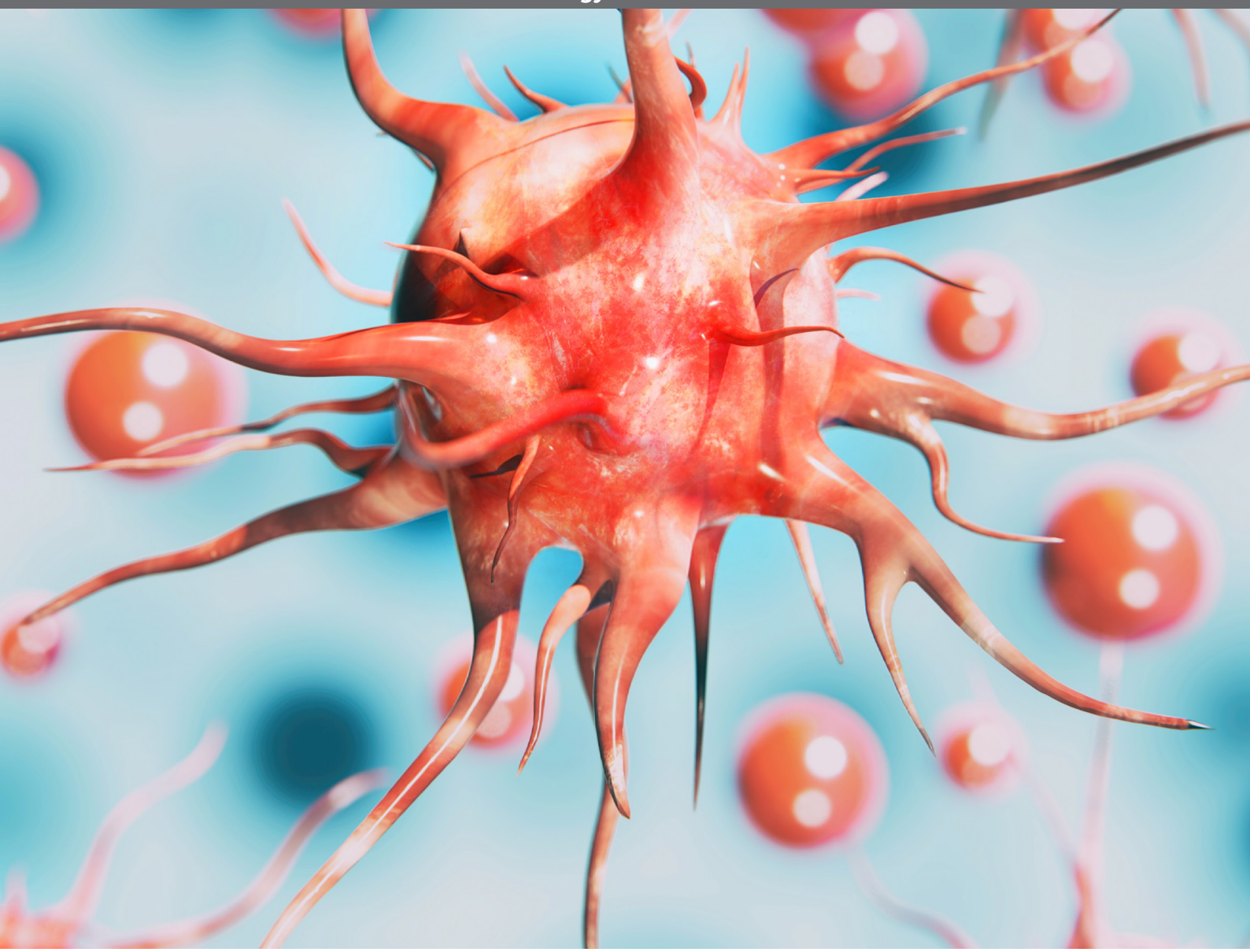
CENTRAL NERVOUS SYSTEM METASTASES IN LUNG CANCER PATIENTS: FROM PREVENTION TO DIAGNOSIS AND TREATMENT

EDITED BY: Lizza E. L. Hendriks, Deepa S. Subramaniam and Anne-Marie C. Dingemans

PUBLISHED IN: Frontiers in Oncology



frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88945-707-6
DOI 10.3389/978-2-88945-707-6

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

CENTRAL NERVOUS SYSTEM METASTASES IN LUNG CANCER PATIENTS: FROM PREVENTION TO DIAGNOSIS AND TREATMENT

Topic Editors:
Lizza E. L. Hendriks, Maastricht University Medical Center+, Netherlands
Deepa S. Subramaniam, Georgetown University, United States
Anne-Marie C. Dingemans, Maastricht University Medical Center+, Netherlands

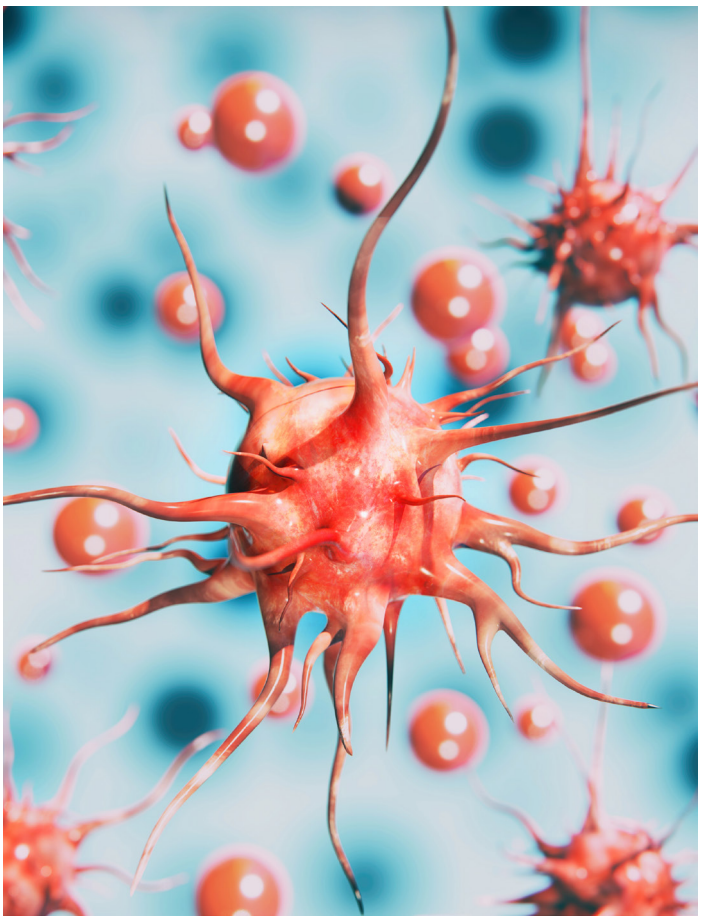


Image: Crevis/Shutterstock.com

Approximately 40% of lung cancer patients will develop central nervous system (CNS) metastases during the course of their disease. Most of these are brain metastases, but up to 10% will develop leptomeningeal metastases. Known risk factors for CNS metastases development are small cell lung cancer (SCLC), adenocarcinoma histology, epidermal growth factor receptor (EGFR) mutant or anaplastic lymphoma kinase (ALK) rearranged lung cancer, advanced nodal status, tumor stage and younger age. CNS metastases can have a negative impact on quality of life (QoL) and overall survival (OS).

The proportion of lung cancer patients diagnosed with CNS metastases has increased over the years due to increased use of brain imaging as part of initial cancer staging, advances in imaging techniques and better systemic disease control. Post contrast gadolinium enhanced magnetic resonance imaging (gd-MRI) is preferred, however when this is contra-indicated a contrast enhanced computed tomography (CE-CT) is mentioned as an alternative option. When CNS metastases are diagnosed, local treatment options consist of radiotherapy (stereotactic or whole brain) and surgery. Local treatment can be complicated by symptomatic radiation necrosis for which no high level evidence based treatment exists. Moreover, differential diagnosis with metastasis progression is difficult. Systemic treatment options have expanded over the last years. Until recently, chemotherapy was the only treatment option with a poor penetration in the CNS. Angiogenesis inhibitors are promising in the treatment of primary CNS tumors as well as radiation necrosis but clinical trials of anti-angiogenic agents in NSCLC have largely excluded patients with CNS metastases. Furthermore, research has also focused on methods to prevent development of CNS disease, for example with prophylactic cranial irradiation. Recently, checkpoint inhibitors have become available for NSCLC patients, and tyrosine kinase inhibitors (TKIs) have improved prognosis significantly in those with a druggable driver mutation. Newer TKIs are often designed to have better CNS penetration compared to first-generation TKIs. Despite advances in treatment options CNS metastases remain a problem in lung cancer and cause morbidity and mortality.

This Research Topic provides an extensive resource of articles describing advances in CNS metastases management in lung cancer patients, from prevention to diagnosis and treatment.

Citation: Hendriks, L. E. L., Subramaniam, D. S., Dingemans, A-M. C., eds. (2019). Central Nervous System Metastases in Lung Cancer Patients: From Prevention to Diagnosis and Treatment. Lausanne: Frontiers Media. doi: 10.3389/978-2-88945-707-6

Table of Contents

frontiers in Oncology

EDITORIAL
published: 06 November 2018
doi: 10.3389/fonc.2018.00511

Editorial: Central Nervous System Metastases in Lung Cancer Patients: From Prevention to Diagnosis and Treatment

Lizza E. L. Hendriks[1]*, *Deepa S. Subramaniam*[2] *and Anne-Marie C. Dingemans*[1]

[1] Department of Pulmonary Diseases, GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht, Netherlands, [2] Division of Hematology-Oncology, Georgetown University, Washington, DC, United States

Keywords: brain metastases from lung cancer, leptomeningeal metastases, treatment—contemporary views, diagnosis, driver mutations, cranial irradiation

Editorial on the Research Topic

Central Nervous System Metastases in Lung Cancer Patients: From Prevention to Diagnosis and Treatment

INTRODUCTION

Approximately 40% of lung cancer patients will develop central nervous system (CNS) metastases during the course of their disease (1). Most of these are brain metastases (BM), but 3–9% will develop leptomeningeal metastases (2, 3). The proportion of lung cancer patients diagnosed with CNS metastases has increased over the years due to increased use of brain imaging as part of initial cancer staging, advances in imaging techniques and better systemic disease control (4–6). CNS metastases can have a negative impact on quality of life (QoL) and overall survival (OS) (7–9). As such, prevention of CNS metastases development, as well as optimal treatment of already established CNS metastases is important.

Contributors in this Research Topic of Frontiers in Oncology, section Thoracic Oncology describe the advances in CNS metastases management in lung cancer patients, from prediction and prevention, to diagnosis and treatment.

PREDICTION AND PREVENTION OF CNS METASTASES DEVELOPMENT AND DIAGNOSTIC PITFALLS

Known risk factors for CNS metastases development are small cell lung cancer, adenocarcinoma histology, advanced nodal status, tumor stage and younger age (10–13). Patients with a driver mutation have a high risk of CNS metastases (14). This seems mainly due to their long survival, combined with the poor blood-brain-barrier penetration of the older generation tyrosine kinase inhibitors (TKIs) (Pedrosa et al.). However, these factors alone cannot predict accurately enough which patients will develop CNS metastases and better prediction models are needed. In the review of Pedrosa et al. the process of BM development and the evidence for the clinical and molecular factors associated with increased risk of BM diagnosis in lung cancer is summarized. In addition, they provide an excellent overview of new promising strategies to identify patients at high risk for BM development,

OPEN ACCESS

Edited and reviewed by:
Stephen V. Liu,
Georgetown University, United States

***Correspondence:**
Lizza E. L. Hendriks
lizza.hendriks@mumc.nl

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *30 September 2018*
Accepted: *19 October 2018*
Published: *06 November 2018*

Citation:
Hendriks LEL, Subramaniam DS and Dingemans A-MC (2018) Editorial: Central Nervous System Metastases in Lung Cancer Patients: From Prevention to Diagnosis and Treatment. Front. Oncol. 8:511. doi: 10.3389/fonc.2018.00511

including signatures derived from circulating tumor DNA measurements, single-nucleotide polymorphisms, copy number alterations, microRNAs and long non-coding RNAs (Pedrosa et al.). As it is known that among the non-small cell lung cancer (NSCLC) patients treated with curative intent, stage III patients have the highest risk of brain metastases development [30% (9, 15, 16)], preventive treatments such as prophylactic cranial irradiation (PCI) have been studied especially in this patient population (15, 16). Most studies have been published before the year 2000, but afterwards three new trials incorporating adequate baseline brain imaging, have reported their results. All studies showed a reduction of BM incidence after PCI compared to no PCI (Witlox et al.). Other important factors to consider before administering PCI are toxicity (acute as well as long-term), QoL and OS. Witlox et al. provide an up-to-date systematic review and meta-analysis of all published studies in this field. They provide detailed data on the effects of PCI on BM reduction, toxicity, QoL and OS and discuss areas for future research.

Although brain imaging techniques have improved over the years facilitating the diagnosis of BM, differential diagnosis can be challenging, especially in a patient with a medical history of cancer, as is discussed in the case report by Vanfleteren et al. It is stressed that even in an immunocompetent patient, a diagnosis of cerebral aspergillosis cannot be excluded. A short review of existing literature on this topic is also provided.

LOCAL TREATMENT OF BRAIN METASTASES

When BM are diagnosed, local treatment options consist of radiotherapy [stereotactic radiosurgery (SRS) or whole brain radiotherapy (WBRT)] and surgery (17, 18). SRS is more and more often used in the treatment of BM. In the past, SRS was mainly used for up to four BM, but a recent trial showed that SRS is feasible for a higher number of BM (19). More than fifty percent of BM patients treated with SRS will experience an intracranial relapse (19, 20), and especially in this palliative setting patient participation in the decision making around available treatment options [e.g., SRS, WBRT, systemic treatment (with/without concurrent cranial irradiation), best supportive care] is important. Hartgerink et al. discuss the current evidence of SRS for NSCLC BM, and the incorporation of decision aid tools in the future directions for NSCLC BM treatment. Furthermore, local treatment can be complicated by symptomatic radiation necrosis for which no high-level evidence-based treatment exists, although bevacizumab is a promising treatment option (21–23). Differential diagnosis of radiation necrosis and BM progression can be difficult (21, 22). Loganadane et al. provide a very nice overview of the pathobiology, epidemiology, predictive factors, diagnosis and emerging treatment of radiation necrosis, with a specific focus on NSCLC.

SYSTEMIC TREATMENT OF CNS METASTASES

Systemic treatment options for BM have expanded over the last years (24, 25). Until recently, chemotherapy was the only treatment option with a poor penetration in the CNS (26). Angiogenesis inhibitors are promising in the treatment of NSCLC BM (23, 27, 28), but clinical trials of anti-angiogenic agents in NSCLC have largely excluded BM patients (29). Furthermore, TKIs have improved prognosis significantly in those with a druggable driver mutation (25, 30, 31). Newer TKIs are often designed to have better CNS penetration compared to first-generation TKIs (24, 30, 31). In the review of Kelly et al. the management of CNS metastases in *EGFR* mutated NSCLC patients is discussed, including the role of newer generation EGFR-TKIs, immunotherapy, and EGFR-TKIs combined with cranial irradiation or angiogenesis inhibition. Remon and Besse provide a broader overview of incidence and treatment of BM in oncogene addicted NSCLC patients, including rare driver mutations such as *ALK*, *ROS1*, *RET*, *BRAF,* and *NTRK*. Relevant research questions such as optimal sequence of treatment (upfront cranial irradiation or upfront TKI, sequence of TKI) are also discussed. In the case report of Meedendorp et al. treatment of a BM patient with acquired resistance to EGFR-TKI is discussed, stressing the importance of a molecular tumor board for decision making. Last, leptomeningeal metastases remain challenging to treat, especially in non-oncogene addicted NSCLC patients. Turkaj et al. provide an up-to-date review of possible treatment options for these patients, including systemic as well as intrathecal chemotherapy as well as radiotherapy options.

