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Principles of Lung Cancer Metastasis to Brain

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Abstract

Lung cancer is a disease associated with significant morbidity and mortality on a global setting. This form of cancer commonly gives raise to metastatic lesions the brain, which can further worsen outcomes. In this focused review, we discuss an overview of lung cancers that metastasize to the brain: known risk factors; means of detection and diagnosis; and options for treatment including a comparison between surgical resection, stereotactic radiosurgery, and whole-brain radiation therapy. These interventions are still being assessed by clinical trials and continue to be modified through evidence-based practice.

Keywords: *lung cancer, brain metastasis, stereotactic radiosurgery, whole-brain radiation therapy.*

Introduction

Lung cancer is the most common form of malignancy and cause of cancer-related deaths in the world, and the second leading form of cancer-related deaths in the United States.[1,2] Several types of lung cancer exist and may roughly be grouped into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with the latter being broken down further into adenocarcinoma, squamous cell cancer, and large cell carcinoma.[3] Cases of respiratory cancers with metastases involving the brain have been associated with significantly higher levels of both morbidity and mortality.[4,5] An estimated 20% of patients who present with lung cancer will have a brain metastasis at the time of diagnosis, and up to 50% of lung cancer patients will develop brain metastases (BrMs) over the course of their illness.[6-8] The formation of BrMs is a complex, multistep process that involves the spread of cancerous cells from the initial site of neoplastic growth to the eventual colonization of the brain.[9,10] Genetic analyses have linked several driver mutations in the development of BrMs in varying lung malignancies: mutations in tumor suppressor LKB1 and KRAS are predictive of BrMs in NSCLCs;[11] lung adenocarcinomas with mutations in EGFR and ALK, and hyperactivity within the WNT signally pathway have demonstrated higher occurrence of BrMs;[12-14] and upregulation of ANGT4 and PDGFRB genes have been linked with SCLC BrMs.[15]

Central Nervous System Diagnosis

BrMs are often initially detected from imaging as part of a metastatic tumor workup, or following the advent of clinical symptoms; with a definitive diagnosis later being confirmed via biopsy.[16,17] BrMs, particularly with those presenting with neurologic symptoms, are associated with a poorer prognosis.[4,18,19] However, outcomes are greatly improved when metastases are detected earlier, and are thus smaller in size.[4,18] Early detection could allow for use of minimally invasive procedures such as LITT,[20] stereotactic radiosurgery,[21-23] gamma knife surgery,[24] whole brain radiotherapy, or chemotherapy.[23] As such, there is increasing research for the detection of early brain metastases, with a focus on identifying risk factors.

Previous research has identified several risk factors

specific for the presence of BrMs in NSCLC: being the female gender; concurrent lymphatic metastases; specific microRNA signatures; a high neutrophil to lymphocyte (NLR) ratio; elevated levels of neurofilament light chain; presence of EGFR driver mutation; and elevated serum levels of CEA, S100B, ProApolipoprotein A1 (apo A-1), Ki-67, VEGF-C, caspace-3, and calcium.[25-37] Sun, et at., have even postulated that ProApolipoprotein A1 and S100B alone may be used for an independent and accurate diagnosis of metastatic brain tumors; which could allow a clinician performing metastatic work ups to administer prophylactic treatments, such as intracranial irradiation.[25]

Preclinical studies using rodent models have demonstrated early detection of BrMs by employing molecular MRI with contrast agents that highlight tumor vascular factors ALCAM21 and VCAM-1.[38-40] Routine pre-operative and post-operative imaging should also be considered: a study by Yokoi, et al., showed that CT and MRI detected brain metastases in 6.8% and 7.1% of 155 and 177 patients, respectively, during the perioperative period for patients with non-squamous cell lung cancer.[41] Preclinical rodent studies have also indicated that brain metastases can be diagnosed even at micrometastatic stages by screening for urine metabolites; however, these were not specific for lung cancer.[42]

The development of machine learning algorithms has also been shown as a promising method of early detection. Machine learning is performed by teaching a machine a dataset with known predictors and outcomes using algorithms. What the machine then “learns” can be used in diagnosis in datasets where the diagnosis is unknown. [43,44] Cho (2021) performed a systematic review and meta-analysis of 12 studies using classical machine learning and deep learning on MRI modalities, revealing pooled 88.7% and 90.1

Imaging Modalities

Several options in terms of imaging modalities are available in the diagnosing of BrMs. Magnetic Resonance Imaging (MRI) is the modality primarily used in the diagnosing and localization of brain tumors in patients with brain lesions, as high level of availability, comparatively high resolution, and excellent capabilities for the characterization of soft tissues are provided by this device; additionally, with specific sequences, supplementary biological information like apoptosis, cell density, or angiogenesis can be measured (diffusion-weighted MRIs or perfusion-weighted MRIs)[48,49] Certain paramagnetic contrast agents (CA) can also reveal impaired blood-brain barriers (BBBs).[50] The downside to the modality is the lack of specificity for neoplastic tissue, which makes it challenging to detect malignancies, monitor cancer progression, or detect potential lesion growth.[51] Additionally, MRI is unable to assess treatment response after surgery, chemotherapy, or radiotherapy nor the quantity of inflammatory, demyelinating, infarction, and ischemia.[48]

