develop brain metastases during the course of their disease. The life expectancy of these patients is poor, with a median survival of only 3.4 months.[10] In addition, many patients lose autonomic impairment due to neurocognitive and functional deficits and morbidity associated with drugs such as steroids and anti-epileptic drugs.[11]

Advances in the ability to study genomes in recent years have driven the concept of personalized medicine based on the molecular classification of oncogenic addictive tumors. The identification of (Epidermal Growth Factor Receptor (EGFR), translocation Reactive Oxygen Species-1 (ROS1), and anaplastic lymphoma kinase-positive (ALK+) has revealed tumor subsets of NSCLC that are responsive to targeted treatment.[12] Concomitantly, the strategies used to treat patients with brain metastases have also progressed. Treatment modalities include biologic targeted therapy, chemotherapy, stereotactic radiosurgery (SRS), case-selected surgery and Whole Brain Radiotherapy Treatment (WBRT). The approach adopted for a particular patient will depend on the performance status, molecular classification of the tumor and distribution intracranial and extracranial diseases.[11]

Substantial evidence supports the adoption of a palliative care approach in patients with lung cancer. Palliative care aims to prevent and relieve suffering by identifying and treating debilitating symptoms early; supporting patients and their families to optimize coping and active living; and addressing physical, psychosocial, and spiritual problems. Most research shows that introducing palliative care at an early stage will give benefit to patients with advanced malignancies, including advanced lung cancer. WHO defines palliative care as a treatment approach designed to improve the quality of life of patients with long-term fatal illnesses and their families by identifying, preventing, and eliminating suffering as early as possible, as well as addressing physical, psychosocial, and spiritual problems. Key features of palliative care include a team-based approach that provides pain and symptom relief, supports patients and their families in optimizing coping and active living, and addresses the psychological and spiritual aspects of care. Palliative care can be provided at any stage of the illness and is used in combination with other treatments designed to cure the disease or prolong survival.[6]

CASE REPORT

A 65 year old male patient visited the hospital polyclinic complaining of a headache. The initial complaint was a month ago with symptoms of spinning sensation, and the felt that this was caused by vertigo because the patient had a history of vertigo. However, at this time, the vertigo did not improve with medication, so the patient decided to receive inpatient care at Telogorejo Hospital, Semarang. Previously, the patient had a history of lung – cancer carcinoma in situ of the Bronchus and Lung, with a histological diagnosis of Non-Small Cell Carcinoma for Adenocarcinoma of the Lung, which was diagnosed in

June 2022. Pathological examination of the anatomy with fine needle aspiration biopsy (FNAB) in 2022 revealed that non-small cell carcinoma favors Lung Adenocarcinoma and continues with EFGR mutation examination. EFGR mutation examination revealed positive mutations in exon 21 (L858R) and exon 20 (S7681). The patient then received erlotinib chemotherapy in six cycles for six months, but in the fourth month, the patient stopped undergoing chemotherapy. In the first month, the erlotinib dose was 150 mg/24 hours. The dose was reduced from the 2nd month to the 6th month to 100g/24 hours.

Paliative Care

The complaints of spinning sensations are not improving, and patients experience nausea and vomiting. This raises suspicion of metastatic lung tumors in the brain. From the patient's family history, it was found that the mother also had vertigo. The patient lives at home with his family and claims to have a jogging hobby. During this period, the patient had a vegetable and fruit diet menu. The patient was a contractor and had built shop bussines. The patient is currently feeling irritated because the disease is not improving and is not recovering, and the patient admits to experience emotional exhaustion, irritability, and despair. The patients also felt that their physical condition was not the same as before. The patient feels that he rarely tells his family about his illness, feels that he does not sleep well, often wakes up in the middle of the night, and cannot go back to sleep. Currently, the patient does not have a wife because the patient's wife has died, and the relationship between the patient and other families is harmonious, judging by the communication between the father and his son, who is also an internist. The patient already knows the neighbors around his house well, because since birth, the patient has lived in that neighborhood and some of his neighbors are still relatives/family members of the patient and often play with their peers near the house.