CONCLUSION

With the articles in this Research Topic, we hope to provide a review of present and future treatment options for lung cancer CNS metastases, including evidence for predictive markers, preventive treatments, and local as well as systemic treatment options for already diagnosed CNS metastases.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Yawn BP, Wollan PC, Schroeder C, Gazzuola L, Mehta M. Temporal and gender-related trends in brain metastases from lung and breast cancer. *Minn Med.* (2003) 86:32–7.
2. Remon J, Le Rhun E, Besse B. Leptomeningeal carcinomatosis in non-small cell lung cancer patients: a continuing challenge in the personalized treatment era. *Cancer Treat Rev.* (2017) 53:128–37. doi: 10.1016/j.ctrv.2016.12.006
3. Kuiper JL, Hendriks LE, van der Wekken AJ, de Langen AJ, Bahce I, Thunnissen E, et al. Treatment and survival of patients with EGFR-mutated non-small cell lung cancer and leptomeningeal metastasis: a retrospective cohort analysis. *Lung Cancer* (2015) 89:255–61. doi: 10.1016/j.lungcan.2015.05.023

4. Costa DB, Shaw AT, Ou SH, Solomon BJ, Riely GJ, Ahn MJ, et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. *J Clin Oncol*. (2015) 33:1881–8. doi: 10.1200/JCO.2014.59.0539
5. Terae S, Yoshida D, Kudo K, Tha KK, Fujino M, Miyasaka K. Contrast-enhanced FLAIR imaging in combination with pre- and postcontrast magnetization transfer T1-weighted imaging: usefulness in the evaluation of brain metastases. *J Magn Reson Imag*. (2007) 25:479–87. doi: 10.1002/jmri.20847
6. Levy A, Faivre-Finn C, Hasan B, De Maio E, Berghoff AS, Girard N, et al. Diversity of brain metastases screening and management in non-small cell lung cancer in Europe: results of the European Organisation for Research and Treatment of Cancer Lung Cancer Group survey. *Eur J Cancer* (2018) 93:37–46. doi: 10.1016/j.ejca.2018.01.067
7. Roughley A, Damonte E, Taylor-Stokes G, Rider A, Munk V. Impact of brain metastases on quality of life and estimated life expectancy in patients with advanced non-small cell lung cancer. *Value Health* (2014) 17:A650. doi: 10.1016/j.jval.2014.08.2364
8. 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 Rad Oncol Biol Phy*. (2010) 77:655–61. doi: 10.1016/j.ijrobp.2009.08.025
9. Peters S, Bexelius C, Munk V, Leighl N. The impact of brain metastasis on quality of life, resource utilization and survival in patients with non-small-cell lung cancer. *Cancer Treat Rev*. (2016) 45:139–62. doi: 10.1016/j.ctrv.2016.03.009
10. Hochstenbag MM, Twijnstra A, Hofman P, Wouters EF, ten Velde GP. MR-imaging of the brain of neurologic asymptomatic patients with large cell or adenocarcinoma of the lung. Does it influence prognosis and treatment? *Lung Cancer* (2003) 42:189–93. doi: 10.1016/S0169-5002(03)00291-5
11. Hendriks LE, Brouns AJ, Amini M, Uyterlinde W, Wijsman R, Bussink J, et al. Development of symptomatic brain metastases after chemoradiotherapy for stage III non-small cell lung cancer: does the type of chemotherapy regimen matter? *Lung Cancer*. (2016) 101:68–75. doi: 10.1016/j.lungcan.2016.09.008
12. Gaspar LE, Chansky K, Albain KS, Vallieres E, Rusch V, Crowley JJ, et al. Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. *J Clin Oncol*. (2005) 23:2955–61. doi: 10.1200/JCO.2005.08.026
13. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. (2007) 357:664–72. doi: 10.1056/NEJMoa071780
14. Rangachari D, Yamaguchi N, VanderLaan PA, Folch E, Mahadevan A, Floyd SR, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer* (2015) 88:108–11. doi: 10.1016/j.lungcan.2015.01.020
15. Sun DS, Hu LK, Cai Y, Li XM, Ye L, Hou HY, et al. A systematic review of risk factors for brain metastases and value of prophylactic cranial irradiation in non-small cell lung cancer. *Asian Pac J Cancer Prev*. (2014) 15:1233–9. doi: 10.7314/APJCP.2014.15.3.1233
16. De Ruysscher D, Dingemans AC, Praag J, Belderbos J, Tissing-Tan C, Herder J, et al. Prophylactic cranial irradiation versus observation in radically treated stage III non-small-cell lung cancer: a randomized phase III NVALT-11/DLCRG-02 Study. *J Clin Oncol*. (2018) 36:2366–77. doi: 10.1200/JCO.2017.77.5817
17. *NCCN Guidelines Central Nervous System Cancers Version 1.2018* (2018).
18. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. (2016) 27 (Suppl. 5):v1–27. doi: 10.1093/annonc/mdw326
19. Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol*. (2014) 15:387–95. doi: 10.1016/S1470-2045(14)70061-0
20. Zindler JD, Slotman BJ, Lagerwaard FJ. Patterns of distant brain recurrences after radiosurgery alone for newly diagnosed brain metastases: implications for salvage therapy. *Radiother Oncol*. (2014) 112:212–6. doi: 10.1016/j.radonc.2014.07.007
21. Tomura N, Kokubun M, Saginoya T, Mizuno Y, Kikuchi Y. Differentiation between treatment-induced necrosis and recurrent tumors in patients with metastatic brain tumors: comparison among (11)C-Methionine-PET, FDG-PET, MR permeability imaging, and MRI-ADC-preliminary results. *Am J Neuroradiol*. (2017) 38:1520–7. doi: 10.3174/ajnr.A5252
22. Soussain C, Ricard D, Fike JR, Mazeron JJ, Psimaras D, Delattre JY. CNS complications of radiotherapy and chemotherapy. *Lancet* (2009) 374:1639–51. doi: 10.1016/S0140-6736(09)61299-X
23. Boothe D, Young R, Yamada Y, Prager A, Chan T, Beal K. Bevacizumab as a treatment for radiation necrosis of brain metastases post stereotactic radiosurgery. *Neuro Oncol* (2013) 15:1257–63. doi: 10.1093/neuonc/not085
24. Frega S, Bonanno L, Guarneri V, Conte P, Pasello G. Therapeutic perspectives for brain metastases in non-oncogene addicted non-small cell lung cancer (NSCLC): towards a less dismal future? *Crit Rev Oncol Hematol*. (2018) 128:19–29. doi: 10.1016/j.critrevonc.2018.05.013
25. Ferrara R, Mezquita L, Besse B. Progress in the management of advanced thoracic malignancies in 2017. *J Thor Oncol*. (2018) 13:301–22. doi: 10.1016/j.jtho.2018.01.002
26. Postmus PE, Smit EF. Chemotherapy for brain metastases of lung cancer: a review. *Ann Oncol*. (1999) 10:753–9. doi: 10.1023/A:1008318515795
27. Besse B, Lasserre SF, Compton P, Huang J, Augustus S, Rohr UP. Bevacizumab safety in patients with central nervous system metastases. *Clin Cancer Res*. (2010) 16:269–78. doi: 10.1158/1078-0432.CCR-09-2439
28. Besse B, Le Moulec S, Mazieres J, Senellart H, Barlesi F, Chouaid C, et al. Bevacizumab in patients with nonsquamous non-small cell lung cancer and asymptomatic, untreated brain metastases (BRAIN): a nonrandomized, phase II Study. *Clin Cancer Res*. (2015) 21:1896–903. doi: 10.1158/1078-0432.CCR-14-2082
29. Russo AE, Priolo D, Antonelli G, Libra M, McCubrey JA, Ferrau F. Bevacizumab in the treatment of NSCLC: patient selection and perspectives. *Lung Cancer* (2017) 8:259–69. doi: 10.2147/LCTT.S110306
30. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. (2017). 377:829–38 doi: 10.1056/NEJMoa1704795
31. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. (2018) 378:113–25. doi: 10.1056/NEJMoa1713137

Conflict of Interest Statement: LH: none related to current manuscript, outside of current manuscript: research funding Roche, Boehringer Ingelheim (both institution), advisory board: Boehringer, BMS, (both institution), travel reimbursement: Roche, BMS (self). DS: speaker's bureau Astra Zeneca, Takeda; advisory board Astra Zeneca, Takeda, BMS; institutional research funding as PI: BMS, Genentech, Incyte, Lilly Oncology, Astra Zeneca, Novocure. A-MD: none related to current manuscript, outside of current manuscript: advisory board BMS, MSD, Roche, Eli Lilly, Takeda, Pfizer, Boehringer Ingelheim (all institution).

frontiers in Oncology

REVIEW
published: 11 May 2018
doi: 10.3389/fonc.2018.00159

Potential Molecular Signatures Predictive of Lung Cancer Brain Metastasis

*Rute M. S. M. Pedrosa[1], Dana A. M. Mustafa[1], Joachim G. J. V. Aerts[2] and Johan M. Kros[1]**

[1] Department of Pathology, Erasmus Medical Center, Rotterdam, Netherlands, [2] Department of Lung Diseases, Erasmus Medical Center, Rotterdam, Netherlands

Brain metastases are the most common tumors of the central nervous system (CNS). Incidence rates vary according to primary tumor origin, whereas the majority of the cerebral metastases arise from primary tumors in the lung (40–50%). Brain metastases from lung cancer can occur concurrently or within months after lung cancer diagnosis. Survival rates after lung cancer brain metastasis diagnosis remain poor, to an utmost of 10 months. Therefore, prevention of brain metastasis is a critical concern in order to improve survival among cancer patients. Although several studies have been made in order to disclose the genetic and molecular mechanisms associated with CNS metastasis, the precise mechanisms that govern the CNS metastasis from lung cancer are yet to be clarified. The ability to forecast, which patients have a higher risk of brain metastasis occurrence, would aid cancer management approaches to diminish or prevent the development of brain metastasis and improve the clinical outcome for such patients. In this work, we revise genetic and molecular targets suitable for prediction of lung cancer CNS disease.

Keywords: brain metastasis, lung cancer, molecular mechanisms, genetic alterations, chemotherapy

OPEN ACCESS

Edited by:
Anne-Marie Dingemans, Academic Hospital Maastricht, Netherlands

Reviewed by:
K. Shilo, The Ohio State University, United States
Timothy F. Burns, University of Pittsburgh Cancer Institute, United States

****Correspondence:***
Johan M. Kros
j.m.kros@erasmusmc.nl

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *07 March 2018*
Accepted: *25 April 2018*
Published: *11 May 2018*

Citation:
Pedrosa RMSM, Mustafa DAM, Aerts JGJV and Kros JM (2018) Potential Molecular Signatures Predictive of Lung Cancer Brain Metastasis. Front. Oncol. 8:159. doi: 10.3389/fonc.2018.00159

INTRODUCTION

Brain metastases are the most common tumors of the central nervous system (CNS). Metastatic brain lesions outnumber primary brain tumors with a 10-fold (1) with incidence rates varying according to the primary tumor origin. The majority of the cerebral metastases arise from primary tumors in the lung (40–50%) and it is estimated that 50% of the patients with small-cell lung cancer (SCLC) or non-small-cell lung cancer (NSCLC) will develop brain metastasis (2, 3). In contrast to cerebral metastases from other primary cancers, where generally a metastatic latency period takes place, brain metastasis from lung cancers often occur months after, or even concurrently, with the diagnosis of the primary tumor (4). Metastatic brain lesions carry a clinical burden of morbidity and mortality, as well as significant neurological deficits, cognitive impairment, and emotional difficulties (5). Despite treatment, lung cancer brain metastases are usually fatal for 90% of patients within two years after the initial diagnosis, with a median survival of 7–10 months five years after diagnosis (2). Previous efforts to characterize patients that are at high risk of developing brain metastasis have been fairly disappointing.

Currently, only clinical and pathologic variables are used to predict the risk of brain metastasis in patients with lung cancer. However, data on predictive parameters are diverse and not clinically usable (**Table 1**). Identifying patients at highest risk of developing brain metastases on the basis

TABLE 1 | Conflicting clinical and pathological risk factors associated with the development of brain metastases.

Reference	Analysis	*N* =	Type Tumor	Pathologic stage	Recurrence site	Age	Tumor status	Lymph-vascular space invasion	Nodal status	Histologic type
Ceresoli et al. (8)	Multivariate	112	Non-small-cell lung cancer (NSCLC)	IIB–IIIB	Brain	<60, $p = 0.03$	ND	ND	$p = 0.003$*	Non-squamous+
Andre et al. (9)	Multivariate	267	NSCLC	IIIN2	Brain	ND	–	ND	ND	Adenocarcinoma+
Bajard et al. (10)	Multivariate	305	NSCLC	I–IIIB	Brain	<62, $p = 0.004$	T4, $p = 0.0009$	ND	N2-3, $p = 0.0057$	Adenocarcinoma, $p = 0.0002$
Carolan et al. (11)	Multivariate	83	NSCLC	IIIB	Brain	<60, $p = 0.022$	ND	ND	ND	–
Chen et al. (12)	Kaplan-Meier	211	NSCLC	IIIA	Brain	–	–	ND	ND	Squamous vs non-squamous, $p = 0.02$
Hubbs et al. (3)	Multivariate	975	NSCLC	I–II	Brain	<77, p<0.01	Size, $p < 0.01$	$p = 0.03$	$p = 0.04$	–
Jacobs et al. (13)	Multivariate	78	NSCLC	II, III	Brain	–	–	ND	N1-2 vs N0, $p < 0.02$	ND
Mujoomdar et al. (14)	Hierarchical logistic regression	264	NSCLC	I–IV	Brain	–	Size, $p < 0.001$	ND	$p < 0.017$	Adenocarcinoma+ undifferentiated vs squamous, $p = 0.001$
Robnett et al. (15)	Multivariate	150	NSCLC	II, III	Brain	–	ND	ND	ND	IIIB non-squamous+
Schouten et al. (16)	Univariate	2724	Div.	I–IV	Brain	<70 (breast and lung cancer)	ND	ND	ND	ND
Tang et al. (17)	Univariate	25	NSCLC	I–III	Brain	–	–	ND	Mediastinale vs hilar, $p = 0.03$	ND
Tang et al. (18)	Multivariate	292	NSCLC	ND	Brain	–	T2 vs T3–4, $p = 0.005$*	ND	N0–1 vs N2–3, $p < 0.001$*	–
Tsuchiya et al. (19)	Multivariate	322	NSCLC	IA	Brain and others	–	Size ≥15 mm, $p = 0.038$	ND	ND	Squamous, $p = 0.002$
Westeel et al. (20)	Multivariate	192	NSCLC	I–IV	Brain and others	<61, $p = 0.01$	ND	ND	ND	ND

ND, not determined; "–", no predictive value ($p > 0.05$); "+", predictive value, no significance.
**Significant for univariate analysis only.*

of standard clinical and pathological factors, such as status of primary tumor, tumor histology, nodal involvement, and patient age, may not be reliable due to small hazard ratios and unknown prognostic factors (6). Recently, Hung et al. (7) demonstrated in a study on 182 lung adenocarcinomas with distant metastases that the micropapillary histology subtype was significantly associated with brain metastasis ($p = 0.01$). However, a more robust method to identify which patients are at risk of developing brain metastasis is urgently needed.

Molecular classification by correlating distinct molecular markers with oncogenic mechanisms has been practiced to improve risk stratification of the TNM staging system (21). The potential of molecular biologic distinction would direct appropriate therapy, thereby improving patient outcome. Among early-stage (I/II) NSCLC patients, the 5-year overall survival (OS) rate is only 45.1% (22). Many clinical trials have confirmed that postoperative adjuvant therapy can prolong the survival of NSCLC patients. In a recent meta-analysis of 3,923 patients, Chen et al. (23) demonstrated the efficacy of postoperative chemotherapy – both cisplatin based ($p < 0.0001$) and single tegafur-uracil (UFT, $p = 0.002$), in stages I–II, IA, and IB NSCLC, and no significant benefit was found in stage IA patients ($p = 0.43$). In addition, cisplatin was shown to be better than single UFT chemotherapy in OS ($p = 0.0005$ and $p = 0.81$, respectively) (23). More trials should be conducted in order to confirm the efficacy of disease-free survival therapies in future clinical practice.