A molecular imaging technique called Positron Emission Tomography (PET), which detects emitted photons from radiotracers, is another advanced imaging technique widely used in brain cancer patients. Using PET imaging, metabolic processes, like glucose metabolism and amino acid uptake, can be measured noninvasively and quantitatively.[52] Despite this, PET is unable to distinguish between grey and white matter structural abnormalities. PET is also limited by its lower spatial resolution, and inability to detect rapid changes in brain activity.[53] However, PET does have the advantage of being able to co-register medical images with other imaging methods. In oncology, integrating these two techniques to develop simultaneous multimodal imaging is particularly relevant, as it allows clinicians to assess the tumor microenvironment with the help of several diagnostic biomarkers. [54,55]

Hybrid PET/MRI scanners enable high-resolution metabolic and anatomical imaging. [53,56] This method combines both the high sensitivity of PET and the high resolution of MRI to provide a comprehensive picture of anatomical details. These coupled PET and MRI examinations may prove to be significantly more advantageous than independent examinations when attempting to understand tumor characteristics and determining whether surgery or radiation therapy would be an more appropriate intervention.[54,57] However, there is no conclusive evidence that PET/MRI is superior to PET/CT in oncology, and hybrid PET/MRI systems typically require longer scanning times and are associated with higher costs when compared to PET/CT systems.[58]

Radiopharmaceuticals should be selected based on the characteristics of the tumor being examined. PET tracers like [18F] fluorodeoxyglucose (FDG) are most used because tumor cells exhibit a higher glucose metabolism than healthy tissues [54,59] In cancer cells, [18F] FDG is trapped after crossing the BBB. Beta-emitting 14Cdeoxyglucose (DG) was demonstrated as a BBB crosser in the early 1970s.[60] By the hexokinase system, [18F] FDG is

phosphorylated by glucose transporters and transported into cells. As a result, it persists in tissues for a long time since it cannot be metabolized.[61] [18F] FDG has a low specificity and shows a high background uptake by the normal brain despite its widespread use in clinical practice. A PET tracer based on amino acids was developed in response to these limitations. [54,62] It can be demonstrated that these amino acid tracers are elevated in malignant tumors because of unregulated protein synthesis, a symptom of increased cell proliferation.[49] The most common examples are 3'-deoxy-3'-[18F] fluorothymidine ([18F] FLT), 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine ([18F] FDOPA), and [11C] methionine ([11C] MET). [54,59,62,63]

Treatment

Current treatments for lung cancer patients with BrMs include supportive care, surgical resection, radiotherapies.[64] The integration of palliative care in the management of BrMs should also be considered as it has been shown to greatly improve the quality of life, appetite, and mood; and is correlated with better survival rates, despite less aggressive treatment.[65] Supportive medications, such as steroids and antiseizure drugs, have also demonstrated increased survival rates when coupled with traditional radiotherapies.[6,66-68]

Surgical Management

The discussion of surgically resecting BrMs is best understood by first outlining the distinct subsets of clinical presentations. One subset is when the tumor size is large and causing severe neurologic symptoms, such as mass effect.[69,70] The former subset often falls under the category of necessarily more urgent or emergent in nature, often requiring hastened neurosurgical intervention.[71,72] The mechanism behind this presentation may be either due to direct pressure on the brain tissue from the tumor itself, or from uncontrolled cerebral edema that secondarily increases intracranial pressure and can lead to acute herniation syndrome.[73] Given that some evidence points to the capacity for brain metastases to cause even more cerebral edema than primary tumors, this may further increase the importance of considering expedited neurosurgical intervention in these patients via resection of the tumor.[74,75]

Another subset of patients who meet criteria for surgical resection are those with a brain metastasis that is not large or causing severe neurologic symptoms, but in patients in which the intracranial disease is limited, systemic disease is controlled, and the patient is functionally independent. [70,76] Furthermore, surgery is often preferred with an extracranial metastasis from lung cancer if there is only one single lesion.[77] Given that radiation therapy is a commonly used treatment modality for brain metastases from lung cancer, it is also important to describe when surgery is preferred in these instances. This is often the case with BrMs that arise from a primary lung cancer that is resistant to radiotherapy.[78,79] Surgery for patients comprised in this subset is also often indicated in patients who have had radiation therapy in the past, as this is often necessary to definitively distinguish between radiation-related tissue necrosis and presence of tumor metastasis.[80-82] Lastly, in patients with multiple brain metastases, surgical resection is commonly indicated for the dominant lesion. [83] A summary of the above indications is outlined in Figure.1