On physical examination, the general condition of the patient was weak, with composmentis awareness (E4V5M6), body weight 70 kg, which decreased by 5 kg from the previous month, pulse 108 ×/min, RR 22 ×/min, temperature 37.2º C per axillary, SpO2 96 %, and good nutritional status. In generalist status, no abnormalities were found on the head and neck examinations. Examination of the lungs revealed movement of the right chest that was the same as the left on inspection, the same right and left chest fremitus on palpation, sonor sounds in both lung fields on percussion, and vesicular base sounds in both lung fields without any additional sounds on auscultation. Cardiological, abdominal, and extremity examination revealed no abnormalities.

On supported examinations, complete blood count, X-ray, ECHO cardiography, and MRI were performed. From laboratory tests, Hb was 12.8 gr/dl, leukocytes 11,800/ul, platelets 331,000, albumin 3.1 gr/dl, uric acid 2.7 mg/dL, blood sugar 437 mg/dL, and total cholesterol 227 mg. /dL. On ECHO examination, left ventricular hypertrophy (LVH) was observed without enlargement of the other heart chambers. Magnetic resonance imaging (MRI) revealed a cerebellar tumor.

The Hospital Anxiety and Depression Scale (HADS) questionnaire was used to assess palliative parameters, namely, anxiety and depression, with an anxiety score of 0 and a depression score of 6, indicating that the patient did not have anxiety or depression disorders. To assess quality of life, an evaluation was carried out using the Karnopsky Questionnaire with a final score of 80, which indicates that the patient is able to carry out activities and work normally and does not need special assistance. Patients were also assessed using the Fatigue Severity Scale (FSS) with a result of 36 which indicated that the patient was not fatigued. For the parameters of palliative care, patients were examined using the Palliative Performance Scale (PPS) questionnaire, and a 90% result was obtained. This indicates that there are no subjects in the risk group

Figure 1. Post surgery and brain metastases specimens

required observation.

Based on the considerations of the palliative team, the patient underwent surgery to remove the tumor (Figure 1). After surgery to remove the tumor, the patient underwent radiotherapy. This therapy was performed by the patient for 1 month, starting on August 17, 2022, with a total of 7 times radiation. After the 8th irradiation, the headache persisted. Currently, the patient is able to perform activities independently. After irradiation, the patient was scheduled to receive a chemotherapy program. The drugs the patient is currently taking are Lapigim (Glimepiride 2 mg and Metformin 500 mg) because the patient has type-2 DM and Gabapentin, Erlotinib Hydrochloride 100 mg. Patients receive palliative care since the diagnosis of cancer is enforced in 2022 in the form of supportive psychotherapy, occupational therapy (patients continue to work while undergoing chemotherapy), clerical assistance, and advance care planning.

DISCUSSION

Lung cancer is characterized by uncontrolled growth of cancer cells in the lung tissue due to malignancy originating from outside the lung or from the lung itself.[13] Uncontrolled growth causes mutations in the essential genes that regulate cell division. Finally, it converts normal cells into cancer cells. Mutations can occur spontaneously or be inherited.[14] Lung cancer often appears hidden and asymptomatic until it reaches an advanced stage. In general, there are currently no suitable screening methods for lung cancer. The recommended screening methods for lung cancer detection are limited to high-risk patient groups. The high-risk group included patients aged >40 years with a smoking history of ≥30 years and who had quit smoking 15 years before the examination, or patients aged ≥50 years with a smoking history of ≥20 years and having at least one other risk factor.[15]

The exact etiology of lung cancer is still not known. Long-term exposure or inhalation of carcinogens is a significant risk factor, along with other risk factors such as immunity and genetics.[16] Several references have reported that the etiology of lung cancer is closely related to smoking habits. Lombard and Doering studies reported a higher incidence of lung cancer in smokers than nonsmokers.[17]

Symptoms and signs of lung cancer vary based on the location, size of the cancer, degree of obstruction, and presence of regional or distant metastases. The most common symptoms are cough or chronic cough changes. Hemoptysis or sputum mixed with blood may also be present. Lung cancer can cause various complications, including pleural effusion, neurological disorders, and heart disease. Lung cancer can also cause other problems such as chest pain, coughing, shortness of breath, coughing up blood, nausea, pain, and fatigue.[18] Based on the 2018 National Cancer Control Committee, systemic clinical symptoms that are sometimes encountered are weight loss in a short time, loss of appetite, and intermittent fever. Symptoms associated with neurological disorders (headache and weakness/paresis) are encountered if they have spread to the brain or spinal cord. Bone pain is often the first symptom of cancer that spreads to the bones. Other symptoms include paraneoplastic symptoms, such as musculoskeletal pain, hematology, vascular, neurology, and others.[15]