In order to predict the rise of cerebral metastasis of lung cancer, we would need a measurable biomarker that correlates well with brain seeding of the lung cancer cells. Molecular markers may be classified into subgroups based on their mechanism of action in the metastatic cascade to the brain (6). The optimal marker to disclose concealed (brain) metastatic disease would be displayed in primary tumors while not detectable in the serum of control subjects (24). The capacity to identify metastatic disease based on proto-oncogenes such as Kirsten rat sarcoma viral oncogene homolog (KRAS) and tumor suppressor p53 (TP53), present in only half of the lung cancer patients (47 and 50%, respectively) (25), demands a more broaden and deepened spectrum of the investigation of primary lung cancers, the molecular interactions with other cells, and the tumor microenvironment.

The process of metastasis is a selective and refined event called organotropism whereby, apart from an overall tendency to spread and invade, primary tumors show predilection for particular distinct organs (26). Cancers that metastasize to brain need to take a number of anatomic, physiologic, and molecular hurdles. The first requirement is intravasation into the blood stream, dependent upon a reversible epithelial-to-mesenchymal transition (EMT). The epithelial cell traits, such as cell polarity and E-cadherin-mediated cell adhesion, are suppressed and replaced by mesenchymal cell characteristics. The cells become motile, invasive, and resistant to apoptosis (27). Through the EMT process, tumor cells acquire stem cell-like features such as self-renewal, differentiation and ability to seed, justifying the term "tumor-initiating cells" (27). EMT molecular regulation is accomplished through an intricate network arranged by different genes and molecule inducers of EMT (28–30). AXL, a receptor tyrosine kinase belonging to the TAM family, and its ligand GAS6, growth arrest-specific gene 6, have been reported to down-regulate several oncogenic signaling pathways (31), through activation of MAPK/ERK and PI3K/AKT signaling pathways (32, 33). Recently, AXL-GAS6 signal axis has been reported to have a potential key role in NSCLC tumor progression and may be suitable as a prognostic biomarker for identifying high-risk NSCLC brain metastasis patients (34). Tumor cell growth in the brain microenvironment is the result of genetic predisposition and cellular adaptation mechanisms and is largely dependent on cross-talk between tumor and brain-resident cells.

Genomic instability and mutations are just two of the characteristics of cells associated with the transition from a preneoplastic lesion to an invasive tumor state and consequent progression to metastatic disease. During tumorigenesis, a sequence of genetic modifications such as gene deletions, copy number alterations (CNAs), and chromosomal rearrangements occur. This review focuses on the use of molecular characteristics that are predictive of tumor progression and development of metastatic NSCLC brain metastasis in particular.

GENETIC ALTERATIONS

Due to the recent discoveries of targetable genetic alterations in the treatment of NSCLC, patients have been stratified according to genetic variations in the primary tumor, including epidermal growth factor receptor (EGFR), KRAS, and anaplastic lymphoma kinase (ALK) (35). A summary of all genetic alterations that will be addressed in this review are presented in **Figure 1**. There are considerable differences in reported incidence and time to development of brain metastases for these genetic alterations.

EPIDERMAL GROWTH FACTOR RECEPTOR

In the Caucasian population, EGFR-activating mutations are present in 10–15% of adenocarcinomas and in less than 5% of squamous cell carcinomas (36). Roughly 90% of all known EGFR mutations reside in exon 19 (in-frame deletions) and in exon 21 (L858R, point mutation) (37, 38). The prevalence of activating EGFR mutations appears to be dependent on gender, smoking status and ethnicity. In patients from East-Asia, EGFR mutation is reportedly up to five times higher than in Caucasian patients (39–41). The relation between EGFR status, brain metastasis and survival are complex and not fully understood. It has been shown that lung cancer patients suffering from tumors with particular EGFR mutations survive longer, probably due to effective treatment. However, data also suggest that brain metastases arise more frequently in patients with primary lung tumors bearing EGFR mutations (42, 43) and the development of brain metastases is relatively frequent during treatment. There are discordance rates of EGFR mutational status between primary tumors and their CNS metastases that vary from 0 to 32% (44–50). In a series of 55 NSCLC primary tumors with matched cerebral metastases, EGFR was found to be more

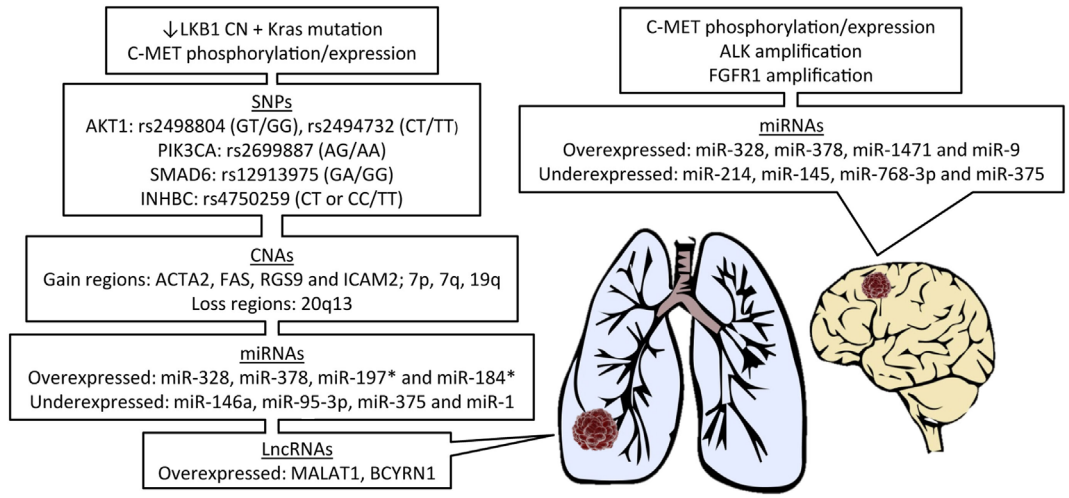


FIGURE 1 | Features of primary lung cancer from patients known to develop brain metastasis and potential biomarker candidates. LKB1, liver kinase B1; CN, copy number; SNPs, single-nucleotide polymorphisms; CNAs, CN alterations; miRNAs, microRNAs; lncRNAs, long non-coding RNAs; *in EGFR-mutant patients.

frequently amplified in the metastatic adenocarcinomas than corresponding primary tumors, with 30 and 10%, respectively (50). Discrepancies regarding the response of the brain metastases may well be due to the timing of administering adjuvant chemotherapy for the primary tumors relative to the occurrence of the brain metastases. The choice of the agents is currently based on the molecular characteristics of the primary, not the metastatic, tumors. Paradoxically, prolonging survival times due to successful response of the primary tumors would create more time for brain metastases to develop as late complication (51, 52). Similar to EGFR, the KRAS status may also be discordant between primary and metastatic tissues (44) and a KRAS mutation in a small subset of tumor cells may confer resistance to EGFR tyrosine kinase inhibitors (TKIs) therapy.

KRAS

Epidermal growth factor receptor and KRAS mutations are generally mutually exclusive (53, 54), but cases of EGFR and KRAS co-mutations have been identified (55–57). Roughly 15–30% of NSCLCs harbor activating mutations in codons 12 and 13 of the KRAS gene (58). KRAS mutations are associated with advanced tumor progression and clinical aggressiveness (59), forming a persistent risk of lung adenocarcinoma and implying to be an early event in the tumorigenesis process (53). The correlation of the presence of KRAS mutations with a smoking history (60) suggests that KRAS mutations are a sequel of the actions of carcinogens of tobacco products (53). However, in a cohort of 482 lung adenocarcinomas, it was demonstrated that KRAS mutations do occur in patients with lung adenocarcinomas without a smoking history (61), but the mutations are different. Significantly more transition mutations (G>A) are being found in non-smokers than the transversion mutations (G>T or G>C, $p < 0.0001$) that occur in former- or current smokers (61). This observation supports the idea that the distinct transition profile – replacement of a purine for a purine or a pyrimidine for a pyrimidine (62) – of never smokers is very unlikely to be caused by passive tobacco vulnerability. No specific KRAS targeting treatment has so far shown efficacy. There is little available data on the KRAS mutational status in primary lung cancers as compared to that in their brain metastases (44, 57). In a relatively small series, Munfus-McCray et al. found 23.5% of brain metastatic lung adenocarcinomas with KRAS mutation exclusively in patients with a smoking history ($p < 0.01$) (59).

ANAPLASTIC LYMPHOMA KINASE

Anaplastic lymphoma kinase rearrangements occur in 2–7% of all NSCLC, with predominance in non- or light smokers, younger age, and adenocarcinomas (63, 64). Fusion between EML4 (echinoderm microtubule-associated protein-like 4) and ALK yields at least 15 molecular variants with different biological behaviors and affected signaling pathways and consequences for therapy choice (65). ALK testing is particularly recommended for non-squamous lung cancers in the absence of EGFR mutation, of patients with non- or light smoking history (66). The recommended method for testing the presence of ALK translocation is fluorescent *in situ* hybridization (FISH) and immunohistochemistry (IHC) as confirmation (67, 68). In a large Western cohort, functional ALK rearrangements appeared to be mutually exclusive with EGFR and KRAS mutations (69). Although ALK translocations seem to be similar in primary tumors and their brain metastases, ALK amplifications are found more frequently in CNS metastasis with discordance rates of only 12.5% (70). Similar to EGFR, ALK rearrangements are predictive of response to TKIs, but the development of brain metastasis in patients with ALK translocations receiving ALK directed TKI is a major clinical problem (71, 72). Recently, second-generation TKI alectinib has shown to delay the development of brain metastases compared to first-generation TKI and also demonstrated promising

efficacy in the CNS for crizotinib-resistant ALK-positive NSCLC patients (73, 74). Similar to EGFR and KRAS mutations and ALK rearrangements, several other molecules such as liver kinase B1 (LKB1, also known as STK11), proto-oncogene tyrosine-protein kinase ROS1, and C-MET that encodes the hepatocyte growth factor receptor were found to be implicated in the development of lung cancer (75–79). However, the connection of these molecules with the development of brain metastases is still under investigation and not yet implicated in clinical decision making. KRAS aberrations have a synergistic effect with LKB1 inactivation on lung cancer development and distant metastasis formation (80, 81). In a cohort of 154 NSCLC patients, Zhao et al. demonstrated that a lower LKB1 copy number (CN), along with KRAS mutation, were significantly associated with a higher number of brain metastasis. Moreover, the odds ratio of brain metastasis was ~20 times higher in patients with one decrease in LKB1 CN values (82). LKB1 is observed to be inactivated in ~30% of all NSCLCs (83).

OTHER MUTATIONS

Although several potential targets may not regularly be expressed in a high number of lung cancer brain metastasis, their potential use for personalized treatment of selected lung cancer patients harboring actionable mutations should not be discarded. In a cohort of 874 brain metastases samples, of which 295 NSCLC, Capper et al. showed that, although a total of 51/874 samples harbored a BRAF V600E mutation, only 1/295 NSCLC brain metastases (~0.3%) was BRAF mutant (84). Despite this low frequency of BRAF mutations in lung brain metastasis, regression of both visceral and brain metastases by BRAF inhibitor vemurafenib was reported in a patient with a BRAF V600E-mutated NSCLC (85). While 3% of primary lung cancers harbor ROS1 alterations, only 1/99 adenocarcinomas bore ROS1 translocations and 1/11 squamous cell carcinomas showed ROS1 amplifications (86).

Activating mutations in EGFR are associated with sensitivity to TKI therapy, but nearly 30% of EGFR positive patients show primary resistance to EGFR inhibitor therapy (87). While C-MET amplification is one of the factors commonly associated with disease progression (88), Benedettini et al., in a first cohort of 23 NSCLC samples of patients harboring an EGFR activating mutation, showed that both C-MET phosphorylation and expression were significantly associated with shorter time to progression, correlating with *de novo* resistance to EGFR TKI. In a second cohort of 40 patients, englobing 18 primary NSCLC from patients who later developed brain metastases and 22 NSCLC from patients that did not develop brain metastases, Benedettini et al. demonstrated that both C-MET expression and phosphorylation, but not C-MET amplification, were significantly higher in the tumors from patients who developed brain metastasis. In 18 matched brain metastasis, amplification was demonstrated (89). In addition, in a cohort of 196 NSCLC brain metastasis samples, Presseur et al. found C-MET gene amplification and overexpression in 21.6 and 44.4%, respectively, confirming that C-MET is commonly activated in brain metastasis manifestation (90). Furthermore, a significant correlation between C-MET and ALK amplification status was observed ($p = 0.039$). In another study, these authors demonstrated that fibroblast growth factor receptor 1 (FGFR1) amplification in brain metastases of adenocarcinomas – but not squamous cell carcinomas, is fivefold more frequent than reported for primary tumors (~3%). Similar to C-MET, a positive correlation of ALK and FGFR1 amplification status in brain metastasis was reported as significant ($p < 0.001$) (91). In a recent study, Keap1, Nrf2, and P300, key genes of the Keap1–Nrf2–ARE survival pathway, were found to be mutated in brain metastatic tissue of progressive NSCLC patients (92). Moreover, mutations in Keap1-Nrf2-ARE pathway were found in circulating tumor cells (CTCs), suggesting a role in the ability of CTCs to bear the rough environment in blood-circulation and attain distant organs (92).

CIRCULATING TUMOR DNA (ctDNA)

An adequate characterization of somatic genetic modifications in human cancers is critical for an optimal diagnosis and subsequent therapy. In brain metastatic tissue, as for all other brain malignancies, repeated biopsies are not a feasible approach to portray the tumor clonal diversity. Several studies have shown that cell-free ctDNA in the plasma could serve to characterize and monitor tumors (93–95). Nevertheless, ctDNA analysis of plasma from patients with brain malignancies has disclosed very low levels of tumor DNA (96). Recently, ctDNA analysis from cerebrospinal fluid (CSF) has been shown promising for brain cancer patients (97–99) and brain metastatic cancer patients (100, 101). CSF is in direct contact with the brain and, therefore, with tumor cells of brain cancer patients. In a comparative study of ctDNA derived from plasma and from CSF of patients with primary or metastatic brain tumors, De Mattos-Arruda et al. showed ctDNA levels of brain malignancies to be more abundantly present in the CSF than in the plasma (100). Moreover, ctDNA from CSF appeared to recapitulate the brain metastasis-specific mutations – private mutations, absent in extracranial tumors of a patient with Her2-positive metastatic breast cancer (100). In addition, the CSF ctDNA proficiency to monitor responses to systemic therapy and brain tumor progression (98, 100), i.e., the capacity of the CSF ctDNA to recapitulate the modulation of mutant allele frequency over time in the brain tumor burden, suggests that genomic CSF analysis may be useful not only in facilitating diagnosis of tumor in the CNS or as guidance to second-line agents choice, but also in pinpointing pathways' intimate related with cancer spread to the CNS and predictive of brain metastases (98).