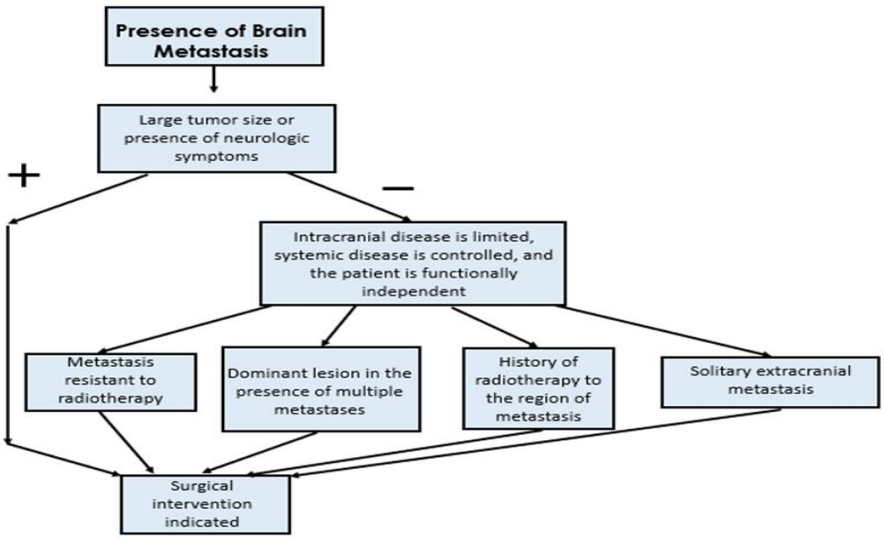

Fig 1: Summary of treatment work process for BrMs.

Table 1: Summary of known risk factors and pre-clinical studies with early detection of BrMs in lung cancer.

Known risk factors	Advanced tumor grade, stage, and size
	Elevated serum CEA, S100b, Apo A-1, Ki-67, VEGF-C, caspace-3, calcium, NLR, NFL
	Female gender
	Lymphatic spread
	Adenocarcinoma, EGFR mutation
Pre-clinical studies	mRNA-378, hsa-miR-210, has-miR-214, hsamiR-15a
	Molecular MRI (contrast specific for ALCAM and VCAM)
	Machine learning models using MRI
	Routine perioperative imaging during lung resections
	Machine learning models using miRNA expression
	Machine learning models using demographic and patient factors
	Urine metabolites

Radiation

Radiotherapies in the treatment of metastatic brain lesions are primarily groups into Stereotactic radiosurgery (SRS), and whole brain radiation therapy (WBRT).[84,85] SRS is a non-invasive form of radiation therapy that uses concentrated, multi-focal beams of radiation to destroy tissues.[84,86] There are multiple radiation delivery methods of SRS: Gamma Knife, Linear accelerator (LINAC), and Proton beam therapy. Gamma knife surgery uses gamma radiation in a very small operating field, while LINAC uses x-ray radiation with greater operating flexibility. Proton beam therapy is like Gamma knife and LINAC; however, it uses protons or neutrons instead of photons and has been thought to prevent some deleterious side effects related to conventional therapy. In contrast to the concentrated nature of SRS, whole brain radiation therapy (WBRT) is an exposure of the entire cranium to radiation.[87] WBRT is the current standard for treatment of BrMs from NSCLC in patients with multiple metastases.[88] Although WBRT is being replaced with SRS for other forms of BrMs, it remains the standard for NSCLC and SCLC metastases.[89]

SRS and WBRT may be used exclusively as well as in conjunction with other modalities.[88] Literature reports that WBRT in addition to SRS has a negative impact on cognitive function post treatment, but also shows lower cancer recurrence rates overall.[85-87,90-92] Aoyama et al. reported tumor reoccurrence rate of about 45% in SRS + WBRT and about 75% in SRS alone.[86] Brown et al. found that adult patients with 1-3 lung cancer metastasis who underwent SRS+WBRT (n=48) treatment had worse post-operative cognitive scores and neurological deterioration compared to those treated with SRS alone (n=63).[90] These studies suggest that using SRS in conjunction with WBRT could lead to worse cognitive outcomes, but lower rates of tumor recurrence compared to exclusive SRS treatment.

Treatment via SRS and WBRT differs in dosage and number of fractions. A fraction refers to dividing up the total radiation dosage into multiple treatments and maximizes the effectiveness of radiotherapy. This is accomplished by administering radiation on regularly time intervals which correlate with radiosensitive stages in the cell cycle of cancer cells.[93] SRS treatment typically consists of one fraction at a dose of 15-24 Gray (Gy).[93-95] However, new therapies like hypo-fractioned SRS (HF-SRS), that deliver multiple fractions, have recently shown to increase outcomes and decrease toxicity for large (>3cm) tumors.[93] A limitation to this approach is the possibility of tumor cell regrowth between fractioned doses.[93] In contrast to single dose SRS, WBRT is administered in multiple fractions. WBRT irradiates the entire cranium and is typically administered in 10 fractions of 3 Grays (Gy).[84,88,96,97] Literature shows that fraction dosages greater than 3 Gy may be associated with WBRT-related neurotoxic effects.[96-98] WBRT may cause cognitive decline, but it may also treat micro-metastases that have gone undetected on imaging.

When ionizing radiation is introduced to tissues, a large quantity of free radicals is created, and these free radicals combined with oxygen in the blood and destroy surrounding tissues.[99-101] Studies have demonstrated hypoxia to decrease radiation therapy results because of free oxygen able to radicalize.[101,102] As such, hypoxic tumors need 2.5-3 times the radiation dosage to reach the same efficacy as non-hypoxic tumors.[99,103] Fractioning schedules allow time for blood to return to tumor cells, increasing the amount of oxygen available to be ionized and the overall effectiveness of radiotherapy.

Table 2: Summary of comparison between Whole Brain Radiation Therapy (WBRT), and Stereotactic Radiation Surgery (SRS).