Several supporting modalities suitable for diagnosing lung cancer include laboratory tests, imaging, transthoracic biopsy (TTB), fine-needle aspiration biopsy (FNAB), and histopathological examination. Lung cancer therapy can be classified based on its type, namely, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Treatment is usually based on the stage of the cancer, with therapeutic modalities including surgery, radiotherapy, and chemotherapy. Chemotherapy modality is standard therapy for stage III A lung cancer patients and for palliative treatment.[17]

Tyrosine Kinase Inhibitors (TKI), such as gefitinib and erlotinib, have been shown to be effective in patients with mutational activation of EGFR and ALK genes, such as NSCLC lung cancer cases. Despite its efficacy in controlling systemic disease, its effectiveness in patients with brain metastases has not been well established because data on the use of erlotinib or gefitinib are available from retrospective non-randomized studies with a limited number of patients.[19] A Chinese study of 136 NSCLC patients with resected brain metastases identified mutations EGFR in 57% of brain metastases, with a concordance rate of 93.3% in EGFR mutation status between primary tumor and brain metastases. This suggests that the EGFR status of the primary tumor is an excellent surrogate for the EGFR mutation status of brain metastases.[20] There is mounting evidence that treatment with TKI results in high response rates (70%–89%), improvement and progression-free survival (PFS) (12.9–19.8 months and 6.6–23.3 months, respectively) which demonstrated better clinical outcomes in a selected population of EGFR-mutated NSCLC patients with brain metastases.[21] Therefore, EGFR and ALK -TKI are valid options for patients with asymptomatic brain metastases from NSCLC, especially for those with EGFR-activating mutations or ALL+.

There are no well-defined treatment timing guidelines for NSCLC patients with EGFR mutations and asymptomatic brain metastases who do not require emergency therapy. In a retrospective study of patients with asymptomatic brain metastases without previous TKI treatment, first-line brain radiotherapy failed to improve long-term survival in patients with NSCLC with EGFR mutations and TKI therapy with asymptomatic brain metastases.[22]

Whether erlotinib or gefitinib can delay or obviate the need for brain radiation is considerable interest. To answer this question, a meta-analysis was performed in NSCLC patients with EGFR mutations and brain metastases. The authors reported improvement in PFS and OS with advanced use of cranial radiotherapy, although with more neurologic side effects compared to TKI alone.[22] Negative results have been recently reported with the use of advanced EGFR-TKIs, with suspension of SRS or WBRT resulting in lower OS in NSCLC patients with EGFR-mutantion and brain metastases. Similarly, no significant difference in OS was reported in 110 patients with EGFR-mutant lung adenocarcinoma who underwent erlotinib versus RT for brain metastases (median, 35 vs. 26 months; P = 0.62). The results of this study suggest that local therapy may still be important for the treatment of brain metastases in patients with EGFR mutations.[23]

Owing to continuous innovation and advances in medical treatment with targeted therapy and immunotherapy in the last decade, the survival of patients with advanced NSCLC has been extended, making it possible and clinically beneficial for radiotherapy to play a more active role in a highly selected subpopulation. For some patients initially unable to tolerate aggressive treatment because of severe symptoms caused by metastases (including lung, bone, and brain) and/or tumor emergencies [such as superior vena cava syndrome (SVCS), malignant spinal cord compression (MSCC), and hemoptysis], timely radiotherapy can significantly improve their general condition and performance status (PS) scores, giving them opportunities for more aggressive treatment and longer survival.[24]