SINGLE-NUCLEOTIDE POLYMORPHISMS (SNPs) ASSOCIATED WITH BRAIN METASTASES

Studying SNPs in signaling pathways that regulate cell proliferation and migration and assessing the relationship between multiple SNPs can be used to estimate the risk of brain metastasis. The PI3K–PTEN–AKT–mTOR pathway, important in the control of cell growth, tumorigenesis, and cell invasion, has been shown

to be abnormally activated in several cancer types, including NSCLC (102, 103). In a study of genetic variations in the PI3K–AKT–mTOR pathway to predict brain metastasis in NSCLC patients, Quianxia et al. identified three SNPs that appeared to be exclusively associated with higher risk of brain metastasis: the GT/GG ($p = 0.006$) and CT/TT ($p = 0.002$) genotypes of AKT1, variant alleles rs2498804 and rs2494732, respectively, and AG/AA ($p = 0.010$) genotype of PIK3CA, variant allele rs2699887 (103). Furthermore, patients carrying at least one variant allele in PIK3CA had roughly twice the risk of brain metastasis as those without those variants (103). Multiple mechanisms of PI3K activation may be responsible for activation of the PI3K pathway (104), and increased PI3K activity would result in increased metastases. In concordance, Paik et al. reported that patients with aberrant PI3K squamous lung carcinomas ($n = 9$) had worse survival (median OS: 8.6 vs 19.1 months, $p < 0.001$), higher metastatic burden (>3 organs, 18 vs 3%, $p = 0.025$), and higher incidence of brain metastases (27 vs 0%, $p < 0.001$) (105). Similar to PIK3K–AKT–mTOR pathway, it was hypothesized that common genetic variants in the TGF-β pathway would be associated with the risk of brain metastasis (106). TGF-β pathway has been demonstrated to suppress early-stage tumor development and to stimulate tumor cell growth and invasiveness at later stages of tumorigenesis (107). Quianxia et al. found the GG genotype of SMAD6: rs12913975 ($p = 0.014$) and the TT genotype of INHBC: rs4750259 ($p = 0.024$) to be associated with risk of brain metastasis in a cohort of 161 blood samples from NSCLC patients. Furthermore, de combination of both genetic variants was shown to be higher for prediction of brain metastasis ($p = 0.001$) (106).

CNAs ASSOCIATED WITH BRAIN METASTASIS

Activation or inhibition of a gene occurs through a variety of mechanisms such as, for example, activating mutations and deletions. Gene deletion can be evaluated by CNA. Animal models have given clear evidence that LKB1 haploinsufficiency stimulates KRAS driven lung cancer in mice (81), and a single copy inactivation of LKB1 can considerably ease brain recurrence (82). Although EGFR CN status is still controversial and some of the available data do not support EGFR CN as a prognostic factor (108, 109), Bonanno et al. have shown, despite the less predictive accuracy of FISH analysis compared to EGFR mutation analysis, that patients with EGFR-FISH-positive tumors have better outcomes (median OS: 177 vs 57 weeks, $p = 0.048$) (110). Considering that primary lung adenocarcinomas with early development of brain metastasis would contain more CNAs predictive of metastatic potential, Lee et al. compared the CN changes of four lung adenocarcinomas with coexistent brain metastasis with 8 lung adenocarcinomas with metachronous brain metastasis (111). Amplification in 5q35.1-2 and 17q23.3-24.1 was detected in 100% and that in 10q23.31 and 17q24.1 was detected in 75% of the cases with synchronous brain metastasis. On the other hand, and in a less frequent ratio, only 5q35.1-2 and 17q24.1 amplification status was found in 12.5% of the metachronous brain metastasis. Moreover, gained regions specific for early (simultaneous) brain metastasis were found to contain ACTA2, FAS, RGS9, and ICAM2 as putative metastasis promoting genes, the latter being most significant ($p = 0.002$) (111). In the same line, another study compared CNAs of primary NSCLC tumor and matched brain metastasis from one single patient (112). Brain metastatic tissue exhibited a higher degree of genetic heterogeneity when compared with the primary tumor with common regions of gain including 7p, 7q, and 19q and common regions of loss including 20q13 (112). In a stage IV SQCLCs study, four brain metastases and matched archived FFPE primary cancers were shown to have complete loss of PTEN by IHC and whole exome sequencing (105). In an early-stage NSCLC report, 30 (24%) of the total of 125 specimens analyzed for PTEN-IHC showed a lack of staining (113). Although genetic alterations of the PTEN gene are unusual in NSCLC, loss of PTEN protein is not a unique event in early-stage NSCLC and Soria et al. demonstrated that besides being a reversible event, PTEN loss may be partially explained by promotor methylation, in addition to point mutations and homozygous deletions (113).

MICRORNAs (miRNAs) ASSOCIATED WITH BRAIN METASTASIS

Recently, molecular studies have stressed the role of miRNAs which are small non-coding endogenous RNAs containing 18–24 nucleotides that regulate gene expression at the post-transcriptional level thereby acting as negative regulators of mRNA translation and/or stability (114). miRNAs appear to regulate several hundred genes and could serve as a better classifier than gene expression profiling (115). miRNAs are known to play a crucial role in normal development, proliferation, differentiation, and apoptosis, and dysregulation of miRNAs has been linked to various pathological conditions, including cancer (116). The role of miRNAs in the development of brain metastases has been recently explored (117, 118).

Several studies have addressed the miRNA expression as biomarkers to predict the occurrence of brain metastases in lung cancer. miRNA-328 appeared to be significantly overexpressed in both primary tumor samples and cerebral metastases of patients with NSCLC, when compared with NSCLC patients without brain metastasis. Moreover, miRNA-328 overexpression has been found to promote migration and subsequent brain metastasis formation of NSCLC cells through PRKCA deregulation (119). PRKCA mediates the expression of urokinase plasminogen activator, leading to the migration of the tumor cells (120). Similar to miRNA-328, miRNA-378 has also been demonstrated as a potential biomarker to assist clinicians in stratifying patients for high-risk of brain metastasis, because miRNA-378 was also found to be overexpressed in NSCLC primary tumor samples and matched brain metastasis of NSCLC patients (121). Also, miRNA-378 promotes cell migration, invasion, tumor growth, and angiogenesis, *in vitro* and *in vivo* (121). Recently, Remon et al. have identified miRNA-197 and miRNA-184 as two significantly overexpressed miRNAs in EGFR-mutant patients with brain metastases, when compared with EGFR-mutant patients with no brain metastasis (122). However, because of lack of patients with EGFR wild-type

(EGFRwt) tumors without BM, no comparison between patients with EGFRwt tumors, with and without BM, could be made. Therefore, the effects of these miRNAs, irrespective of the EGFR status, need further scrutiny.

MicroRNAs' expression status varies according to their targeted genes. Zhao et al. have reported the significant up-regulation of miRNA-1471 and miRNA-9 and down-regulation of miRNA-214 and miRNA-145 in 11 brain metastatic lung cancer samples, when compared with 40 primary lung adenocarcinomas ($p < 0.001$ for all four miRNAs) (123). The up-regulation of miRNA-145 in primary lung adenocarcinomas was shown to suppress proliferation of tumor cells (123), consistent with other reports that show inhibition of cell proliferation in human lung adenocarcinomas through miRNA-145 targeting c-Myc, EGFR and NUDT1 (124, 125). Subramani et al. have shown the miRNA-768-3p to be underexpressed in several brain metastases, compared to matched primary tumors (126). miRNA-768-3p was found to be underexpressed in *in vitro* lung cancer cells after co-culture with astrocytes, driving to increased KRAS protein and downstream effectors ERK1/2 and BRAF, thereby boosting tumor cell viability and promoting metastasis. From various studies, it appears that miRNAs regulate the growth of metastases either by under- or overexpression, within the tumor tissue or in the tumor environment. The brain microenvironment negatively regulates miRNA-768-3p to enhance KRAS expression that promotes the propagation of lung cancer brain metastasis (126). miRNA-146 was shown to be significantly up-regulated in NSCLC tissue when compared to healthy adjacent lung tissue ($p < 0.05$) (127). In another study, miRNA-146a expression in primary NSCLC was correlated with advanced clinical TNM stages and distant metastasis ($p < 0.05$). The patients with a high miRNA-146a expression showed longer progression-free-survival times than those with a low expression of miRNA-146a (25.6 and 4.8 weeks, respectively, $p < 0.05$) (128). In the same line with these findings, in a xenograft model, Hwang et al. showed high expression of miRNA-146a in parental cells, while diminished expression in the brain-seeking cells. Moreover, miRNA-146a overexpression in the brain-seeking cancer cells suppressed their metastatic potential, which was correlated to the up-regulation of β-catenin and down-regulation of heterogeneous nuclear ribonucleoprotein C1/C2 (129). Taken together, these findings suggest that miRNA-146a serve as a valid clinical biomarker for prediction of brain metastasis in lung cancer patients. However, validation of miRNA-146a expression levels in a large cohort of human matched primary and brain metastatic lung tumors is essential to confirm this finding. Similar to miRNA-146a, overexpression of miRNA-95-3p suppresses brain metastasis of lung adenocarcinoma through down-regulation of cyclin D1 (130). miRNA-95-3p is decreased in brain metastases of lung cancers as compared to the primary tumors and higher cyclin D1 expression correlates with poorer prognoses (130). In a recent study, Chen et al. reported miRNA-375 deregulation to be associated with NSCLC brain metastasis (131). miRNA-375 is another miRNA documented to be down-regulated in primary tumors of NSCLC patients with brain metastasis. miRNA-375 expression was significantly decreased in matched brain metastatic NSCLC tissues ($p < 0.05$) and significantly correlates with total number of brain metastasis ($p < 0.001$). In addition, VEGF and MMP9 – which roles have been extensively studied in the development of brain metastasis – were over-expressed in down-regulated miRNA-375 tumors (131).

MicroRNAs are linked with several molecular pathways. Several studies have correlated the overexpression of ADAM9 in NSCLC patients with brain metastases (4, 132). ADAM9 has been demonstrated to enhance the ability of tissue plasminogen activator to cleave and stimulate the function of CUB domain containing protein 1 (CDCP1) – promigratory protein, to promote brain metastasis (4). Recently, Chiu et al. reported that ADAM9 down-regulates miRNA-1 via EGFR signaling pathways activation, enhancing CDCP1 expression to promote lung cancer progression (133). miRNA-1 expression was shown to be down-regulated in primary lung tumors but increased in ADAM9-knockdown lung cancer cells. Moreover, miRNA-1 negatively correlates with CDCP1 expression and with migration ability of lung cancer cells (133). Another study has identified miRNA-21 as a target of signal transducers and activators of transcription 3 (STAT3) pathway activity in lung-derived brain metastasis initiating cells (134). STAT3 is admitted as a central regulator in the metastatic process (135), and STAT3-knockdown has been demonstrated to reduce expression of known downstream targets of miRNA-21, while STAT3 and miRNA-21 act as cooperative regulators of stemness, migration and tumor initiation in lung-derived brain metastasis (134). miRNAs appear very promising as diagnostics, prognostics and therapeutics to improve cancer patient outcome; however, the clinical use of miRNA therapeutics to treat brain metastases has yet to be achieved. Advances in pre-clinical and translational studies to identify miRNAs that change after growth in the brain microenvironment have been made, but validation of large cohorts from patient tumor samples is required.

LONG NON-CODING RNAs (lncRNAs) ASSOCIATED WITH BRAIN METASTASIS

Long non-coding RNAs have been recently identified as effective players in tumorigenesis. lncRNAs represent a class of non-protein coding transcripts longer than 200 nucleotides (136) that covers a broad spectrum of physiological and pathological functions by implementing different modes of action (137). Similar to miRNAs that regulate several hundred genes, lncRNAs are involved in the regulation of multiple miRNAs, impacting the expression of thousands of genes (136). Besides performing a single function, some lncRNAs act at multiple functional levels in different types of cells. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), localized in nuclear speckles and highly conserved among mammals, regulates alternative splicing (138) and gene expression through additional splicing-independent mechanisms in lung cancer metastasis (139). In a recent study, Shen et al. have shown lncRNA-MALAT1 levels to be significantly higher in primary NSCLC from patients who developed brain metastasis when compared with primary NSCLC from patients without brain metastasis ($p < 0.001$) (140). Additional *in vitro* functional studies showed overexpression of

vimentin in a highly invasive subline of brain metastasis lung cancer cells overexpressing MALAT1, while overexpression of E-cadherin was observed when MALAT1 was silenced, indicating that MALAT1 overexpression promotes lung cancer brain metastasis by inducing EMT (140). Accordingly, RNAi-mediated suppression of MALAT1-RNA, negatively influenced migration and clonogenic growth in established human NSCLC cell lines. Forced expression of MALAT1 in mouse NIH 3T3 fibroblasts significantly increased migration (141). Concordantly, long non-coding MALAT1 expression was found to enhance cell motility through transcriptional and post-transcriptional regulation of motility related gene expression (142), displaying the strongest association with genes involved in cancer, like cellular growth, movement, proliferation, signaling and immune regulation genes (141). MALAT1 and thymosin β4 expression levels were identified as prognostic parameters for patient survival in stage I NSCLC that are at high risk to develop metastasis ($p = 0.04$ and $p = 0.01$, respectively) (143). Tumorigenesis and metastases may be driven by tumor suppressive and oncogenic pathways deregulation through aberrant expression of cancer metastasis-associated lncRNA (144). In a recent *in vitro* study, the lncRNA brain cytoplasmatic RNA 1 (BCYRN1) was found up-regulated and targeted by c-MYC in human NSCLC cell lines (145). c-MYC is a commonly inhibited oncogene and becomes activated in oncogenic pathways, and correlates with metastasis of NSCLC (146). Besides demonstrating that lncRNA BCYRN1 is essential in the c-MYC-regulated cell migration and invasion, BCYRN1 positively correlates with the expression levels of MMP9 and MMP13 (145). MMP9 and MMP13, two members of the matrixin subfamily of the metzincin superfamily of Zn-dependent metalloproteinases (147), are extracellular matrix degrading proteins proven to induce migration and invasion of tumor cells (147, 148), thereby regulating cancer cell metastasis (149).

CONCLUDING REMARKS

Lung adenocarcinoma establishes distant clinical detectable metastasis within months of initial diagnosis (26, 150). This short abeyance indicates that metastatic ability would arise from early oncogenic events that stimulate primary tumor growth rather than late-arising, scarce genomic alterations specific for metastasis (151). Thus, monitoring persistent chromosomal changes in the primary NSCLC alongside with prospective multicenter studies of patient-matched primary and CNS metastatic lesions could help identify targetable approaches for brain metastasis-specific signatures.

AUTHOR CONTRIBUTIONS

RP, DM, JA, and JK wrote and revised the article.

FUNDING

This paper was carried out in the framework of a project on cerebral metastases of common cancers by the Dutch cancer society (KWF).