Therapy Type	Treatment	Dosage/Fraction	Benefits	Drawbacks
WBRT	Radiation to the entire cranium	Multiple small doses fractionated treatments 3 Gy x 10 Fractions	May treat micro-metastasis not seen on imaging	Greater radiation dosage to healthy tissue
SRS	Multifocal beams of radiation concentrated on the tumor only	Single or multiple high-dosage fractions/treatments 15-24 Gy x 1 Fraction	Decreased tumor toxicity >3cm Limits radiation dosage to healthy tissues	Higher probability of tumor resurgence

Conclusion

The development of brain metastases in lung cancer patients continues to be a major health concern on a global scale. These metastatic tumors significantly increase both morbidity and mortality rates among patients. Despite advances in medical technology, no treatment yet exists without adverse effects, or low remission rates: surgical resection alone leaves concern for untreated micrometases; and radiotherapies are associated with gross cognitive decline. Optimum dosing and fractioning in both stereotactic radiosurgery and whole brain radiation therapy have been investigated to find an optimal approach, but results are not without there drawbacks. Ultimately, the most promising option for improving mortality and morbidity rates lies in the detection of brain metastases as early as possible; thereby minimizing the intensity of treatment—and therefore adverse consequences—needed.

References

1. Cancer Facts & Figures 2021. Published online 1930:72.
2. Ferlay J, Soerjomataram I, Dikshit R, et al. (2012), Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN. International Journal of Cancer. 2015;136(5): E359-E386. doi:10.1002/ijc.29210
3. Types of lung cancer | Cancer Research UK. Accessed August 28, 2022. https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types
4. Sperduto, P. W., Kased, N., Roberge, D., Xu, Z., Shanley, R., Luo, X., ... & Mehta, M. (2012). Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. Journal of Clinical Oncology, 30(4), 419.
5. Sacks P, Rahman M. (2020), Epidemiology of Brain Metastases. Neurosurgery Clinics of North America.31(4):481-488.
6. Sørensen, J. B., Hansen, H. H., Hansen, M., & Dombernowsky, P. (1988). Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis. Journal of Clinical Oncology, 6(9), 1474-1480.
7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: A Cancer Journal for Clinicians. 2019;69(1):7-34. doi:10.3322/caac.21551
8. Barnholtz-Sloan, J. S., Sloan, A. E., Davis, F. G., Vigneau, F. D., Lai, P., & Sawaya, R. E. (2004). Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. Journal of clinical oncology, 22(14), 2865-2872.
9. Valastyan S, Weinberg RA. Tumor Metastasis: Molecular Insights and Evolving Paradigms. Cell. 2011;147(2):275-292.
10. Achrol, A. S., Rennert, R. C., Anders, C., Soffietti, R., Ahluwalia, M. S., Nayak, L., ... & Chang, S. D. (2019). Brain metastases. Nature Reviews Disease Primers, 5(1), 5.
11. Zhao, N., Wilkerson, M. D., Shah, U., Yin, X., Wang, A., Hayward, M. C., ... & Hayes, D. N. (2014). Alterations of LKB1 and KRAS and risk of brain metastasis: comprehensive characterization by mutation analysis, copy number, and gene expression in non-small-cell lung carcinoma. Lung Cancer, 86(2), 255-261.
12. Hayes, D. N., Monti, S., Parmigiani, G., Gilks, C. B., Naoki, K., Bhattacharjee, A., ... & Meyerson, M. (2006). Gene expression profiling reveals reproducible human lung adenocarcinoma subtypes in multiple independent patient cohorts. Journal of Clinical Oncology, 24(31), 5079-5090.
13. Cancer Genome Atlas Research Network. (2014). Comprehensive molecular profiling of lung adenocarcinoma. Nature, 511(7511), 543.
14. Nguyen, D. X., Chiang, A. C., Zhang, X. H. F., Kim, J. Y., Kris, M. G., Ladanyi, M., ... & Massagué, J. (2009). WNT/TCF signaling through LEF1 and HOXB9 mediates lung adenocarcinoma metastasis. Cell, 138(1), 51-62.
15. Ilhan-Mutlu, A., Siehs, C., Berghoff, A. S., Ricken,

G., Widhalm, G., Wagner, L., & Preusser, M. (2016). Expression profiling of angiogenesis-related genes in brain metastases of lung cancer and melanoma. Tumor Biology, 37, 1173-1182.

