The Gulf Journal of Oncology

Indexed By PubMed and Medline Database

Issue 46, Sep 2024
ISSN No. 2078-2101

The International Tobacco Control Conference on

The Scourge of Smoking and Conflicts of Interest

October 27-28, 2024

STATE OF KUWAIT



The Official Journal of the Gulf Federation For Cancer Control

Table of Contents

Original Articles

Immunohistochemical Expression of Calretinin in Invasive Breast Carcinoma and its Correlation with Clinicopathological Parameters **07**
Gargi Madhukar Patil, Siddhi Gaurish Sinai Khandeparkar, Shital Subhash Gosavi, Chaitnya D. Khillare, Bageshri P. Gogate, Avinash R. Joshi, Ketki Ghanekar, Asmita S. Pawar

Immunohistochemical Study of Cyclin D1 and HER2/neu in Pre–neoplastic and Neoplastic Epithelial Lesions of Cervix **14**
Neha D. Newadkar, Siddhi Gaurish Sinai Khandeparkar, Bageshri P. Gogate, Aishawarya Gotekar, Priyanka Bhave, Rashmi Shinde, Aanchal Goyal

Survival Outcomes and Predictive Factors to Evaluate the Efficacy of Neoadjuvant Chemoradiation in Carcinoma Esophagus: An Institutional Experience from India **24**
Bhargav Shreeram Gundapuneedi, Vedamanasa Ikkurthi, Jagadesan Pandjatcharam, Y. Sree Sowmya, Raghuveer Reddy Janamolla

Open Nephron–Sparing Surgery for Renal Tumors is an Effective Surgical Option for Low HealthResource Settings in the Era of Laparoscopic Surgery **36**
Adil Ibrahim, Mohamed Mustafa, Imad Fadl Elmula

Brain metastasis: Types, methods of diagnosis and treatment in Nineveh province. **43**
Bassam Jasim1, Alya A Al Zobair, Ahmed Ali Albakr, Barrak F. Al Obeidy

Review Article

Relationship Between Social Support, Coping Strategies, Spirituality and Psychological Status among Breast Cancer Survivors **49**
Maryam Hasan, Leena Khonji, Gayathripriya Narayanan

Postoperative Radiotherapy in Resected Non–Small Cell Lung Cancer: Current Status and Enduring Challenges in 2024 ..... **54**
Fadila Kouhen, Hanaa El Gouach, Nadia Errafiy

Case Report

Synchronous Cutaneous and Brain Metastasis in a Treated Case of Squamous Carcinoma of Left Lower Alveolus: A rare Case report **61**
Prarabdh Singh, Sambit S Nanda, Ashutosh Mukherji

Lived Experiences of Pregnancy, Childbirth and Breastfeeding in Iranian Breast Cancer Survivors: a Qualitative Case Study **65**
Mohadeseh Pourzamani , Hadis Ashrafizadeh, Maryam Kiarsi, Marzieh Beigom Bigdeli Shamloo

Pembrolizumab in the Management of Chemorefractory Gestational Choriocarcinoma: Report of Two Cases. **74**
Fatma Al Zaabi, Ajit Venniyoor, Suad Al Kharusi

Extramedullary Hairy Cell Leukemia in Parotid Gland, Case Report and Review of the literature **79**
Mohammed Shafi Abdul Salam, Shaima Al Shammari, Dina Ismail Abd El Razik, Moustafa El–Kabany, Ramesh Pandita, Ahmad Alhuraiji

Conference Highlights/Scientific Contributions

- **News Notes** **83**
- **Advertisements** **85**
- **Scientific Activities** **87**

Original Article

Brain metastasis: Types, methods of diagnosis and treatment in Nineveh province.

Bassam Jasim[1, 2, 3], Alya A Al Zobair [2,3], Ahmed Ali Albakr [4], Barrak F. Al Obeidy [5]

[1] Department of Medicine, College of Medicine, Nineveh University, Mosul, Iraq.
[2] Oncology Unite, Iben Sena Teaching Hospital, Mosul, Iraq.
[3] Department of Oncology, Medical Research & Care Centers, University of Mosul\ Mosul\ Iraq.
[4] Mosul Oncology Hospital, Mosul, Iraq
[5] Laboratory of Molecular Biology, Alhadbaa Hospital for Blood Diseases and Bone Marrow Transplantation, Mosul, Iraq.