REFERENCES

1. Gril B, Evans L, Palmieri D, Steeg PS. Translational research in brain metastasis is identifying molecular pathways that may lead to the development of new therapeutic strategies. *Eur J Cancer* (2010) 46:1204–10. doi:10.1016/j.ejca.2010.02.033
2. Castrucci WA, Knisely JP. An update on the treatment of CNS metastases in small cell lung cancer. *Cancer J* (2008) 14:138–46. doi:10.1097/PPO.0b013e318172d6e1
3. Hubbs JL, Boyd JA, Hollis D, Chino JP, Saynak M, Kelsey CR. Factors associated with the development of brain metastases: analysis of 975 patients with early stage nonsmall cell lung cancer. *Cancer* (2010) 116:5038–46. doi:10.1002/cncr.25254
4. Lin CY, Chen HJ, Huang CC, Lai LC, Lu TP, Tseng GC, et al. ADAM9 promotes lung cancer metastases to brain by a plasminogen activator-based pathway. *Cancer Res* (2014) 74:5229–43. doi:10.1158/0008-5472.CAN-13-2995
5. Laack NN, Brown PD. Cognitive sequelae of brain radiation in adults. *Semin Oncol* (2004) 31:702–13. doi:10.1053/j.seminoncol.2004.07.013
6. D'Amico TA, Aloia TA, Moore MB, Conlon DH, Herndon JE II, Kinch MS, et al. Predicting the sites of metastases from lung cancer using molecular biologic markers. *Ann Thorac Surg* (2001) 72:1144–8. doi:10.1016/S0003-4975(01)02979-4
7. Hung JJ, Jeng WJ, Wu YC, Chou TY, Hsu WH. Factors predicting organ-specific distant metastasis in patients with completely resected lung adenocarcinoma. *Oncotarget* (2016) 7:58261–73. doi:10.18632/oncotarget.11338
8. Ceresoli GL, Reni M, Chiesa G, Carretta A, Schipani S, Passoni P, et al. Brain metastases in locally advanced nonsmall cell lung carcinoma after multimodality treatment: risk factors analysis. *Cancer* (2002) 95:605–12. doi:10.1002/cncr.10687
9. Andre F, Grunenwald D, Pujol JL, Girard P, Dujon A, Brouchet L, et al. Patterns of relapse of N2 non-small cell lung carcinoma patients treated with preoperative chemotherapy: should prophylactic cranial irradiation be reconsidered? *Cancer* (2001) 91:2394–400. doi:10.1002/1097-0142(20010615)91:12<2394::AID-CNCR1273>3.0.CO;2-6
10. Bajard A, Westeel V, Dubiez A, Jacoulet P, Pernet D, Dalphin JC, et al. Multivariate analysis of factors predictive of brain metastases in localised non-small cell lung carcinoma. *Lung Cancer* (2004) 45:317–23. doi:10.1016/j.lungcan.2004.01.025
11. Carolan H, Sun AY, Bezjak A, Yi Q-L, Payne D, Kane G, et al. Does the incidence and outcome of brain metastases in locally advanced non-small cell lung cancer justify prophylactic cranial irradiation or early detection? *Lung Cancer* (2005) 49:109–15. doi:10.1016/j.lungcan.2004.12.004
12. Chen AM, Jahan TM, Jablons DM, Garcia J, Larson DA. Risk of cerebral metastases and neurological death after pathological complete response to neoadjuvant therapy for locally advanced nonsmall-cell lung cancer: clinical implications for the subsequent management of the brain. *Cancer* (2007) 109:1668–75. doi:10.1002/cncr.22565
13. Jacobs RH, Awan A, Bitran JD, Hoffman PC, Little AG, Ferguson MK, et al. Prophylactic cranial irradiation in adenocarcinoma of the lung. A possible role. *Cancer* (1987) 59:2016–9.
14. Mujoomdar A, Austin JH, Malhotra R, Powell CA, Pearson GD, Shiau MC, et al. Clinical predictors of metastatic disease to the brain from non-small cell lung carcinoma: primary tumor size, cell type, and lymph node metastases. *Radiology* (2007) 242:882–8. doi:10.1148/radiol.2423051707
15. Robnett TJ, Machtay M, Stevenson JP, Algazy KM, Hahn SM. Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung carcinoma. *J Clin Oncol* (2001) 19:1344–9. doi:10.1200/JCO.2001.19.5.1344
16. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer* (2002) 94:2698–705. doi:10.1002/cncr.10541
17. Tang SG, Lin FJ, Leung WM. Impact of prophylactic cranial irradiation in adenocarcinoma of the lung. *J Formos Med Assoc* (1993) 92:413–9.

18. Tang SG, Tseng CK, Tsay PK, Chen CH, Chang JW, Pai PC, et al. Predictors for patterns of brain relapse and overall survival in patients with non-small cell lung cancer. *J Neurooncol* (2005) 73:153–61. doi:10.1007/s11060-004-3725-4
19. Tsuchiya T, Akamine S, Muraoka M, Kamohara R, Tsuji K, Urabe S, et al. Stage IA non-small cell lung cancer: vessel invasion is a poor prognostic factor and a new target of adjuvant chemotherapy. *Lung Cancer* (2007) 56:341–8. doi:10.1016/j.lungcan.2007.01.019
20. Westeel V, Choma D, Clement F, Woronoff-Lemsi MC, Pugin JF, Dubiez A, et al. Relevance of an intensive postoperative follow-up after surgery for non-small cell lung cancer. *Ann Thorac Surg* (2000) 70:1185–90. doi:10.1016/S0003-4975(00)01731-8
21. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, 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) 11:39–51. doi:10.1016/j.jtho.2015.09.009
22. Chansky K, Sculier JP, Crowley JJ, Giroux D, Van Meerbeeck J, Goldstraw P, et al. The International Association for the Study of Lung Cancer Staging Project: prognostic factors and pathologic TNM stage in surgically managed non-small cell lung cancer. *J Thorac Oncol* (2009) 4:792–801. doi:10.1097/JTO.0b013e3181a7716e
23. Chen YY, Wang LW, Wang SY, Wu BB, Wang ZM, Chen FF, et al. Meta-analysis of postoperative adjuvant chemotherapy without radiotherapy in early stage non-small cell lung cancer. *Onco Targets Ther* (2015) 8:2033–43. doi:10.2147/OTT.S88700
24. D'Amico TA. Molecular biologic substaging of non-small cell lung cancer. *J Thorac Cardiovasc Surg* (2002) 123:409–10. doi:10.1067/mtc.2002.120339
25. Ahrendt SA, Yang SC, Wu L, Roig CM, Russell P, Westra WH, et al. Molecular assessment of lymph nodes in patients with resected stage I non-small cell lung cancer: preliminary results of a prospective study. *J Thorac Cardiovasc Surg* (2002) 123:466–473;discussion473–464. doi:10.1067/mtc.2002.120343
26. Hess KR, Varadhachary GR, Taylor SH, Wei W, Raber MN, Lenzi R, et al. Metastatic patterns in adenocarcinoma. *Cancer* (2006) 106:1624–33. doi:10.1002/cncr.21778
27. Mani SA, Guo W, Liao MJ, Eaton EN, Ayyanan A, Zhou AY, et al. The epithelial-mesenchymal transition generates cells with properties of stem cells. *Cell* (2008) 133:704–15. doi:10.1016/j.cell.2008.03.027
28. Jeevan DS, Cooper JB, Braun A, Murali R, Jhanwar-Uniyal M. Molecular pathways mediating metastases to the brain via epithelial-to-mesenchymal transition: genes, proteins, and functional analysis. *Anticancer Res* (2016) 36:523–32.
29. Risolino M, Mandia N, Iavarone F, Dardaei L, Longobardi E, Fernandez S, et al. Transcription factor PREP1 induces EMT and metastasis by controlling the TGF-beta-SMAD3 pathway in non-small cell lung adenocarcinoma. *Proc Natl Acad Sci U S A* (2014) 111:E3775–84. doi:10.1073/pnas.1407074111
30. Vega S, Morales AV, Ocana OH, Valdes F, Fabregat I, Nieto MA. Snail blocks the cell cycle and confers resistance to cell death. *Genes Dev* (2004) 18:1131–43. doi:10.1101/gad.294104
31. Linger RM, Keating AK, Earp HS, Graham DK. TAM receptor tyrosine kinases: biologic functions, signaling, and potential therapeutic targeting in human cancer. *Adv Cancer Res* (2008) 100:35–83. doi:10.1016/S0065-230X(08)00002-X
32. Hasanbasic I, Cuerquis J, Varnum B, Blostein MD. Intracellular signaling pathways involved in Gas6-Axl-mediated survival of endothelial cells. *Am J Physiol Heart Circ Physiol* (2004) 287:H1207–13. doi:10.1152/ajpheart.00020.2004
33. Lee WP, Wen Y, Varnum B, Hung MC. Akt is required for Axl-Gas6 signaling to protect cells from E1A-mediated apoptosis. *Oncogene* (2002) 21:329–36. doi:10.1038/sj.onc.1205066
34. Wu X, Ma W, Zhou Q, Yan H, Lim ZF, Huang M, et al. AXL-GAS6 expression can predict for adverse prognosis in non-small cell lung cancer with brain metastases. *J Cancer Res Clin Oncol* (2017) 143:1947–57. doi:10.1007/s00432-017-2408-4
35. Wang TJ, Saad S, Qureshi YH, Jani A, Nanda T, Yaeh AM, et al. Does lung cancer mutation status and targeted therapy predict for outcomes and local control in the setting of brain metastases treated with radiation? *Neuro Oncol* (2015) 17:1022–8. doi:10.1093/neuonc/nov043
36. Perez-Moreno P, Brambilla E, Thomas R, Soria JC. Squamous cell carcinoma of the lung: molecular subtypes and therapeutic opportunities. *Clin Cancer Res* (2012) 18:2443–51. doi:10.1158/1078-0432.CCR-11-2370
37. Jain D, Iqbal S, Walia R, Malik P, Cyriac S, Mathur SR, et al. Evaluation of epidermal growth factor receptor mutations based on mutation specific immunohistochemistry in non-small cell lung cancer: a preliminary study. *Indian J Med Res* (2016) 143:308–14. doi:10.4103/0971-5916.182621
38. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. *Nat Rev Cancer* (2007) 7:169–81. doi:10.1038/nrc2088
39. Bauml J, Mick R, Zhang Y, Watt CD, Vachani A, Aggarwal C, et al. Frequency of EGFR and KRAS mutations in patients with non small cell lung cancer by racial background: do disparities exist? *Lung Cancer* (2013) 81:347–53. doi:10.1016/j.lungcan.2013.05.011
40. Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol* (2014) 9:154–62. doi:10.1097/JTO.0000000000000033
41. Tanaka T, Matsuoka M, Sutani A, Gemma A, Maemondo M, Inoue A, et al. Frequency of and variables associated with the EGFR mutation and its subtypes. *Int J Cancer* (2010) 126:651–5. doi:10.1002/ijc.24746
42. Eichler AF, Kahle KT, Wang DL, Joshi VA, Willers H, Engelman JA, et al. EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. *Neuro Oncol* (2010) 12:1193–9. doi:10.1093/neuonc/noq076
43. Li Z, Lu J, Zhao Y, Guo H. The retrospective analysis of the frequency of EGFR mutations and efficacy of gefitinib in NSCLC patients with brain metastases. *J Clin Oncol* (2011) 29:e18065. doi:10.1200/jco.2011.29.15_suppl.e18065
44. Cortot AB, Italiano A, Burel-Vandenbos F, Martel-Planche G, Hainaut P. KRAS mutation status in primary nonsmall cell lung cancer and matched metastases. *Cancer* (2010) 116:2682–7. doi:10.1002/cncr.25014
45. Daniele L, Cassoni P, Bacillo E, Cappia S, Righi L, Volante M, et al. Epidermal growth factor receptor gene in primary tumor and metastatic sites from non-small cell lung cancer. *J Thorac Oncol* (2009) 4:684–8. doi:10.1097/JTO.0b013e3181a52359
46. Gomez-Roca C, Raynaud CM, Penault-Llorca F, Mercier O, Commo F, Morat L, et al. Differential expression of biomarkers in primary non-small cell lung cancer and metastatic sites. *J Thorac Oncol* (2009) 4:1212–20. doi:10.1097/JTO.0b013e3181b44321
47. Gow CH, Chang YL, Hsu YC, Tsai MF, Wu CT, Yu CJ, et al. Comparison of epidermal growth factor receptor mutations between primary and corresponding metastatic tumors in tyrosine kinase inhibitor-naive non-small-cell lung cancer. *Ann Oncol* (2009) 20:696–702. doi:10.1093/annonc/mdn679
48. Italiano A, Vandenbos FB, Otto J, Mouroux J, Fontaine D, Marcy PY, et al. Comparison of the epidermal growth factor receptor gene and protein in primary non-small-cell-lung cancer and metastatic sites: implications for treatment with EGFR-inhibitors. *Ann Oncol* (2006) 17:981–5. doi:10.1093/annonc/mdl038
49. Matsumoto S, Takahashi K, Iwakawa R, Matsuno Y, Nakanishi Y, Kohno T, et al. Frequent EGFR mutations in brain metastases of lung adenocarcinoma. *Int J Cancer* (2006) 119:1491–4. doi:10.1002/ijc.21940
50. Sun M, Behrens C, Feng L, Ozburn N, Tang X, Yin G, et al. HER family receptor abnormalities in lung cancer brain metastases and corresponding primary tumors. *Clin Cancer Res* (2009) 15:4829–37. doi:10.1158/1078-0432.CCR-08-2921
51. Stanic K, Zwitter M, Hitij NT, Kern I, Sadikov A, Cufer T. Brain metastases in lung adenocarcinoma: impact of EGFR mutation status on incidence and survival. *Radiol Oncol* (2014) 48:173–83. doi:10.2478/raon-2014-0016
52. Zhou Q, Zhang XC, Chen ZH, Yin XL, Yang JJ, Xu CR, et al. Relative abundance of EGFR mutations predicts benefit from gefitinib treatment for advanced non-small-cell lung cancer. *J Clin Oncol* (2011) 29:3316–21. doi:10.1200/JCO.2010.33.3757
53. Ahrendt SA, Decker PA, Alawi EA, Zhu Yr YR, Sanchez-Cespedes M, Yang SC, et al. Cigarette smoking is strongly associated with mutation

of the K-ras gene in patients with primary adenocarcinoma of the lung. *Cancer* (2001) 92:1525–30. doi:10.1002/1097-0142(20010915)92:6<1525::AID-CNCR1478>3.0.CO;2-H