16. Fink, K. R., & Fink, J. R. (2013). Imaging of brain metastases. Surgical neurology international, 4(Suppl 4), S209.
17. Posner JB. Management of brain metastases. Rev Neurol (Paris). 1992;148(6-7):477-487.
18. Ali, A., Goffin, J. R., Arnold, A., & Ellis, P. M. (2013). Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases. Current Oncology, 20(4), 300-306.
19. de Cos, J. S., González, M. A. S., Montero, M. V., Calvo, M. C. P., Vicente, M. J. M., & Valle, M. H. (2009). Non-small cell lung cancer and silent brain metastasis: Survival and prognostic factors. Lung cancer, 63(1), 140-145.
20. Bastos, D. C. D. A., Fuentes, D. T., Traylor, J., Weinberg, J., Kumar, V. A., Stafford, J., ... & Prabhu, S. S. (2020). The use of laser interstitial thermal therapy in the treatment of brain metastases: a literature review. International Journal of Hyperthermia, 37(2), 53-60.
21. Linskey, M. E., Andrews, D. W., Asher, A. L., Burri, S. H., Kondziolka, D., Robinson, P. D., ... & Kalkanis, S. N. (2010). The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. Journal of neuro-oncology, 96, 45-68.
22. Swinson, B. M., & Friedman, W. A. (2008). Linear accelerator stereotactic radiosurgery for metastatic brain tumors: 17 years of experience at the University of Florida. Neurosurgery, 62(5), 1018-1032.
23. Chi, A., & Komaki, R. (2010). Treatment of brain metastasis from lung cancer. Cancers, 2(4), 2100-2137.
24. Sansur, C. A., Chin, L. S., Ames, J. W., Banegura, A. T., Aggarwal, S., Ballesteros, M., ... & Eisenberg, H. (2000). Gamma knife radiosurgery for the treatment of brain metastases. Stereotactic and functional neurosurgery, 74(1), 37-51.
25. Sun, D. S., Hu, L. K., Cai, Y., Li, X. M., Ye, L., Hou, H. Y., ... & Jiang, Y. H. (2014). A systematic review of risk factors for brain metastases and value of prophylactic cranial irradiation in non-small cell lung cancer. Asian Pacific Journal of Cancer Prevention, 15(3), 1233-1239.
26. An, N., Jing, W., Wang, H., Li, J., Liu, Y., Yu, J., & Zhu, H. (2018). Risk factors for brain metastases in patients with non–small-cell lung cancer. Cancer medicine, 7(12), 6357-6364.
27. Chen S, Hua X, Jia J, et al. Risk factors for brain metastases in patients with non-small cell lung cancer: a meta-analysis of 43 studies. Annals of Palliative Medicine. 2021;10(4):3657672-3653672. doi:10.21037/apm-20-1722
28. Lee, D. S., Kim, Y. S., Jung, S. L., Lee, K. Y., Kang, J. H., Park, S., ... & Yoon, S. C. (2012). The relevance of serum carcinoembryonic antigen as an indicator of brain metastasis detection in advanced non-small cell lung cancer. Tumor Biology, 33, 1065-1073.
29. Choi, H., Puvenna, V., Brennan, C., Mahmoud, S., Wang, X. F., Phillips, M., ... & Mazzone, P. (2016). S100B and S100B autoantibody as biomarkers for early detection of brain metastases in lung cancer. Translational lung cancer research, 5(4), 413.
30. Winther-Larsen, A., Hviid, C. V. B., Meldgaard, P., Sorensen, B. S., & Sandfeld-Paulsen, B. (2020). Neurofilament light chain as a biomarker for brain metastases. Cancers, 12(10), 2852.
31. Gaebe, K., Li, A. Y., & Das, S. (2021). Clinical biomarkers for early identification of patients with intracranial metastatic disease. Cancers, 13(23), 5973.
32. Chen L tao, Xu S dong, Xu H, Zhang J feng, Ning J feng, Wang S fa. MicroRNA-378 is associated with non-small cell lung cancer brain metastasis by promoting cell migration, invasion and tumor angiogenesis. Med Oncol. 2012;29(3):1673-1680. doi:10.1007/s12032-011-0083-x
33. Naresh, G., Malik, P. S., Khurana, S., Pushpam, D., Sharma, V., Yadav, M., ... & Pathy, S. (2021). Assessment of brain metastasis at diagnosis in non–small-cell lung cancer: a prospective observational study from North India. JCO Global Oncology, 7, 593-601.
34. Milano, M. T., Bates, J. E., Budnik, J., Qiu, H., Hardy, S., Cummings, M. A., ... & Usuki, K. Y. (2020). Risk of brain metastases in T1–3N0 NSCLC: a population-based analysis. Lung Cancer Management, 9(1), LMT25.
35. Ji, Z., Bi, N., Wang, J., Hui, Z., Xiao, Z., Feng, Q., ... & Wang, L. (2014). Risk factors for brain metastases in locally advanced non-small cell lung cancer with definitive chest radiation. International Journal of Radiation Oncology* Biology* Physics, 89(2), 330-337.