Abstract:

Background: Brain metastasis is the most frequent brain tumor associated with poor survival. Solitary metastasis can be treated with excision or stereotactic radiosurgery. Systemic therapy remains challenging & is evolving for different types of primary cancers.

Patient and Method: This study was conducted to evaluate the most common types of primary tumors that can spread to the brain, methods of diagnosis, treatments, and survival outcomes in 72 patients with brain metastasis from primary solid tumors who were presented and treated in the Mosul oncology hospital between Jan 2018 to 2020 in Nineveh province.

Results: Breast and lung primary tumors are the most frequent primaries causing brain metastasis. Imaging studies using MRI & CT scans are more available and accessible for most of the patients. We found that WBRT is the main treatment used.

Discussion and Conclusion: Stereotactic radiotherapy was not available at the time of performing this study. Surgical resections are limited to a minority of our patients. We recommend more studies for each primary tumor focusing on its pathologic and molecular characteristics and its relation to brain metastasis.

Key Words: Brain metastasis, breast cancer, lung cancer.

Introduction:

Intracranial metastasis is the most frequent brain tumor, it is more common than primary brain tumor. It occurs in 25–50 % of all types of cancers [(1)]. It constitutes a major healthcare problem and represents an important cause of morbidity and mortality because of the high rate of metastasis in many primary solid tumor patients during their illness.

Worldwide the most common primary tumors that metastasize to the brain include bronchogenic cancer, cancer of breast, and melanoma. [(2)]

The incidence of brain metastasis is increasing due to the increased use of imaging studies in symptomatic and asymptomatic patients in cases of locally advanced tumors allowing the detection of smaller and subclinical metastasis. [(3)]

Brain metastasis carries a dismal prognosis as it is a hallmark of extracranial metastasis although survival outcomes improve especially for brain–limited metastasis because of improvements in local treatment strategies and targeted therapies that can cross the blood–brain barrier. [(3)]

The management of brain metastasis includes removal of the tumor surgically, radiosurgery, and whole–brain radiotherapy, in addition to systemic therapy. [(4)]

There are few studies in Iraq focused on metastatic brain tumors. In this study, we highlighted on most common types of primary tumors that metastasize to the brain, subtypes of certain common tumors that lead to higher brain metastasis, site of brain metastasis, ways of diagnosis, and types of management in Nineveh province. In this study, we exclude hematological malignancies and primary CNS malignancies.

Corresponding author: Assistant Professor Alya A. Al Zobair, Consultant Clinical Oncologist, Department of Oncology, Medical Research & Care Centers, University of Mosul\ Mosul\ Iraq, aliaabdulaziz@uomosul.edu.iq.

Patients & methods:

This prospective study included 72 patients with cranial metastasis from solid tumors who were presented and treated in the Mosul oncology hospital between Jan 2018 to 2020. This study was authorized by the College of Medicine/University of Nineveh's Scientific Committee and carried out following the Helsinki Declaration. All the patients were evaluated for histopathological confirmation for either the primary tumor or the metastatic brain lesion with medical imaging tests.

Both patient's characteristics (age, gender), and tumor characteristics (site of primary tumor, histopathology, molecular subtypes, site, and number of lesions), were evaluated, Furthermore, clinical characteristics were also evaluated including; presenting symptoms and signs, time between the primary tumor diagnosis and the development of brain metastases, status of primary tumor [whether controlled or not, presence of other site of metastasis out site the brain], the patients were followed up for at least 2 years, and given treatment characteristic were evaluated, overall survival of the included patients were calculated from the time of brain metastasis diagnosis to time of death or time of last follow up visit.

Statistical analysis: SPSS version 20 was used for data analysis, Kaplan–Meier survival test was used for survival analysis.

The result:

In this study, 72 patients with metastatic tumors to the brain were included, 46 (63.9%) were female and 26 (36.1%) were male, breast cancer was the primary tumor of 38 cases (52.7%%), while lung cancer was the primary tumor of 28 patients (38.8%%), the primary tumors in the remaining cases were malignant melanoma, gastric carcinoma, pancreatic carcinoma, soft tissue tumor and osteosarcoma. As shown in Table 1. Metachronous Brain metastasis was found in 52(72.2%) cases and synchronous brain metastasis was found in 20 (27.8%) cases.

Regarding the molecular subtypes of the included breast cancer patients, Luminal B, Her2 +ve, and HER2 enriched subtypes were the types of the majority of the cases as shown in Table 2.