54. Marks JL, Broderick S, Zhou Q, Chitale D, Li AR, Zakowski MF, et al. Prognostic and therapeutic implications of EGFR and KRAS mutations in resected lung adenocarcinoma. *J Thorac Oncol* (2008) 3:111–6. doi:10.1097/JTO.0b013e318160c607
55. Fujimoto N, Wislez M, Zhang J, Iwanaga K, Dackor J, Hanna AE, et al. High expression of ErbB family members and their ligands in lung adenocarcinomas that are sensitive to inhibition of epidermal growth factor receptor. *Cancer Res* (2005) 65:11478–85. doi:10.1158/0008-5472.CAN-05-1977
56. Han SW, Kim TY, Jeon YK, Hwang PG, Im SA, Lee KH, et al. Optimization of patient selection for gefitinib in non-small cell lung cancer by combined analysis of epidermal growth factor receptor mutation, K-ras mutation, and Akt phosphorylation. *Clin Cancer Res* (2006) 12:2538–44. doi:10.1158/1078-0432.CCR-05-2845
57. Kalikaki A, Koutsopoulos A, Trypaki M, Souglakos J, Stathopoulos E, Georgoulias V, et al. Comparison of EGFR and K-RAS gene status between primary tumours and corresponding metastases in NSCLC. *Br J Cancer* (2008) 99:923–9. doi:10.1038/sj.bjc.6604629
58. Rodenhuis S, van de Wetering ML, Mooi WJ, Evers SG, van Zandwijk N, Bos JL. Mutational activation of the K-ras oncogene. A possible pathogenetic factor in adenocarcinoma of the lung. *N Engl J Med* (1987) 317:929–35. doi:10.1056/NEJM198710083171504
59. Munfus-McCray D, Harada S, Adams C, Askin F, Clark D, Gabrielson E, et al. EGFR and KRAS mutations in metastatic lung adenocarcinomas. *Hum Pathol* (2011) 42:1447–53. doi:10.1016/j.humpath.2010.12.011
60. Eberhard DA, Johnson BE, Amler LC, Goddard AD, Heldens SL, Herbst RS, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* (2005) 23:5900–9. doi:10.1200/JCO.2005.02.857
61. Riely GJ, Kris MG, Rosenbaum D, Marks J, Li A, Chitale DA, et al. Frequency and distinctive spectrum of KRAS mutations in never smokers with lung adenocarcinoma. *Clin Cancer Res* (2008) 14:5731–4. doi:10.1158/1078-0432.CCR-08-0646
62. Hainaut P, Pfeifer GP. Patterns of p53 G – >T transversions in lung cancers reflect the primary mutagenic signature of DNA-damage by tobacco smoke. *Carcinogenesis* (2001) 22:367–74. doi:10.1093/carcin/22.3.367
63. Shaw AT, Engelman JA. ALK in lung cancer: past, present, and future. *J Clin Oncol* (2013) 31:1105–11. doi:10.1200/JCO.2012.44.5353
64. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* (2007) 448:561–6. doi:10.1038/nature05945
65. Sabir SR, Yeoh S, Jackson G, Bayliss R. EML4-ALK variants: biological and molecular properties, and the implications for patients. *Cancers (Basel)* (2017) 9:2–3. doi:10.3390/cancers9090118
66. Peters S, Adjei AA, Gridelli C, Reck M, Kerr K, Felip E, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2012) 23(Suppl 7):vii56–64. doi:10.1093/annonc/mds226
67. Cooper W, Fox S, O'Toole S, Morey A, Frances G, Pavlakis N, et al. National Working Group Meeting on ALK diagnostics in lung cancer. *Asia Pac J Clin Oncol* (2014) 10(Suppl 2):11–7. doi:10.1111/ajco.12190
68. Houang M, Toon CW, Clarkson A, Sioson L, Watson N, Farzin M, et al. Reflex ALK immunohistochemistry is feasible and highly specific for ALK gene rearrangements in lung cancer. *Pathology* (2014) 46:383–8. doi:10.1097/PAT.0000000000000114
69. Gainor JF, Varghese AM, Ou SH, Kabraji S, Awad MM, Katayama R, et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. *Clin Cancer Res* (2013) 19:4273–81. doi:10.1158/1078-0432.CCR-13-0318
70. Preusser M, Berghoff AS, Ilhan-Mutlu A, Magerle M, Dinhof C, Widhalm G, et al. ALK gene translocations and amplifications in brain metastases of non-small cell lung cancer. *Lung Cancer* (2013) 80:278–83. doi:10.1016/j.lungcan.2013.01.019
71. Peled N, Zach L, Liran O, Ilouze M, Bunn PA Jr, Hirsch FR. Effective crizotinib schedule for brain metastases in ALK rearrangement metastatic non-small-cell lung cancer. *J Thorac Oncol* (2013) 8:e112–3. doi:10.1097/JTO.0000000000000038
72. Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA Jr, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol* (2012) 7:1807–14. doi:10.1097/JTO.0b013e3182745948
73. Gandhi L, Ou SI, Shaw AT, Barlesi F, Dingemans AC, Kim DW, et al. Efficacy of alectinib in central nervous system metastases in crizotinib-resistant ALK-positive non-small-cell lung cancer: comparison of RECIST 1.1 and RANO-HGG criteria. *Eur J Cancer* (2017) 82:27–33. doi:10.1016/j.ejca.2017.05.019
74. Lockney NA, Wu AJ. Alectinib for the management of ALK-positive non-small cell lung cancer brain metastases. *J Thorac Dis* (2017) 9:E152–4. doi:10.21037/jtd.2017.02.05
75. Demuth C, Andersen MN, Jakobsen KR, Madsen AT, Sorensen BS. Increased PD-L1 expression in erlotinib-resistant NSCLC cells with MET gene amplification is reversed upon MET-TKI treatment. *Oncotarget* (2017) 8:68221–9. doi:10.18632/oncotarget.19920
76. Ji M, Liu Y, Li Q, Li XD, Zhao WQ, Zhang H, et al. PD-1/PD-L1 pathway in non-small-cell lung cancer and its relation with EGFR mutation. *J Transl Med* (2015) 13:5. doi:10.1186/s12967-014-0373-0
77. Killock D. Lung cancer: alternative rearrangements – targeting ROS1 in NSCLC. *Nat Rev Clin Oncol* (2014) 11:624. doi:10.1038/nrclinonc.2014.180
78. Li A, Gao HF, Wu YL. Targeting the MET pathway for potential treatment of NSCLC. *Expert Opin Ther Targets* (2015) 19:663–74. doi:10.1517/14728222.2014.995093
79. Matsumoto S, Iwakawa R, Takahashi K, Kohno T, Nakanishi Y, Matsuno Y, et al. Prevalence and specificity of LKB1 genetic alterations in lung cancers. *Oncogene* (2007) 26:5911–8. doi:10.1038/sj.onc.1210418
80. Carretero J, Shimamura T, Rikova K, Jackson AL, Wilkerson MD, Borgman CL, et al. Integrative genomic and proteomic analyses identify targets for Lkb1-deficient metastatic lung tumors. *Cancer Cell* (2010) 17:547–59. doi:10.1016/j.ccr.2010.04.026
81. Ji H, Ramsey MR, Hayes DN, Fan C, McNamara K, Kozlowski P, et al. LKB1 modulates lung cancer differentiation and metastasis. *Nature* (2007) 448:807–10. doi:10.1038/nature06030
82. Zhao N, Wilkerson MD, Shah U, Yin X, Wang A, Hayward MC, et al. 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* (2014) 86:255–61. doi:10.1016/j.lungcan.2014.08.013
83. Sanchez-Cespedes M, Parrella P, Esteller M, Nomoto S, Trink B, Engles JM, et al. Inactivation of LKB1/STK11 is a common event in adenocarcinomas of the lung. *Cancer Res* (2002) 62:3659–62.
84. Capper D, Berghoff AS, Magerle M, Ilhan A, Wohrer A, Hackl M, et al. Immunohistochemical testing of BRAF V600E status in 1,120 tumor tissue samples of patients with brain metastases. *Acta Neuropathol* (2012) 123:223–33. doi:10.1007/s00401-011-0887-y
85. Robinson SD, O'Shaughnessy JA, Cowey CL, Konduri K. BRAF V600E-mutated lung adenocarcinoma with metastases to the brain responding to treatment with vemurafenib. *Lung Cancer* (2014) 85:326–30. doi:10.1016/j.lungcan.2014.05.009
86. Preusser M, Streubel B, Birner P. ROS1 translocations and amplifications in lung cancer brain metastases. *J Neurooncol* (2014) 118:425–6. doi:10.1007/s11060-014-1446-x
87. Jackman D, Pao W, Riely GJ, Engelman JA, Kris MG, Janne PA, et al. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. *J Clin Oncol* (2010) 28:357–60. doi:10.1200/JCO.2009.24.7049
88. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* (2007) 316:1039–43. doi:10.1126/science.1141478
89. Benedettini E, Sholl LM, Peyton M, Reilly J, Ware C, Davis L, et al. Met activation in non-small cell lung cancer is associated with de novo resistance to EGFR inhibitors and the development of brain metastasis. *Am J Pathol* (2010) 177:415–23. doi:10.2353/ajpath.2010.090863

90. Preusser M, Streubel B, Berghoff AS, Hainfellner JA, von Deimling A, Widhalm G, et al. Amplification and overexpression of CMET is a common event in brain metastases of non-small cell lung cancer. *Histopathology* (2014) 65:684–92. doi:10.1111/his.12475
91. Preusser M, Berghoff AS, Berger W, Ilhan-Mutlu A, Dinhof C, Widhalm G, et al. High rate of FGFR1 amplifications in brain metastases of squamous and non-squamous lung cancer. *Lung Cancer* (2014) 83:83–9. doi:10.1016/j.lungcan.2013.10.004
92. Aljohani HM, Aittaleb M, Furgason JM, Amaya P, Deeb A, Chalmers JJ, et al. Genetic mutations associated with lung cancer metastasis to the brain. *Mutagenesis* (2018) 33:137–45. doi:10.1093/mutage/gey003
93. Dawson SJ, Tsui DW, Murtaza M, Biggs H, Rueda OM, Chin SF, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. *N Engl J Med* (2013) 368:1199–209. doi:10.1056/NEJMoa1213261
94. De Mattos-Arruda L, Weigelt B, Cortes J, Won HH, Ng CK, Nuciforo P, et al. Capturing intra-tumor genetic heterogeneity by de novo mutation profiling of circulating cell-free tumor DNA: a proof-of-principle. *Ann Oncol* (2014) 25:1729–35. doi:10.1093/annonc/mdu239
95. Forshew T, Murtaza M, Parkinson C, Gale D, Tsui DW, Kaper F, et al. Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA. *Sci Transl Med* (2012) 4:136ra168. doi:10.1126/scitranslmed.3003726
96. Bettegowda C, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci Transl Med* (2014) 6:224ra224. doi:10.1126/scitranslmed.3007094
97. Pan W, Gu W, Nagpal S, Gephart MH, Quake SR. Brain tumor mutations detected in cerebral spinal fluid. *Clin Chem* (2015) 61:514–22. doi:10.1373/clinchem.2014.235457
98. Pentsova EI, Shah RH, Tang J, Boire A, You D, Briggs S, et al. Evaluating cancer of the central nervous system through next-generation sequencing of cerebrospinal fluid. *J Clin Oncol* (2016) 34:2404–15. doi:10.1200/JCO.2016.66.6487
99. Wang Y, Springer S, Zhang M, McMahon KW, Kinde I, Dobbyn L, et al. Detection of tumor-derived DNA in cerebrospinal fluid of patients with primary tumors of the brain and spinal cord. *Proc Natl Acad Sci U S A* (2015) 112:9704–9. doi:10.1073/pnas.1511694112
100. De Mattos-Arruda L, Mayor R, Ng CK, Weigelt B, Martinez-Ricarte F, Torrejon D, et al. Cerebrospinal fluid-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma. *Nat Commun* (2015) 6:8839. doi:10.1038/ncomms9839
101. Li Y, Pan W, Connolly ID, Reddy S, Nagpal S, Quake S, et al. Tumor DNA in cerebral spinal fluid reflects clinical course in a patient with melanoma leptomeningeal brain metastases. *J Neurooncol* (2016) 128:93–100. doi:10.1007/s11060-016-2081-5
102. Brognard J, Clark AS, Ni Y, Dennis PA. Akt/protein kinase B is constitutively active in non-small cell lung cancer cells and promotes cellular survival and resistance to chemotherapy and radiation. *Cancer Res* (2001) 61:3986–97.
103. Li Q, Yang J, Yu Q, Wu H, Liu B, Xiong H, et al. Associations between single-nucleotide polymorphisms in the PI3K–PTEN–AKT–mTOR pathway and increased risk of brain metastasis in patients with non–small cell lung cancer. *Clin Cancer Res* (2013) 19:6252–60. doi:10.1158/1078-0432.CCR-13-1093
104. Adamo B, Deal AM, Burrows E, Geradts J, Hamilton E, Blackwell KL, et al. Phosphatidylinositol 3-kinase pathway activation in breast cancer brain metastases. *Breast Cancer Res* (2011) 13:R125. doi:10.1186/bcr3071
105. Paik PK, Shen R, Won H, Rekhtman N, Wang L, Sima CS, et al. Next-generation sequencing of stage IV squamous cell lung cancers reveals an association of PI3K aberrations and evidence of clonal heterogeneity in patients with brain metastases. *Cancer Discov* (2015) 5:610–21. doi:10.1158/2159-8290.CD-14-1129
106. Li Q, Wu H, Chen B, Hu G, Huang L, Qin K, et al. SNPs in the TGF-beta signaling pathway are associated with increased risk of brain metastasis in patients with non-small-cell lung cancer. *PLoS One* (2012) 7:e51713. doi:10.1371/journal.pone.0051713
107. Massague J. TGFbeta in cancer. *Cell* (2008) 134:215–30. doi:10.1016/j.cell.2008.07.001
108. Jeon YK, Sung SW, Chung JH, Park WS, Seo JW, Kim CW, et al. Clinicopathologic features and prognostic implications of epidermal growth factor receptor (EGFR) gene copy number and protein expression in non-small cell lung cancer. *Lung Cancer* (2006) 54:387–98. doi:10.1016/j.lungcan.2006.08.015
109. Mao C, Qiu LX, Liao RY, Du FB, Ding H, Yang WC, et al. KRAS mutations and resistance to EGFR-TKIs treatment in patients with non-small cell lung cancer: a meta-analysis of 22 studies. *Lung Cancer* (2010) 69:272–8. doi:10.1016/j.lungcan.2009.11.020
110. Bonanno L, Schiavon M, Nardo G, Bertorelle R, Bonaldi L, Galligioni A, et al. Prognostic and predictive implications of EGFR mutations, EGFR copy number and KRAS mutations in advanced stage lung adenocarcinoma. *Anticancer Res* (2010) 30:5121–8.
111. Lee HW, Seol HJ, Choi YL, Ju HJ, Joo KM, Ko YH, et al. Genomic copy number alterations associated with the early brain metastasis of non-small cell lung cancer. *Int J Oncol* (2012) 41:2013–20. doi:10.3892/ijo.2012.1663
112. Li F, Sun L, Zhang S. Acquirement of DNA copy number variations in non-small cell lung cancer metastasis to the brain. *Oncol Rep* (2015) 34:1701–7. doi:10.3892/or.2015.4188
113. Soria JC, Lee HY, Lee JI, Wang L, Issa JP, Kemp BL, et al. Lack of PTEN expression in non-small cell lung cancer could be related to promoter methylation. *Clin Cancer Res* (2002) 8:1178–84.
114. Markopoulos GS, Roupakia E, Tokamani M, Chavdoula E, Hatziapostolou M, Polytarchou C, et al. A step-by-step microRNA guide to cancer development and metastasis. *Cell Oncol (Dordr)* (2017) 40:303–39. doi:10.1007/s13402-017-0341-9
115. Liu CG, Calin GA, Volinia S, Croce CM. MicroRNA expression profiling using microarrays. *Nat Protoc* (2008) 3:563–78. doi:10.1038/nprot.2008.14
116. Chen PS, Su JL, Hung MC. Dysregulation of microRNAs in cancer. *J Biomed Sci* (2012) 19:90. doi:10.1186/1423-0127-19-90
117. Alsidawi S, Malek E, Driscoll JJ. MicroRNAs in brain metastases: potential role as diagnostics and therapeutics. *Int J Mol Sci* (2014) 15:10508–26. doi:10.3390/ijms150610508
118. McDermott R, Gabikian P, Sarvaiya P, Ulasov I, Lesniak MS. MicroRNAs in brain metastases: big things come in small packages. *J Mol Med (Berl)* (2013) 91:5–13. doi:10.1007/s00109-012-0971-3
119. Arora S, Ranade AR, Tran NL, Nasser S, Sridhar S, Korn RL, et al. MicroRNA-328 is associated with (non-small) cell lung cancer (NSCLC) brain metastasis and mediates NSCLC migration. *Int J Cancer* (2011) 129:2621–31. doi:10.1002/ijc.25939
120. Cheng CY, Hsieh HL, Sun CC, Lin CC, Luo SF, Yang CM. IL-1 beta induces urokinase-plasminogen activator expression and cell migration through PKC alpha, JNK1/2, and NF-kappaB in A549 cells. *J Cell Physiol* (2009) 219:183–93. doi:10.1002/jcp.21669
121. Chen LT, Xu SD, Xu H, Zhang JF, Ning JF, Wang SF. MicroRNA-378 is associated with non-small cell lung cancer brain metastasis by promoting cell migration, invasion and tumor angiogenesis. *Med Oncol* (2012) 29:1673–80. doi:10.1007/s12032-011-0083-x
122. Remon J, Alvarez-Berdugo D, Majem M, Moran T, Reguart N, Lianes P. miRNA-197 and miRNA-184 are associated with brain metastasis in EGFR-mutant lung cancers. *Clin Transl Oncol* (2016) 18:153–9. doi:10.1007/s12094-015-1347-2
123. Zhao C, Xu Y, Zhang Y, Tan W, Xue J, Yang Z, et al. Downregulation of miR-145 contributes to lung adenocarcinoma cell growth to form brain metastases. *Oncol Rep* (2013) 30:2027–34. doi:10.3892/or.2013.2728
124. Cho WC, Chow AS, Au JS. miR-145 inhibits cell proliferation of human lung adenocarcinoma by targeting EGFR and NUDT1. *RNA Biol* (2011) 8:125–31. doi:10.4161/rna.8.1.14259
125. Cho WC, Chow AS, Au JS. Restoration of tumour suppressor hsa-miR-145 inhibits cancer cell growth in lung adenocarcinoma patients with epidermal growth factor receptor mutation. *Eur J Cancer* (2009) 45:2197–206. doi:10.1016/j.ejca.2009.04.039
126. Subramani A, Alsidawi S, Jagannathan S, Sumita K, Sasaki AT, Aronow B, et al. The brain microenvironment negatively regulates miRNA-768-3p to promote K-ras expression and lung cancer metastasis. *Sci Rep* (2013) 3:2392. doi:10.1038/srep02392
127. Li J, Yang H, Li Y, Liu Y, Chen S, Qi C, et al. MicroRNA-146 up-regulation predicts the prognosis of non-small cell lung cancer by miRNA in situ hybridization. *Exp Mol Pathol* (2014) 96:195–9. doi:10.1016/j.yexmp.2013.11.004