36. Marchi, N., Mazzone, P., Fazio, V., Mekhail, T., Masaryk, T., & Janigro, D. (2008). ProApolipoprotein A1: a serum marker of brain metastases in lung cancer patients. Cancer: Interdisciplinary International Journal of the American Cancer Society, 112(6), 1313-1324.
37. He, J., Wang, X., Xiao, R., Zuo, W., Zhang, W., & Yao, H. (2021). Risk factors for brain metastases from non-small-cell lung cancer: a protocol for observational study. Medicine, 100(9).
38. Cheng, V. W., de Pennington, N., Zakaria, R., Larkin, J. R., Serres, S., Sarkar, M., ... & Sibson, N. R. (2022). VCAM-1–targeted MRI Improves Detection of the Tumor-brain Interface. Clinical Cancer Research, 28(11), 2385-2396.
39. Cheng, V. W., Soto, M. S., Khrapitchev, A. A., Perez-Balderas, F., Zakaria, R., Jenkinson, M. D., ... & Sibson, N. R. (2019). VCAM-1–targeted MRI enables detection of brain micrometastases from different primary tumors. Clinical Cancer Research, 25(2), 533-543.
40. Serres, S., Soto, M. S., Hamilton, A., McAteer, M. A., Carbonell, W. S., Robson, M. D., ... & Sibson, N. R. (2012). Molecular MRI enables early and sensitive detection of brain metastases. Proceedings of the National Academy of Sciences, 109(17), 6674-6679.
41. Yokoi, K., Kamiya, N., Matsuguma, H., Machida, S., Hirose, T., Mori, K., & Tominaga, K. (1999). Detection of brain metastasis in potentially operable non-small cell lung cancer: a comparison of CT and MRI. Chest, 115(3), 714-719.
42. Larkin, J. R., Dickens, A. M., Claridge, T. D., Bristow, C., Andreou, K., Anthony, D. C., & Sibson, N. R. (2016). Early diagnosis of brain metastases using a biofluids-metabolomics approach in mice. Theranostics, 6(12), 2161.
43. Erickson BJ, Korfiatis P, Akkus Z, Kline TL. Machine Learning for Medical Imaging. Radiographics. 2017;37(2):505-515. doi:10.1148/rg.2017160130
44. Wagner MW, Namdar K, Biswas A, Monah S, Khalvati F, Ertl-Wagner BB. Radiomics, machine learning, and artificial intelligence—what the neuroradiologist needs to know. Neuroradiology. 2021;63(12):1957-1967. doi:10.1007/s00234-021-02813-9
45. Cho, S. J., Sunwoo, L., Baik, S. H., Bae, Y. J., Choi, B. S., & Kim, J. H. (2021). Brain metastasis detection using machine learning: a systematic review and meta-analysis. Neuro-oncology, 23(2), 214-225.
46. Wang, K. J., Makond, B., & Wang, K. M. (2014). Modeling and predicting the occurrence of brain metastasis from lung cancer by Bayesian network: a case study of Taiwan. Computers in biology and medicine, 47, 147-160.
47. Zhao, S., Yu, J., & Wang, L. (2018). Machine learning based prediction of brain metastasis of patients with IIIA-N2 lung adenocarcinoma by a three-miRNA signature. Translational oncology, 11(1), 157-167.
48. Marner, L., Henriksen, O. M., Lundemann, M., Larsen, V. A., & Law, I. (2017). Clinical PET/MRI in neurooncology: opportunities and challenges from a single-institution perspective. Clinical and translational imaging, 5, 135-149.
49. Lopci, E., Franzese, C., Grimaldi, M., Zucali, P. A., Navarria, P., Simonelli, M., ... & Chiti, A. (2015). Imaging biomarkers in primary brain tumours. European journal of nuclear medicine and molecular imaging, 42, 597-612.
50. Catana, C., Drzezga, A., Heiss, W. D., & Rosen, B. R. (2012). PET/MRI for neurologic applications. Journal of nuclear medicine, 53(12), 1916-1925.
51. Lohmann, P., Werner, J. M., Shah, N. J., Fink, G. R., Langen, K. J., & Galldiks, N. (2019). Combined amino acid positron emission tomography and advanced magnetic resonance imaging in glioma patients. Cancers, 11(2), 153.
52. Mier, W., & Mier, D. (2015). Advantages in functional imaging of the brain. Frontiers in human neuroscience, 9, 249.
53. Overcast, W. B., Davis, K. M., Ho, C. Y., Hutchins, G. D., Green, M. A., Graner, B. D., & Veronesi, M. C. (2021). Advanced imaging techniques for neuro-oncologic tumor diagnosis, with an emphasis on PET-MRI imaging of malignant brain tumors. Current Oncology Reports, 23, 1-15.
54. Ferda J, Ferdová E, Hes O, Mraček J, Kreuzberg B, Baxa J. PET/MRI: Multiparametric imaging of brain tumors. European Journal of Radiology. 2017;94:A14-A25.
55. Rosenkrantz, A. B., Friedman, K., Chandarana, H., Melsaether, A., Moy, L., Ding, Y. S., ... & Jain, R. (2016). Current status of hybrid PET/MRI in oncologic imaging. AJR. American journal of roentgenology, 206(1), 162.
56. Heiss, W. D. (2009). The potential of PET/MR for

brain imaging. European journal of nuclear medicine and molecular imaging, 36, 105-112.