While the histological subtype included lung cancer cases, adenocarcinoma of the lung was the most frequent histological type.

Regarding the diagnostic imaging test used for visualizing the tumor, MRI is the most frequently used one (88%), while CT scan was used in only 4 cases (5.6%) as shown in Table 3.

The types of treatments that were given to the included patients are shown in Table 4, The majority of the included patients were treated with chemotherapy and radiotherapy whole brain radiotherapy (WBRT), while surgical removal of the metastatic brain lesion was done on only one–quarter of the cases.

Extracranial metastasis was found in 39 cases (54%), while metastasis to the brain was only in 33 (45%) cases.

Primary	Frequency	Percent
Breast cancer	38	52.7%
Lung cancer	28	38.8%
Melanoma	2	2.7%
Gastric carcinoma	1	1.3%
Pancreatic tumor	1	1.3%
Soft tissue sarcoma	1	1.3%
Osteosarcoma	1	1.3%
Total	72	100%

Table 1: Primary tumors in patients with brain metastasis.

Molecular subtypes of breast cancer	Frequency	Percent
Luminal A	2	5.2%
Luminal B	6	15.7%
Luminal B , Her2 +ve	13	34.2%
Her2 enriched	11	28.9%
Triple–negative	6	15.7%
Total	38	100%
Histopathology of Lung cancer	**Frequency**	**Percent**
Adenocarcinoma	14	50
Squamous cell carcinoma	9	32.1
Small cell carcinoma	5	17.9
Total	28	100%

Table 2: Molecular subtypes and histopathological types of the included breast and lung cancer cases with brain metastasis.

Imaging test	Frequency	Percentage
MRI	64	88.8%
CT scan	4	5.6%
PET CT	4	5.6%
Total	72	100

Table 3: Imaging tests used for diagnosis of brain metastasis.

Treatment	Chemotherapy		Surgery		Targeted		WBRT		SRS	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Number	51	21	18	54	23	49	69	3	23	49
Percentage	70.8%	29.1%	25%	75%	31.9%	68%	95.8%	4.1%	31.9%	68%

Table 4: Types of treatment given to the patients with brain metastasis.

Primary	Metachronous	Synchronous	Total	P value
Breast	33	5	38	0.001
Lung	18	10	28	
others	1	5	6	
Total	52	20	72	

Table 5: Timing of brain metastasis.

Primary	Solitary lesion	2–3 lesions	More than 3	Total	P value
Breast	3	17	18	38	<0.01
Lung	2	15	11	28	
Others	0	0	6	6	
Total	5	32	35	72	

Table 6: Number of cerebellar metastatic lesions.

Metachronous brain metastasis was found more frequently in breast cancer patients than in patients with other primary tumors as shown in table 5.

Regarding the number of metastatic lesions in the brain, patients with lung primary had significantly more metastatic lesions compared with breast cancer patients as shown in Table 6, while no association between the primary tumor and the site of metastasis was found as shown in Table 7.

The median survival of patients with metastatic breast cancer to the brain was 18.3 months (SD=1.2), which is significantly higher than the median survival of patients with metastatic lung cancer to the lung 8.2 months (SD=0.5) as shown in figure 1.

Discussion:

Brain metastasis from solid tumors outside CNS in adults represents the most common kind of tumor affecting the brain. It is estimated to be 10 times more common than primary tumors of the brain. [5]

In our study, there was female predominance in the included patients with secondary brain metastasis, with an overall female–to–male ratio of 1.79:1. This predominance could be due higher number of breast cancer incidences in females. Excluding this sex–specific cancer, males have higher rates of brain metastasis in most of the other solid tumors which is compatible with other reported studies in the world. [6]

Cancer of the breast is the most common primary tumor that metastasized to the brain in this study, while in most other studies lung cancer was the most common cause irrespective of sex [2], although many reports found that incidence & prevalence of brain metastasis from breast cancer is increasing. [7] This result could be due to the higher incidence of the breast compared to other types of solid tumors in Iraq. [8,9]

Interestingly, the most molecular subtype was Luminal B, Her2 +ve and Her2 enriched, and the subtype that has the least incidence was luminal A, these findings suggest that HER2 expressive breast cancer has a higher incidence to spread to the brain than other subtypes. These results are compatible with other studies in the world. The ability of HER2 to enhance brain metastasis may be partially explained by HER2's potential interactions with other receptors. Brain metastasis has been linked to interactions and signaling from HER2 and its family members, particularly the epidermal growth factor receptor (EGFR) and HER3. [10,11,12]

Primary	Frontal	Parietal	Occipital	Brainstem	Total	P value
Breast	9	17	6	6	38	0.1
Lung	3	13	9	3	28	
Others	0	2	4	0	6	
Total	12	32	19	9	72	

Table 7: Site of metastatic lesions in brain.