To provide timely palliative care, ASCO guidelines recommend that palliative care be initiated within eight weeks of advanced lung cancer diagnosis. Historically, with palliative care as the primary goal, local treatment including surgery and radiotherapy was the standard of care for NSCLC patients with brain metastases because of the poor ability of chemotherapy drugs to cross the blood-brain barrier (BBB). Stereotactic radiosurgery (SRS) and whole brain radiotherapy treatment (WBRT) were performed according to the number and size of brain metastases. With the emergence of various small-molecule TKIs that exhibit increased penetration of the BBB, promising survival results have been reported in patients with brain metastases with anaplastic ALK or EGFR mutations. Pre-clinical studies have uncovered reasons for the synergistic anti-cancer effects of TKIs combined with radiotherapy. Accumulating data suggest that cranial radiotherapy, when performed in selected subgroups of oncogene-addicted NSCLC patients with brain metastases using the right radiation technique at the right time, not only contributes to symptom control but can also lead to longer survival. Based on data from previous studies, radiotherapy has immunomodulatory qualities that can enhance the antitumor immune response, making the integration of radiotherapy with immunotherapy as new therapeutic option for advanced NSCLC.[24]

According to Fitri *et al*., cancer is a terminal or palliative disease and patients with advanced conditions require services that can improve the quality of life of patients and families through palliative care. Palliative care is a form of health care that aims to improve the quality of life for patients and families with life-threatening illnesses, with prevention and eradication through early detection, appropriate assessment, and treatment of pain and physical problems, as well as psychosocial and spiritual problems.[25] In the National Consensus Project (NCP) Clinical Practice Guidelines for Quality Palliative Care in 2009, defines palliative care as "medical care provided by an interdisciplinary team, including medicine, nursing, social work, chaplaincy, counselling, nursing assistants, and other health care professions that focus on eliminating suffering and support for the best quality of life for patients facing serious life-threatening illnesses and their families. Palliative care included pain management, management of other physical complaints, psychological support, nursing care, social support, cultural and spiritual support, as well as assistance in preparation for and during bereavement. In this case, the patient received palliative care since the diagnosis of cancer was made in the form of supportive psychotherapy, occupational therapy, chaplain assistance, and advance care planning. The assessment and evaluation of patient complaints require the knowledge and attitudes of nurses related to palliative care. Nurse collaboration with various scientific team members can develop and implement a comprehensive treatment plan to improve the patient's quality of life.[26]

CONCLUSION

Palliative care is an approach for treating patients with life-threatening illnesses, including lung cancer. If introduced at an early stage, it can relieve symptoms and improve the quality of life. ASCO guidelines recommend that palliative care be started within 8 weeks of the diagnosis of advanced lung cancer. Palliative care should involve a combination of treatment methods based on available resources, and patients' responses should be monitored regularly. Providing proper holistic care will give patients the opportunity to live with the best quality of life for as long as possible.