128. Chen G, Umelo IA, Lv S, Teugels E, Fostier K, Kronenberger P, et al. miR-146a inhibits cell growth, cell migration and induces apoptosis in non-small cell lung cancer cells. *PLoS One* (2013) 8:e60317. doi:10.1371/journal.pone.0060317
129. Hwang SJ, Seol HJ, Park YM, Kim KH, Gorospe M, Nam DH, et al. MicroRNA-146a suppresses metastatic activity in brain metastasis. *Mol Cells* (2012) 34:329–34. doi:10.1007/s10059-012-0171-6
130. Hwang SJ, Lee HW, Kim HR, Song HJ, Lee DH, Lee H, et al. Overexpression of microRNA-95-3p suppresses brain metastasis of lung adenocarcinoma through downregulation of cyclin D1. *Oncotarget* (2015) 6:20434–48. doi:10.18632/oncotarget.3886
131. Chen LJ, Li XY, Zhao YQ, Liu WJ, Wu HJ, Liu J, et al. Down-regulated microRNA-375 expression as a predictive biomarker in non-small cell lung cancer brain metastasis and its prognostic significance. *Pathol Res Pract* (2017) 213:882–8. doi:10.1016/j.prp.2017.06.012
132. Shintani Y, Higashiyama S, Ohta M, Hirabayashi H, Yamamoto S, Yoshimasu T, et al. Overexpression of ADAM9 in non-small cell lung cancer correlates with brain metastasis. *Cancer Res* (2004) 64:4190–6. doi:10.1158/0008-5472.CAN-03-3235
133. Chiu KL, Lin YS, Kuo TT, Lo CC, Huang YK, Chang HF, et al. ADAM9 enhances CDCP1 by inhibiting miR-1 through EGFR signaling activation in lung cancer metastasis. *Oncotarget* (2017) 8:47365–78. doi:10.18632/oncotarget.17648
134. Singh M, Garg N, Venugopal C, Hallett R, Tokar T, McFarlane N, et al. STAT3 pathway regulates lung-derived brain metastasis initiating cell capacity through miR-21 activation. *Oncotarget* (2015) 6:27461–77. doi:10.18632/oncotarget.4742
135. Devarajan E, Huang S. STAT3 as a central regulator of tumor metastases. *Curr Mol Med* (2009) 9:626–33. doi:10.2174/156652409788488720
136. Vitiello M, Tuccoli A, Poliseno L. Long non-coding RNAs in cancer: implications for personalized therapy. *Cell Oncol (Dordr)* (2015) 38:17–28. doi:10.1007/s13402-014-0180-x
137. Gutschner T, Diederichs S. The hallmarks of cancer: a long non-coding RNA point of view. *RNA Biol* (2012) 9:703–19. doi:10.4161/rna.20481
138. Tripathi V, Ellis JD, Shen Z, Song DY, Pan Q, Watt AT, et al. The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. *Mol Cell* (2010) 39:925–38. doi:10.1016/j.molcel.2010.08.011
139. Gutschner T, Hammerle M, Eissmann M, Hsu J, Kim Y, Hung G, et al. The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. *Cancer Res* (2013) 73:1180–9. doi:10.1158/0008-5472.CAN-12-2850
140. Shen L, Chen L, Wang Y, Jiang X, Xia H, Zhuang Z. Long noncoding RNA MALAT1 promotes brain metastasis by inducing epithelial-mesenchymal transition in lung cancer. *J Neurooncol* (2015) 121:101–8. doi:10.1007/s11060-014-1613-0
141. Schmidt LH, Spieker T, Koschmieder S, Schaffers S, Humberg J, Jungen D, et al. The long noncoding MALAT-1 RNA indicates a poor prognosis in non-small cell lung cancer and induces migration and tumor growth. *J Thorac Oncol* (2011) 6:1984–92. doi:10.1097/JTO.0b013e3182307eac
142. Tano K, Mizuno R, Okada T, Rakwal R, Shibato J, Masuo Y, et al. MALAT-1 enhances cell motility of lung adenocarcinoma cells by influencing the expression of motility-related genes. *FEBS Lett* (2010) 584:4575–80. doi:10.1016/j.febslet.2010.10.008
143. Ji P, Diederichs S, Wang W, Boing S, Metzger R, Schneider PM, et al. MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene* (2003) 22:8031–41. doi:10.1038/sj.onc.1206928
144. Singla AK, Thirukkumaran C, Dixit R, Wu W. Genomic landscape of cancer metastasis. In: Wu W, Choudhry H, editors. *Next Generation Sequencing in Cancer Research: Volume 1: Decoding the Cancer Genome*. New York: Springer (2013). p. 75–90.
145. Hu T, Lu YR. BCYRN1, a c-MYC-activated long non-coding RNA, regulates cell metastasis of non-small-cell lung cancer. *Cancer Cell Int* (2015) 15:36. doi:10.1186/s12935-015-0183-3
146. Rapp UR, Korn C, Ceteci F, Karreman C, Luetkenhaus K, Serafin V, et al. MYC is a metastasis gene for non-small-cell lung cancer. *PLoS One* (2009) 4:e6029. doi:10.1371/journal.pone.0006029
147. Nabeshima K, Inoue T, Shimao Y, Sameshima T. Matrix metalloproteinases in tumor invasion: role for cell migration. *Pathol Int* (2002) 52:255–64. doi:10.1046/j.1440-1827.2002.01343.x
148. Yu T, Wu Y, Helman JI, Wen Y, Wang C, Li L. CXCR4 promotes oral squamous cell carcinoma migration and invasion through inducing expression of MMP-9 and MMP-13 via the ERK signaling pathway. *Mol Cancer Res* (2011) 9:161–72. doi:10.1158/1541-7786.MCR-10-0386
149. Ghosh S, Basu M, Roy SS. ETS-1 protein regulates vascular endothelial growth factor-induced matrix metalloproteinase-9 and matrix metalloproteinase-13 expression in human ovarian carcinoma cell line SKOV-3. *J Biol Chem* (2012) 287:15001–15. doi:10.1074/jbc.M111.284034
150. Hoffman PC, Mauer AM, Vokes EE. Lung cancer. *Lancet* (2000) 355:479–85. doi:10.1016/S0140-6736(99)08003-4
151. Bernards R, Weinberg RA. A progression puzzle. *Nature* (2002) 418:823. doi:10.1038/418823a

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

REVIEW
published: 26 July 2018
doi: 10.3389/fonc.2018.00241

The Prevention of Brain Metastases in Non-Small Cell Lung Cancer by Prophylactic Cranial Irradiation

Willem J. A. Witlox[1], Bram L. T. Ramaekers[1], Jaap D. Zindler[2], Daniëlle B. P. Eekers[2], Judith G. M. van Loon[2], Lizza E. L. Hendriks[3], Anne-Marie C. Dingemans[3] and Dirk K. M. De Ruysscher[2,4]*

[1] Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, Netherlands, [2] Department of Radiation Oncology (Maastro Clinic), Maastricht University Medical Centre, GROW School of Oncology and Developmental Biology, Maastricht, Netherlands, [3] Department of Pulmonology, Maastricht University Medical Centre, GROW School of Oncology and Developmental Biology, Maastricht, Netherlands, [4] Radiation Oncology, KU Leuven, Leuven, Belgium

OPEN ACCESS

Edited by:
Yanis Boumber,
Fox Chase Cancer Center,
United States

Reviewed by:
Meng Xu Welliver,
The Ohio State University
James Cancer Center, United States
Desiree Hao,
University of Calgary, Canada

***Correspondence:**
Willem J. A. Witlox
willem.witlox@mumc.nl

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: 30 January 2018
Accepted: 18 June 2018
Published: 26 July 2018

Citation:
Witlox WJA, Ramaekers BLT, Zindler JD, Eekers DBP, van Loon JGM, Hendriks LEL, Dingemans A-MC and De Ruysscher DKM (2018) The Prevention of Brain Metastases in Non-Small Cell Lung Cancer by Prophylactic Cranial Irradiation. Front. Oncol. 8:241. doi: 10.3389/fonc.2018.00241

Background: Non-small cell lung cancer (NSCLC) patients frequently develop brain metastases (BM), even though the initial imaging with brain CT or MRI was negative. Stage III patients have the highest risk to develop BM, with an incidence of approximately 30%. BM can lead to neurocognitive disorders, loss of quality of life (QoL), and they are the most important factors influencing patient's overall survival (OS). Although a radical local treatment of BM may be possible with primary radiosurgery or after resection, the prognosis often remains poor. Preventing the development of BM through prophylactic cranial irradiation (PCI) may improve the outcome of these patients.

Methods: Data from published randomized trials comparing PCI with non-PCI were sought using electronic database (PubMed) searching, hand searching, and by contacting experts. Trials were included if they considered a randomized comparison of PCI and non-PCI, enrolled NSCLC patients, excluded patients with recurrent or metastatic disease, and reported results on BM occurrence. Each randomized controlled trial (RCT) was assessed for methodological quality using the Cochrane collaboration's tool for the assessment of risk of bias. Study estimates were pooled using a fixed effects sample-weighted meta-analysis approach to calculate an overall estimate and 95% confidence interval (CI). Results on PCI-related toxicity, QoL, and OS were only reported descriptively.

Results: Seven RCTs were included in the meta-analysis. In total, 1,462 patients were analyzed, including 717 patients who received PCI and 745 patients who did not. The risk of developing BM was significantly decreased through PCI (13% reduction, RR 0.33; 95% CI 0.22–0.45). PCI-related toxicity and QoL data were limited. Acute toxicity mostly included fatigue, skin-related toxicity, and nausea or vomiting. Late toxicities such as headache, dyspnea, lethargy, and low grade cognitive impairments were also reported in some of the included RCTs. Results on OS were inconclusive.

Conclusion: The risk of developing BM was reduced in patients who received PCI compared to patients who did not. To implement PCI as the standard treatment for patients

with NSCLC, the impact of PCI-related toxicity on QoL should be further investigated, as well as long-term OS. A future individual patient data meta-analysis could produce definitive answers to this clinical question.

Keywords: non-small cell lung cancer, prophylactic cranial irradiation, brain metastases, toxicity, survival, quality of life

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most important cause of death due to cancer worldwide, and accounts for about 85% of all lung cancers. At present, more than 50% of all patients are diagnosed with adenocarcinoma, less than 10% are diagnosed with large cell cancer and the rest with squamous cell carcinoma. One-third of NSCLC present with locally advanced (stage III) disease, 20% with stage I–II, and the rest have metastases (stage IV) at diagnosis (1).

Non-small cell lung cancer patients frequently develop brain metastases (BM), even though the initial staging with brain CT or MRI was negative. The more advanced the disease stage is, the more frequent BM occur. They are also more frequent in adenocarcinoma than in squamous cell cancer (1). Stage III patients have a BM incidence of approximately 30% (2). With longer overall survival (OS) and better imaging techniques, this percentage might increase. For example, in drive-mutated patients (e.g., EGFR and ALK) with a survival beyond 5 years, this percentage increases to more than 50% (3). BM can lead to neurocognitive disorders, loss of quality of life (QoL), and they are the most important factors influencing patients' OS (2). Although a radical local treatment of BM may be possible with radiosurgery or resection, the prognosis often remains poor. In order to improve QoL as well as OS, there is an unmet need to prevent the occurrence of BM (4).

Prophylactic cranial irradiation (PCI) was shown to significantly improve OS (5.4% improvement of 3-year OS) in localized small cell lung cancer with complete remission or stable disease after multimodality treatment, as a result of decreasing BM incidence by about 50% (5). Also in patients with NSCLC, several randomized controlled trials (RCTs) studied the value of PCI in the prevention of BM (6–14). However, PCI might deteriorate QoL as a result of neurocognitive decline associated with cranial irradiation. Recently, a randomized phase III trial conducted by the NVALT/DLCRG (14) showed that PCI reduced the incidence of symptomatic BM [7.0% in PCI vs 27.2% in no PCI, hazard ratio 0.25; 95% confidence interval (95% CI) 0.11–0.58]. Therefore, it is time to update the previously published literature and revisit the role of PCI in the prevention of BM in NSCLC patients. Here, we report on the results of a meta-analysis assessing the impact of PCI on the reduction of BM in primary stage I–III NSCLC patients, with PCI-related toxicity, QoL, and OS as secondary endpoints.

METHODS

Data Collection

Data from published RCTs comparing PCI with non-PCI were sought using electronic database searching between 1980 and December 1, 2017 (PubMed), hand searching (reference checking of individual studies and review articles), and by contacting experts in the field. The following keywords were used as search terms: "Carcinoma, Non-Small-Cell Lung," "NSCLC," "Cranial Irradiation," "Cranial Neoplasms/radiotherapy," "Brain Metastasis," "Overall Survival," and "RCT." Details of the search strategy and corresponding flow chart can be found in Appendix S1 in Supplementary Material.

Selection Criteria

Trials were included if they considered a randomized comparison of PCI and non-PCI, enrolled NSCLC patients, excluded patients with recurrent or metastatic disease, and reported results on BM occurrence.

Quality Assessment

Two investigators (Willem J. A. Witlox and Bram L. T. Ramaekers) independently assessed each RCT for methodological quality using the Cochrane collaboration's tool for the assessment of risk of bias (15). This tool consists of seven items, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each item was scored "low risk," "unclear risk," or "high risk" of bias (Appendix S2 in Supplementary Material).

Statistical Analysis

Data of the primary endpoint (BM occurrence) was analyzed using Stata/SE 14.2 (16). Relative risk (RR) and accompanying 95% CI of the individual studies were calculated based on the number of events and group totals. Subsequently, the estimates were pooled using a fixed effects sample-weighted meta-analysis approach to calculate an overall estimate and 95% CI. Heterogeneity of the studies was tested using chi-square- and I^2-tests (15). Publication bias and small study effects were assessed by visual inspection of funnel plots and performing Egger's test, respectively (17, 18). If Egger's test is significant, a sensitivity analysis will be performed excluding small studies (weight < 10%).

Results on PCI-related toxicity, QoL, and OS will only be reported descriptively.

RESULTS

Literature Search and Quality Assessment of Publications

The electronic literature search yielded 360 unique publications. Another two publications were identified through hand searching and contacting experts. After screening of titles and/or abstracts, 354 trials were excluded. One RCT (12) was excluded after reading the full text, because local treatment was different

between both arms. Methodological quality of the remaining seven RCTs was checked and most of the items were at "low risk" of bias (**Figure 1**). Three studies (6–8) did only perform a brain scan when indicated by a change in neurological status of the patients, without adequately defining how neurological status was assessed. Therefore, the reviewers judged these studies to be at high risk of introducing bias in assessing the outcome. The reviewers suspected possible selection bias in the study of Cox et al. (6), because randomized patients were excluded from evaluation, which is not in accordance with the intention to treat principle. Although blinding of participants and personnel was not performed in any of the included studies, based on the nature of the intervention, this item was judged by the reviewers as low risk of introducing bias (Appendix S2 in Supplementary Material).