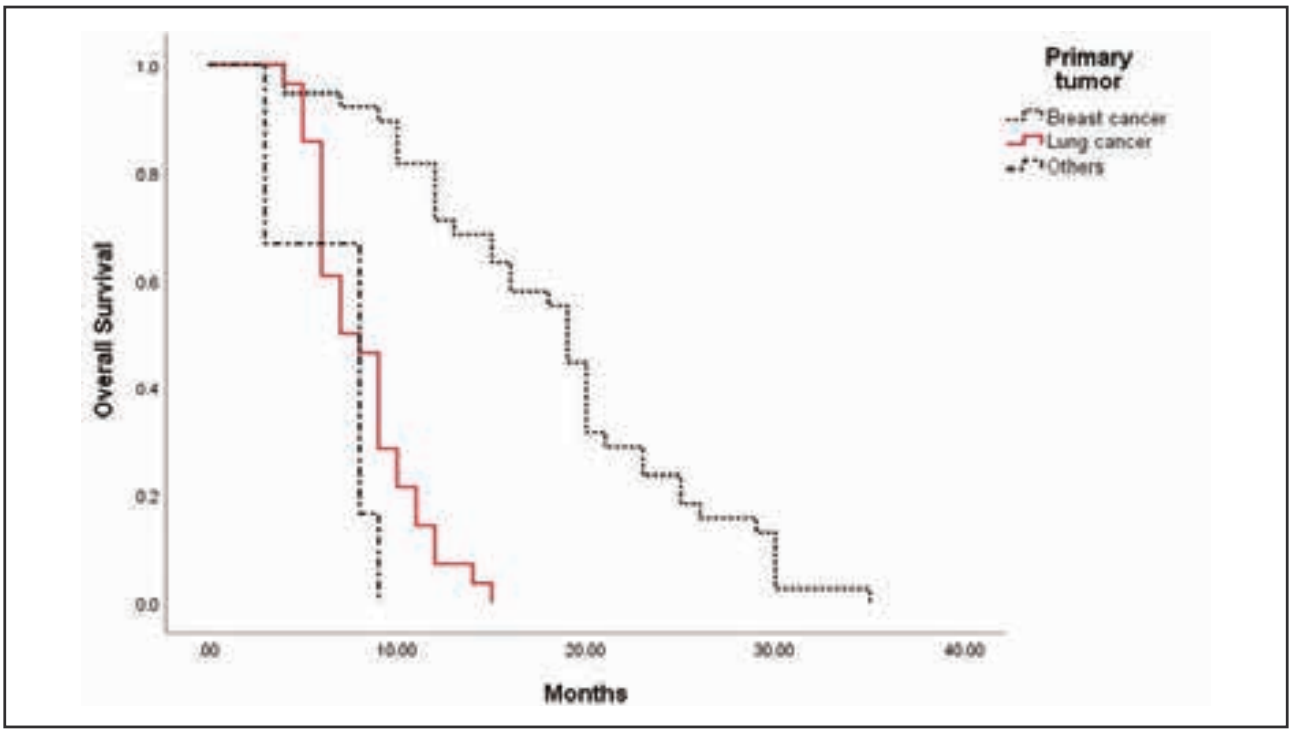


Figure 1: Showing the overall survival of patients with brain metastasis from different primaries.

Regarding lung cancer as a primary cause of brain metastasis, SCLC was the most common cause of brain metastasis in most previous studies [13], although in other studies, NSCLC particularly adenocarcinoma is becoming the most common cause of primary lung cancer that metastasizes to the brain & this is may be due to improvement in treatment modalities by using prophylactic radiotherapy in SCLC which is become crucial in the treatment of limited and extensive types of SCLC. [14] In this study, Out of the included lung cancer cases responsible for 38.8% of brain metastasis, we found that lung adenocarcinoma is the most common primary lung cancer that metastasized to the brain (14 out of 28 cases, 50%). Squamous cell lung cancer was the second most common cause (9 out of 28, 32.1%) while SCLC was found in 5 out of 28 cases (17.9%), this result could be related to the small sample size of the included cases.