57. Rausch, I., Rischka, L., Ladefoged, C. N., Furtner, J., Fenchel, M., Hahn, A., ... & Beyer, T. (2017). PET/MRI for oncologic brain imaging: a comparison of standard MR-based attenuation corrections with a model-based approach for the Siemens mMR PET/MR system. Journal of Nuclear Medicine, 58(9), 1519-1525.
58. Mayerhoefer, M. E., Prosch, H., Beer, L., Tamandl, D., Beyer, T., Hoeller, C., ... & Haug, A. R. (2020). PET/MRI versus PET/CT in oncology: a prospective single-center study of 330 examinations focusing on implications for patient management and cost considerations. European journal of nuclear medicine and molecular imaging, 47, 51-60.
59. Puttick, S., Bell, C., Dowson, N., Rose, S., & Fay, M. (2015). PET, MRI, and simultaneous PET/MRI in the development of diagnostic and therapeutic strategies for glioma. Drug discovery today, 20(3), 306-317.
60. Quartuccio, N., Laudicella, R., Vento, A., Pignata, S., Mattoli, M. V., Filice, R., ... & Cistaro, A. (2020). The additional value of 18F-FDG PET and MRI in patients with glioma: a review of the literature from 2015 to 2020. Diagnostics, 10(6), 357.
61. Verberne S, Temmerman O. Imaging of prosthetic joint infections. In: Management of Periprosthetic Joint Infections (PJIs). Elsevier; 2017:259-285.
62. Nandu H, Wen PY, Huang RY. Imaging in neuro-oncology. Therapeutic advances in neurological disorders. 2018;11:1756286418759865.
63. Glaudemans, A. W., Enting, R. H., Heesters, M. A., Dierckx, R. A., van Rheenen, R. W., Walenkamp, A. M., & Slart, R. H. (2013). Value of 11 C-methionine PET in imaging brain tumours and metastases. European journal of nuclear medicine and molecular imaging, 40, 615-635.
64. Mehta, M. P., Rodrigus, P., Terhaard, C. H. J., Rao, A., Suh, J., Roa, W., ... & Renschler, M. F. (2003). Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. Journal of Clinical Oncology, 21(13), 2529-2536.
65. Temel, J. S., Greer, J. A., Muzikansky, A., Gallagher, E. R., Admane, S., Jackson, V. A., ... & Lynch, T. J. (2010). Early palliative care for patients with metastatic non–small-cell lung cancer. New England Journal of Medicine, 363(8), 733-742.
66. Langer, C. J., & Mehta, M. P. (2005). Current management of brain metastases, with a focus on systemic options. Journal of clinical oncology, 23(25), 6207-6219.
67. Ruderman, N. B., & Hall, T. C. (1965). Use of glucocorticoids in the palliative treatment of metastatic brain tumors. Cancer, 18(3), 298-306.
68. Khuntia, D., Brown, P., Li, J., & Mehta, M. P. (2006). Whole-brain radiotherapy in the management of brain metastasis. Journal of Clinical Oncology, 24(8), 1295-1304.
69. Kotecha, R., Gondi, V., Ahluwalia, M. S., Brastianos, P. K., & Mehta, M. P. (2018). Recent advances in managing brain metastasis. F1000Research, 7.
70. Hatiboglu, M. A., Akdur, K., & Sawaya, R. (2020). Neurosurgical management of patients with brain metastasis. Neurosurgical review, 43, 483-495.
71. Bruzzaniti, P., Lapolla, P., D'AMICO, A. L. E. S. S. I. A., Zancana, G., Katsev, M., Relucenti, M., ... & Familiari, P. (2022). En Bloc Resection of Solitary Brain Metastasis: The Role of Perilesional Edema. in vivo, 36(3), 1274-1284.
72. Wen, P. Y., & Loeffler, J. S. (2000). Brain metastases. Current treatment options in oncology, 1, 447-457.
73. Esquenazi, Y., Lo, V. P., & Lee, K. (2017). Critical care management of cerebral edema in brain tumors. Journal of intensive care medicine, 32(1), 15-24.
74. Baris, M. M., Celik, A. O., Gezer, N. S., & Ada, E. (2016). Role of mass effect, tumor volume and peritumoral edema volume in the differential diagnosis of primary brain tumor and metastasis. Clinical neurology and neurosurgery, 148, 67-71.
75. Yaltirik Bilgin E, Unal O, Ciledag N. Vasogenic Edema Pattern in Brain Metastasis. J Coll Physicians Surg Pak. 2022;32(8):1020-1025. doi:10.29271/jcpsp.2022.08.1020
76. Kalkanis, S. N., Kondziolka, D., Gaspar, L. E., Burri, S. H., Asher, A. L., Cobbs, C. S., ... & Linskey, M. E. (2010). The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. Journal of neuro-oncology, 96, 33-43.
77. Nemeth, A. J., Henson, J. W., Mullins, M. E., Gonzalez, R. G., & Schaefer, P. W. (2007).

Improved detection of skull metastasis with diffusion-weighted MR imaging. American journal of neuroradiology, 28(6), 1088-1092.