REFERENCES

1. Kementerian Kesehatan Republik Indonesia. Pedoman Pengendalian Faktor Risiko Kanker Paru. *Direktorat Jenderal*

Pencegah dan Pengendali Penyakit. Published online 2018:29.
2. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer stat facts: Lung and bronchus cancer. U.S. Department of Health and Human Services. Published 2022. Accessed December 3, 2022. https://seer.cancer.gov/statfacts/html/lungb.html.
3. Kementrian Kesehatan Republik Indonesia. Laporan Riskesdas 2018 Nasional.pdf. Published online 2019:674.
4. Mendoza TR, Kehl KL, Bamidele O, *et al*. Assessment of baseline symptom burden in treatment-naïve patients with lung cancer: an observational study. *Support Care Cancer*. 2019;27(9):3439–3447. https://doi:10.1007/s00520-018-4632-0
5. Iyer S, Roughley A, Rider A, Taylor-Stokes G. The symptom burden of non-small cell lung cancer in the USA: A real-world cross-sectional study. *Support Care Cancer*. 2014;22(1):181–187. doi:10.1007/s00520-013-1959-4
6. Yip Y-C, Yip K-H, Tsui W-K. Palliative Care for Patients with Lung Cancer: A Review of the Current Developments in the Field and Perspectives on the Implementation of Care. *Support Palliat Care Cancer Patients [Working Title]*. 2022;(November). doi:10.5772/intechopen.106797
7. Goldstraw P, Chansky K, Crowley J, *et al*. The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM Classification for lung cancer. *J Thorac Oncol*. 2016;11(1):39–51. doi:10.1016/j.jtho.2015.09.009
8. Wao H, Mhaskar R, Kumar A, Miladinovic B, Djulbegovic B. Survival of patients with non-small cell lung cancer without treatment: a systematic review and meta-analysis. *Syst Rev*. 2013;2(1):10. doi:10.1186/2046-4053-2-10
9. Nichols L, Saunders R, Knollmann FD. Causes of death of patients with lung cancer. *Arch Pathol Lab Med*. 2012;136(12):1552–1557. doi:10.5858/arpa.2011-0521-OA
10. Lagerwaard F, Levendag P, Nowak PC., Eijkenboom W., Hanssens P., Schmitz P. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys*. 1999;43(4):795–803. doi:10.1016/S0360-3016(98)00442-8
11. Owen S, Souhami L. The management of brain metastases in non-small cell lung cancer. Front Oncol. 2014;4(SEP):1–6. doi:10.3389/fonc.2014.00248
12. Jamal-Hanjani M, Spicer J. Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of epidermal growth factor receptor-mutant non-small cell lung cancer metastatic to the brain. *Clin Cancer Res*. 2012;18(4):938–944. doi:10.1158/1078-0432.CCR-11-2529
13. Purba A, Wibisono B. Pola Klinis Kanker Paru Rsup Dr. Kariadi Semarang Periode Juli 2013 – Juli 2014. *J Kedokt Diponegoro*. 2015;4(4):389–398. http://ejournal-s1.undip.ac.id/index.php/medico%0AArdina
14. Yopi Andry Lesnussa. Model Matematika Kemoterapi Kanker dan Simulasinya dengan Software Matlab. *J Kedokt*. 2012;5(1):19–23.
15. Komite Penanggulangan Kanker Nasional. Panduan Penatalaksanaan Kanker Paru. Published online 2018:1-33.
16. Husen A. Hubungan Antara Derajat Nyeri Dengantingkat Kualitas Hidup Pasien Kanker Paruyang Menjalani Kemoterapi. *Diponegoro Med J (Jurnal Kedokt Diponegoro)*. 2016;5(4):545–557.
17. Joseph J, Rotty LWA. Kanker Paru: Laporan Kasus. *Med Scope J*. 2020;2(1):17–25. doi:10.35790/msj.v2i1.31108
18. Ananda RR, Ermayanti S, Abdiana A. Hubungan Staging Kanker Paru dengan Skala Nyeri pada Pasien Kanker Paru yang Dirawat di Bagian Paru RSUP DR M Djamil Padang. *J Kesehat Andalas*. 2018;7(3):430. doi:10.25077/jka.v7i3.898
19. Baik CS, Chamberlain MC, Chow LQ. Targeted Therapy for Brain Metastases in EGFR-Mutated and ALK-Rearranged Non-Small-Cell Lung Cancer. *J Thorac Oncol*. 2015;10(9):1268–1278. doi:10.1097/JTO.0000000000000615
20. Luo D, Ye X, Hu Z, *et al*. EGFR mutation status and its impact on survival of Chinese non-small cell lung cancer patients with brain metastases. *Tumor Biol*. 2014;35(3):2437–2444. doi:10.1007/s13277-013-1323-9
21. Miles B, Mackey JD. Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors and Lung Cancer: History, Epidemiology, and Market Outlook. *Cureus*. 2021;13(2):0–4. doi:10.7759/cureus.13470
22. Srivastava H, Negi P, Kingsley PA, Sachdeva J. Management of lung cancer brain metastasis: An overview. *Asian J Oncol*. 2017;03(02):121–127. doi:10.4103/asjo.asjo_79_16
23. Gerber NK, Yamada Y, Rimner A, *et al*. Erlotinib versus radiation therapy for brain metastases in patients with EGFR-mutant lung adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2014;89(2):322-329. doi:10.1016/j.ijrobp.2014.02.022
24. Zhou Y, Yu F, Zhao Y, *et al*. A narrative review of evolving roles of radiotherapy in advanced non-small cell lung cancer: From palliative care to active player. *Transl Lung Cancer Res*. 2020;9(6):2479–2493. doi:10.21037/tlcr-20-1145
25. Fitri EkY, Natosba J, Andhini D. Gambaran Pengetahuan, Sikap, dan Tindakan Perawatan Paliatif Perawat. *Semin Work Nas*. Published online 2017:218–222.
26. Ekowati FD. Gambaran Pengetahuan dan Sikap Perawat tentang Perawatan Paliatif Pada Pasien Kanker. *Univ Muhammadiyah Surakarta*. Published online 2021:19. http://eprints.ums.ac.id/id/eprint/91713