The most common anatomical site of metastasis in the brain was the parietal lobe for breast cancer (17 cases out of 38, 44%) & lung cancer (13 out of 28/ 46%). In other literature, the cerebellum was the most common site. High blood volume and long perfusion time to the parietal, frontal lobes & cerebellum may explain the higher incidence of metastasis to these sites. [14] However, we found no significant association between the site of metastasis and primary tumor.

Regarding the number of metastatic lesions in the brain, we found that multiple metastases (more than 3) were found in 48.6%. 2–3 metastatic lesions in 44.4% while solitary metastasis was found in 6.9% only. For breast cancer, multiple metastases (more than 3) were found more than others (18/38) while for lung cancer 2–3 metastatic lesions were found more than others (15/28). This distribution is similar to the result of another study. [14]

For diagnosis, MRI was the most commonly used tool (88% of cases), and it is widely accepted as the best method of evaluating the number, size of the metastatic lesions , and location of brain tumors. [15,16,17]

Moreover, synchronous brain metastasis was found less frequently than metachronous metastasis (27.8%, 72.2% respectively). This is compatible with other studies. [18]

Regarding the presence of extracranial metastasis, we found that when brain metastasis is diagnosed, extracranial metastasis occurs in 54% of instances. This result is very similar to the result of the previous study that compared those patients with brain metastasis and extracranial metastasis with those without extracranial metastasis. [19]

Regarding the type of treatment In this study, the majority of patients received chemotherapy and whole brain radiotherapy (WBRT); 70.8% of patients received chemotherapy, 95.8% received WBRT and 31.9% were treated by SRS. Only 25% underwent surgical resection. Indeed, this depends on the performance state of the patient, the number of metastases, the presence of extracranial metastasis, and the availability of the treatment modalities.

Brain metastasis carries a dismal prognosis. The median survival differs with different primary tumors. For breast cancer the median survival was 18.3 months while for lung cancer it was 8.2 months, This is quite reasonable since lung cancer is more aggressive with more difficult control of extracranial metastasis and more resistant tumor to treatment than breast cancer [20,21,22], this high overall survival of metastatic breast cancer to the brain is similar to the results reported by other studies. [23].

Conclusion:

The finding of our study demonstrated that breast and lung primary tumors are the most frequent primaries causing brain metastasis. Imaging studies using MRI & CT scans are more available and accessible for most of the patients. We found that WBRT is the main treatment used. Sterotactic radiotherapy was not available at the time of performing this study. Surgical resections are limited to a minority of our patients. We recommend more studies for each primary tumor focusing on its pathologic & molecular characteristics & its relation to brain metastasis.

Acknowledgment:

This study was supported by Nineveh University and the University of Mosul.

Conflict of Interest:

Non–declared

References:

1. Posner JB. Brain metastases: 1995. A brief review. J Neurooncol. 1996; 27(3):287–93. doi: 10.1007/BF00165486.
2. Johnson JD, Young B. Demographics of brain metastasis. Neurosurg Clin N Am. 1996; 7(3):337–44.
3. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, et al. Diagnosis–specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi–institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys. 2010; 77(3):655–61. doi: 10.1016/j.ijrobp.2009.08.025.
4. Nabors. LB, Portnow J, Bhatia A, Bloch O, Brew S, Butowski N, et al., editors. Central Nervous System Cancer: NCCN Clinical Practice Guidelines in Oncology. version 1. National Comprehensive Cancer Network, Inc. 2023. p.56–65.
5. Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE. Abeloff Clinical Oncology. 6th ed. Philadelphia, PA: Mosby Elsevier; 2019
6. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Curr Oncol Rep. 2012; 14(1):48–54. doi: 10.1007/s11912–011–0203–y.
7. Pestalozzi BC, Zahrieh D, Price KN, Holmberg SB, Lindtner J, Collins J, Crivellari D, Fey MF, Murray E, Pagani O, Simoncini E, Castiglione–Gertsch M, Gelber RD, Coates AS, Goldhirsch A; International Breast Cancer Study Group (IBCSG). Identifying breast cancer patients at risk for Central Nervous System (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). Ann Oncol. 2006; 17(6):935–44. doi: 10.1093/annonc/mdl064.
8. Olson EM, Abdel–Rasoul M, Maly J, Wu CS, Lin NU, Shapiro CL. Incidence and risk of central nervous system metastases as site of first recurrence in patients with HER2–positive breast cancer treated with adjuvant trastuzumab. Ann Oncol. 2013; 24(6):1526–33. doi: 10.1093/annonc/mdt036.
9. Al Obeidy BF, Al Zobair AA, Jawher NMT, Zheng F. Relationship between Vitamin D3 Level and Body Mass Index in Postmenopausal Breast Cancer Patients. 2022; 19 (4) :671–675.
10. Zimmer AS, Van Swearingen AED, Anders CK. HER2–positive breast cancer brain metastasis: A new and exciting landscape. Cancer Rep (Hoboken). 2022; 5(4):e1274. doi: 10.1002/cnr2.1274.
11. Garcia–Alvarez A, Papakonstantinou A, Oliveira M. Brain Metastases in HER2–Positive Breast Cancer: Current and Novel Treatment Strategies. Cancers (Basel). 2021; 13(12):2927. doi: 10.3390/cancers13122927.
12. Al Zobair, A., Hayawi, M., Al Obeidy, B. Reliability of CA15–3 Tumor Marker in Monitoring Therapeutic Response in Different Molecular Subtypes of Metastatic Breast Cancer. Middle East Journal of Cancer, 2022; 13(3): 438–448. doi: 10.30476/mejc.2022.87357.1412
13. Schild SE, Sio TT, Daniels TB, Chun SG, Rades D. Prophylactic Cranial Irradiation for Extensive Small–Cell Lung Cancer. J Oncol Pract. 2017;13(11):732–738. doi: 10.1200/JOP.2017.026765.
14. Wang G, Xu J, Qi Y, Xiu J, Li R, Han M. Distribution Of Brain Metastasis From Lung Cancer. Cancer Manag Res. 2019;11:9331–9338. doi: 10.2147/CMAR.S222920.
15. Takano K, Kinoshita M, Takagaki M, Sakai M, Tateishi S, Achiha T, Hirayama R, Nishino K, Uchida J, Kumagai T, Okami J, Kawaguchi A, Hashimoto N, Nakanishi K, Imamura F, Higashiyama M, Yoshimine T. Different spatial distributions of brain metastases from lung cancer by histological subtype and mutation status of epidermal growth factor receptor. Neuro Oncol. 2016;18(5):716–24. doi: 10.1093/neuonc/nov266.
16. Derks SHAE, van der Veldt AAM, Smits M. Brain metastases: the role of clinical imaging. Br J Radiol. 2022 Feb 1;95(1130):20210944. doi: 10.1259/bjr.20210944.
17. Taj al–Din QAH. The validity of diffusion–weight MRI in differentiation cystic brain tumors from brain abscess: prospective study. Medical Journal of Babylon. 2017;14, (1): 48–56.

18. Shibahara I, Kanamori M, Watanabe T, Utsunomiya A, Suzuki H, Saito R, Sonoda Y, Jokura H, Uenohara H, Tominaga T. Clinical Features of Precocious, Synchronous, and Metachronous Brain Metastases and the Role of Tumor Resection. World Neurosurg. 2018;113:e1–e9. doi: 10.1016/j.wneu.2017.10.145.

19. Rades D, Segedin B, Nagy V, Schild SE, Trang NT, Khoa MT. Predicting the presence of extracranial metastases in patients with brain metastases upon first diagnosis of cancer. Strahlenther Onkol. 2014;190(4):405–7. doi: 10.1007/s00066–013–0516–x.

20. Carney DN. Lung cancer––time to move on from chemotherapy. N Engl J Med. 2002; 346(2):126–8. doi: 10.1056/NEJM200201103460211.

21. Valachis A, Carlqvist P, Ma Y, Szilcz M, Freilich J, Vertuani S, et al. Overall survival of patients with metastatic breast cancer in Sweden: a nationwide study. Br J Cancer. 2022; 127(4):720–725. doi: 10.1038/s41416–022–01845–z.

22. Al Zobair AA, Al Obeidy BF, Yang L, Yang C, Hui Y, Yu H, et al. Concomitant overexpression of EGFR and CXCR4 is associated with worse prognosis in a new molecular subtype of non–small cell lung cancer. Oncol Rep. 2013; 29(4):1524–32. doi: 10.3892/or.2013.2254.

23. Sun H, Xu J, Dai S, Ma Y, Sun T. Breast cancer brain metastasis: Current evidence and future directions. Cancer Med. 2023 Jan;12(2):1007–1024. doi: 10.1002/cam4.5021.