78. Tirinato, L., Onesto, V., Garcia-Calderon, D., Pagliari, F., Spadea, M. F., Seco, J., & Gentile, F. (2022). Human lung-cancer-cell radioresistance investigated through 2D network topology. Scientific Reports, 12(1), 12980.
79. Yao, Y., Fareed, R., Zafar, A., Saleem, K., Huang, T., Duan, Y., & Rehman, M. U. (2022). State-of-the-art combination treatment strategies for advanced stage non–small cell lung cancer. Frontiers in Oncology, 12, 958505.
80. Ozcan, G., Singh, M., & Vredenburgh, J. J. (2023). Leptomeningeal Metastasis from Non–Small Cell Lung Cancer and Current Landscape of Treatments. Clinical Cancer Research, 29(1), 11-29.
81. Park, S. J., Lim, S. H., Kim, Y. J., Moon, K. S., Kim, I. Y., Jung, S., ... & Jung, T. Y. (2021). The tumor control according to radiation dose of gamma knife radiosurgery for small and medium-sized brain metastases from non-small cell lung cancer. Journal of Korean Neurosurgical Society, 64(6), 983-994.
82. Devan, S. P., Jiang, X., Luo, G., Xie, J., Quirk, J. D., Engelbach, J. A., ... & Xu, J. (2022). Selective cell size MRI differentiates brain tumors from radiation necrosis. Cancer research, 82(19), 3603-3613.
83. Paek, S. H., Audu, P. B., Sperling, M. R., Cho, J., & Andrews, D. W. (2005). Reevaluation of surgery for the treatment of brain metastases: review of 208 patients with single or multiple brain metastases treated at one institution with modern neurosurgical techniques. Neurosurgery, 56(5), 1021-1034.
84. Desai, R., & Rich, K. M. (2020). Therapeutic role of gamma knife stereotactic radiosurgery in neuro-oncology. Missouri medicine, 117(1), 33.
85. Goldberg, S. B., Contessa, J. N., Omay, S. B., & Chiang, V. (2015). Lung cancer brain metastases. The Cancer Journal, 21(5), 398-403.
86. Abe, E., & Aoyama, H. (2012). The role of whole brain radiation therapy for the management of brain metastases in the era of stereotactic radiosurgery. Current oncology reports, 14, 79-84.
87. Perlow, H. K., Dibs, K., Liu, K., Jiang, W., Rajappa, P., Blakaj, D. M., ... & Raval, R. R. (2020). Whole-brain radiation therapy versus stereotactic radiosurgery for cerebral metastases. Neurosurgery Clinics, 31(4), 565-573.
88. Sas-Korczynska, B., & Rucinska, M. (2021). WBRT for brain metastases from non-small cell lung cancer: for whom and when?—Contemporary point of view. Journal of Thoracic Disease, 13(5), 3246.
89. Rusthoven, C. G., Yamamoto, M., Bernhardt, D., Smith, D. E., Gao, D., Serizawa, T., ... & Robin, T. P. (2020). Evaluation of first-line radiosurgery vs whole-brain radiotherapy for small cell lung cancer brain metastases: the FIRE-SCLC cohort study. JAMA oncology, 6(7), 1028-1037.
90. Brown PD, Jaeckle K, Ballman KV, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. JAMA. 2016;316(4):401-409. doi:10.1001/jama.2016.9839
91. Tallet, A. V., Azria, D., Barlesi, F., Spano, J. P., Carpentier, A. F., Gonçalves, A., & Metellus, P. (2012). Neurocognitive function impairment after whole brain radiotherapy for brain metastases: actual assessment. Radiation Oncology, 7(1), 1-8.
92. Lee, J., & Ahn, M. J. (2021). Brain metastases in patients with oncogenic-driven non-small cell lung cancer: Pros and cons for early radiotherapy. Cancer Treatment Reviews, 100, 102291.
93. Kirkpatrick, J. P., Soltys, S. G., Lo, S. S., Beal, K., Shrieve, D. C., & Brown, P. D. (2017). The radiosurgery fractionation quandary: single fraction or hypofractionation?. Neuro-oncology, 19(suppl_2), ii38-ii49.
94. Badiyan, S. N., Regine, W. F., & Mehta, M. (2016). Stereotactic radiosurgery for treatment of brain metastases. Journal of oncology practice, 12(8), 703-712.
95. Gondi, V., Bauman, G., Bradfield, L., Burri, S. H., Cabrera, A. R., Cunningham, D. A., ... & Brown, P. D. (2022). Radiation therapy for brain metastases: an ASTRO clinical practice guideline. Practical radiation oncology, 12(4), 265-282.
96. Rades, D., Haatanen, T., Schild, S. E., & Dunst, J. (2007). Dose escalation beyond 30 grays in 10 fractions for patients with multiple brain

metastases. Cancer, 110(6), 1345-1350.

97. Trifiletti DM, Ballman KV, Brown PD, et al. Optimizing Whole Brain Radiation Therapy Dose and Fractionation: Results From a Prospective Phase 3 Trial (NCCTG N107C [Alliance]/CEC.3). Int J Radiat Oncol Biol Phys. 2020;106(2):255-260. doi:10.1016/j.ijrobp.2019.10.024
98. Jairam, V., Chiang, V. L., Bond, J., & James, B. Y. (2015). Equivalent whole brain dose for patients undergoing gamma knife for multiple lesions. Journal of Radiosurgery and SBRT, 3(3), 187.
99. Sørensen, B. S., & Horsman, M. R. (2020). Tumor hypoxia: impact on radiation therapy and molecular pathways. Frontiers in oncology, 10, 562.
100. Horsman, M. R., Mortensen, L. S., Petersen, J. B., Busk, M., & Overgaard, J. (2012). Imaging hypoxia to improve radiotherapy outcome. Nature reviews Clinical oncology, 9(12), 674-687.
101. Overgaard, J. (2007). Hypoxic radiosensitization: adored and ignored. Journal of Clinical Oncology, 25(26), 4066-4074.
102. Yoshimura M, Itasaka S, Harada H, Hiraoka M. Microenvironment and radiation therapy. Biomed Res Int. 2013;2013:685308. doi:10.1155/2013/685308
103. Gray, L. H., Conger, A., Ebert, M., Hornsey, S., & Scott, O. C. A. (1953). The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. The British journal of radiology, 26(312), 638-648.