Characteristics of the Included Trials

Characteristics of the seven included trials are listed in **Table 1** below. There were little differences between the selected patient groups of the trials. Four studies (9, 10, 13, 14) included stage III

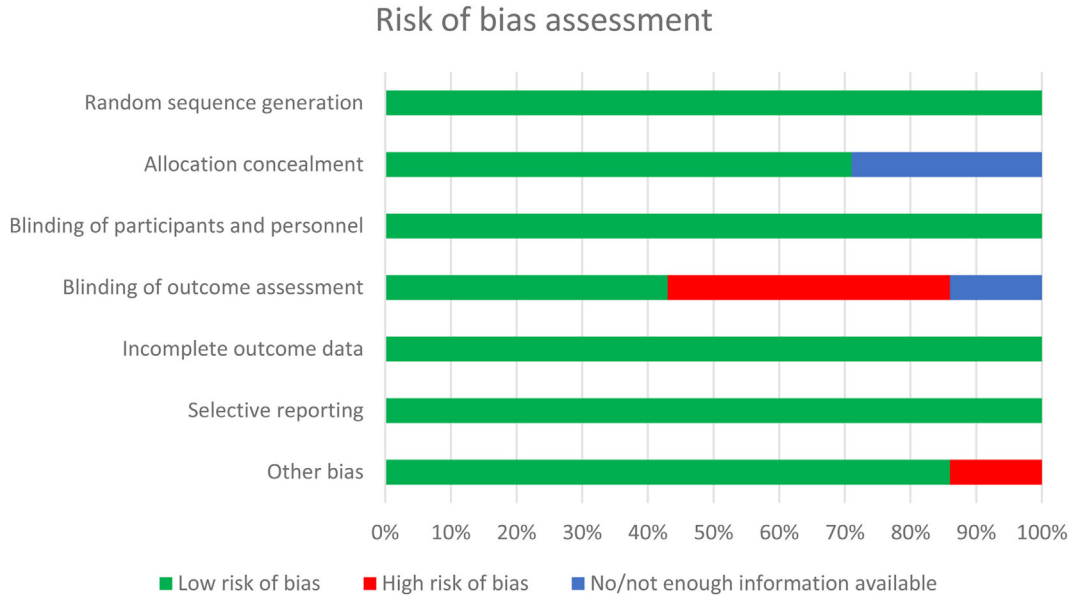


FIGURE 1 | Methodological quality assessment of the included randomized controlled trials evaluating the effect of prophylactic cranial irradiation on brain metastases in non-small cell lung cancer.

TABLE 1 | Study characteristics of the included RCTs evaluating PCI.

Study	Year of publication	Local treatment	Stage	Brain imaging	PCI dose	Primary endpoint	N[a]	Systematic Follow-up for BM
VALG	1981	RT alone	All[b]	Radionuclide scan	10 Gy × 2 Gy	BM rate	281	No
MDACC	1984	Chemo-RT RT alone	I–III	Radionuclide scan/CT scan	10 Gy × 3 Gy	CNS metastases rate	97	No
RTOG 8403	1991	RT alone Surgery and RT	I–III	CT scan	10 Gy × 3 Gy	Time to BM	187	No
SWOG	1998	Chemo-RT RT alone	III	Unclear	15 Gy × 2–2.5 Gy	OS rate	226	Not reported
RTOG 0214	2012	Chemo-RT	III	MRI scan	15 Gy × 2 Gy	OS rate	340	Yes
Li	2015	Surgery-chemo	IIIA	MRI scan	10 Gy × 3 Gy	DFS	156	Yes
NVALT-11	2018	RT alone	III	CT scan/MRI scan	18 Gy × 2 Gy/12 Gy × 2.5 Gy/10 Gy × 3 Gy	Symptomatic BM rate	175	Yes

[a]*Number of eligible patients.*
[b]*All inoperable patients; stage not clear.*
PCI, prophylactic cranial irradiation; RT, radiotherapy; Chemo; chemotherapy; BM, brain metastases; CNS, central nervous system; OS, overall survival; DFS, disease-free survival; RCTs, randomized controlled trials.

NSCLC patients only, two studies (7, 8) included stage I, II, and III patients, and in one study (6) staging was unclear. For treatment of the primary tumor, two trials (6, 14) treated their patients with radiotherapy alone, one trial (11) used chemo-radiotherapy, and the four remaining trials used either combinations of chemo-radiotherapy and radiotherapy alone (7, 9, 10), chemotherapy and surgery (13), or radiotherapy and surgery (8). Brain imaging was mainly done by a radionuclide scan in two studies (6, 7). One study (8) used CT scans, three more recent studies (11, 13, 14) used MRI and in one study (9, 10) the technology of brain imaging was unclear. Dosing of cranial irradiation ranged from 20 to 37.5 Gy (10 fractions of 2 Gy to 15 fractions of 2.5 Gy).

Incidence of BM After PCI

Taken all RCTs together, in total, 1,462 patients were analyzed, including 717 patients who received PCI and 745 patients who did not. The BM incidence in the PCI arm ranged from 0.9 to 12.3%, and from 11.0 to 30.7% in the non-PCI arm (**Table 2**). The overall effect estimate of the impact of PCI on the occurrence of BM is presented in **Figure 2**. The risk of developing BM was significantly decreased in the PCI arm compared to no PCI (13% reduction, RR 0.33; 95% CI 0.22–0.45). Heterogeneity across the studies was low ($I^2 = 0\%$; $p = 0.468$). Furthermore, Egger's test indicated that smaller studies showed larger effect sizes ($p = 0.048$), which is also reflected in the asymmetric funnel plot (**Figure 3**). Nevertheless, results of the sensitivity analysis excluding small studies (7, 9, 10) (weight < 10%) were similar (RR 0.38; 95% CI 0.24–0.51).

PCI-Related Toxicity, QoL, and OS

Few trials reported on PCI-related toxicity and QoL with most details in the study of Gore et al. (11) (**Table 3**). Acute toxicity mostly included

TABLE 2 | Data on BM events [(a)symptomatic BM occurrence] and incidence of the included RCTs evaluating PCI.

	PCI			No PCI			
Study	**Events**	**Total**	**Incidence (%)**	**Events**	**Total**	**Incidence (%)**	**Weight (%)**
VALG	7	136	5.1	16	145	11.0	10.5
MDACC	2	46	4.3	14	51	27.5	9.0
RTOG 8403	8	93	8.6	18	94	19.1	12.2
SWOG	1	111	0.9	13	115	11.3	8.7
RTOG 0214	13	163	8.0	32	177	18.1	20.9
Li	10	81	12.3	29	75	38.7	20.5
NVALT-11	7	87	8.0	27	88	30.7	18.3
Total	48	717		149	745		

PCI, prophylactic cranial irradiation; BM, brain metastasis; RCTs, randomized controlled trials.

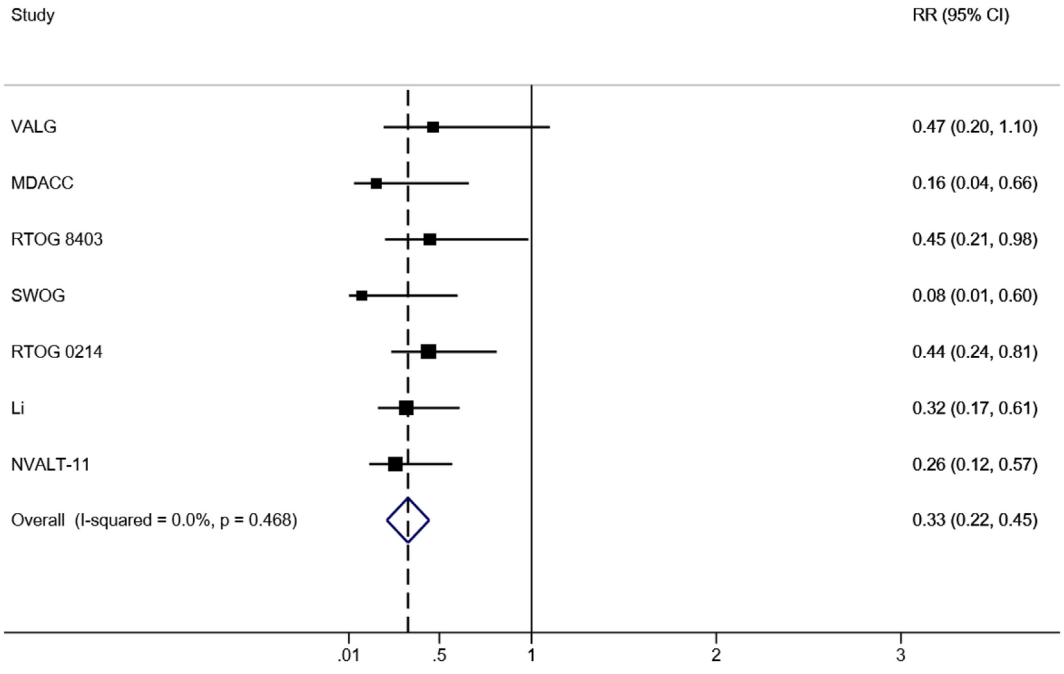


FIGURE 2 | Forrest plot of the meta-analysis of RCTs evaluating the effect of PCI on BM in NSCLC. Abbreviations: RR, relative risk; 95% CI, 95% confidence interval; RCTs, randomized controlled trials; PCI, prophylactic cranial irradiation; BM, brain metastases; NSCLC, non-small cell lung cancer.

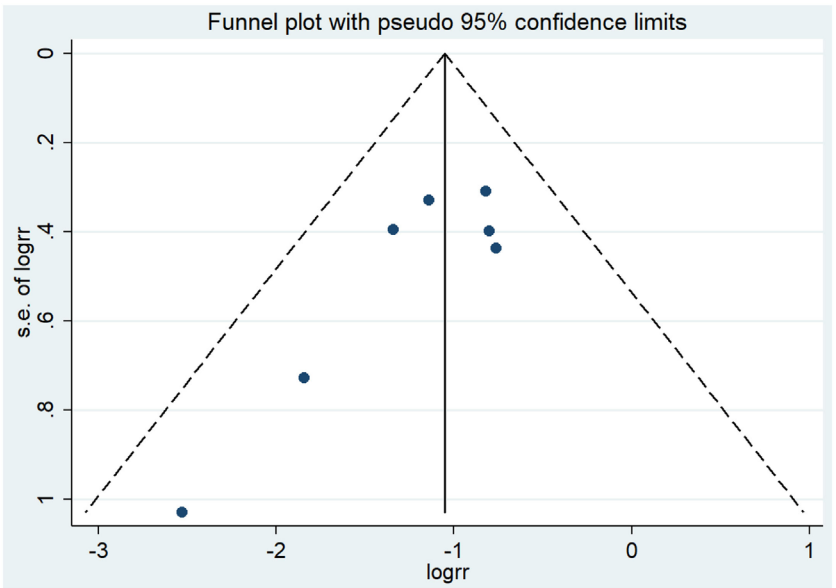


FIGURE 3 | Results of the funnel plot of RCTs evaluating the effect of PCI on BM in NSCLC. Abbreviations: logrr: logarithm of the relative risk; RCTs, randomized controlled trials; PCI, prophylactic cranial irradiation; BM, brain metastases; NSCLC, non-small cell lung cancer.

TABLE 3 | RCTs evaluating PCI-related toxicity and QoL in NSCLC.

Study	PCI dose (Gy/fraction)	Neuropsychological test	Evaluation after PCI	Impairment after PCI	QoL instruments and results
MDACC	30/10	Not reported	Not reported	Acute toxicity: one patient developed transient memory loss for 2.5 weeks Late toxicity: none	Not reported
RTOG 8403	30/10	Neurological physical examinations	Intervals of 3 months	Acute toxicity: epilation and skin reactions Late toxicity: none	Not reported
RTOG 0214	30/15	MMSE ADLS HVLT	At 3, 6, 12, 18, 24, 30, 36, and 48 months, and then yearly	Acute toxicity: constitutional (grade 1 and 2), gastrointestinal (grade 1), dermatologic (grade 2), hematologic (grade 3), fatigue (grade 3), dyspnea (grade 3), ataxia (grade 3), depression (grade 3 and 4) Late toxicity: dyspnea, syncope, weakness, fatigue (all grade 3)	EORTC QLQ-C30 and EORTC QLQ-BN20 Global health status/QoL was similar between both arms
Li	30/10	CTC-AE RTOG/ EORTC-LRMSS	First 2 years every 3 months, every 6 months thereafter	Acute toxicity: headache (grade 1, 2, and 3), nausea or vomiting (grade 1 and 2), fatigue (grade 1, 2, and 3), skin toxicity (grade 1 and 2), insomnia (grade 2) Late toxicity: mild, moderate, and severe headache, slight or great lethargy, skin atrophy, fatigue	FACT-L questionnaire No significant differences were noted in deterioration rate for QoL and symptoms between the two groups
NVALT-11	36/18 30/12 30/10	CTC-AE	4 weeks, 3, 6, 12, 24, and 36 months	Memory impairment (grade 1 and 2), cognitive disturbance (grade 1 and 2), alopecia, fatigue, headache	EORTC QLQ-C30 EORTC QLQ-BN20 EuroQol 5D Results not reported

PCI, prophylactic cranial irradiation; QoL, quality of life; MMSE, Mini Mental Status Exam; ADLS, Activities of Daily Living Scale; HVLT, Hopkins Verbal Learning Test; CTC-AE, Common Terminology Criteria Adverse Events; RTOG/EORTC-LRMSS, RTOG/ERTOC late radiation morbidity scoring schema; EORTC QLQ-C30, EORTC quality of life questionnaire-C30; EORTC QLQ-BN20, EORTC quality of life questionnaire-BN20; FACT-L questionnaire, Functional Assessment of Cancer Therapy-Lung questionnaire; NSCLC, non-small cell lung cancer; RCTs, randomized controlled trials.

fatigue, skin-related toxicity, and nausea or vomiting. Late toxicities such as headache, dyspnea, and lethargy were also reported in some of the included RCTs. Low grade (1 and 2) memory impairments and cognitive disturbances were only reported in the study of De Ruysscher et al. (14). Results reporting on QoL were limited, and no significant differences were observed between both arms.

TABLE 4 | RCTs evaluating PCI-related OS in NSCLC.

Study	Median follow-up in months	Median OS in months (PCI vs no PCI)	*p*-Value
VALG	Not reported	Not reported	Not reported
MDACC	13.6 (PCI), 12.7 (no PCI)	60.3 vs 56.3	Not significant
RTOG 8403	Not reported	8.4 vs 8.3	0.36
SWOG	Not reported	8.0 vs 11.0	Significant
RTOG 0214	23.8	25.8 vs 24.8	0.86
Li	68.1 (PCI), 65.2 (no PCI)	31.2 vs 27.4	0.31
NVALT-11	53.3	24.2 vs 21.9	0.56

OS, overall survival; PCI, prophylactic cranial irradiation; NSCLC, non-small cell lung cancer; RCTs, randomized controlled trials.

In addition to BM occurrence, all included trials, except for the trial of Cox et al. (6), also reported on PCI-related OS in NSCLC (**Table 4**). Nearly all studies only report on short-term survival, and most trials did not use contemporary staging and systemic therapy. Taking these shortcomings in mind, no statistically significant OS difference was found between the PCI arm and no PCI arm, except for the study of Miller et al. (9, 10), which showed a significant OS benefit in favor of the no PCI arm ($p = 0.004$).

DISCUSSION

This study aimed to review published literature and revisit the role of PCI in the prevention of BM in NSCLC. The analysis included seven RCTs, involving 1,462 NSCLC patients in total. The current meta-analysis shows that the risk of developing BM was reduced in patients who received PCI compared to patients who did not (RR 0.33; 95% CI 0.22–0.45).

Previously published results from reviews that investigated the role of PCI in the prevention of BM in NSCLC are in line with our findings. The most recently published meta-analyses of Sun et al. (4) and Xie et al. (19), evaluating the impact of PCI on BM occurrence in NSCLC, showed highly significant results in favor of PCI. However, these reviews could not evaluate the recent RCTs of Li et al. (13) and De Ruysscher et al. (14). Including the two most recent RCTs does not only add to the sample size of our meta-analysis, but the proper methodological quality and the use of more advanced brain imaging methods also add value to the conclusiveness of our results. Furthermore, unlike our study, the RCT of Pottgen et al. (12) was included in these meta-analyses. Local treatment was different between the two arms in this study (primary curative resection followed by postoperative thoracic radiation therapy vs chemotherapy and concurrent chemo-radiotherapy followed by thoracic surgery). Therefore, we judged that it was not possible to assess the impact on prevention of BM attributable to PCI.

Although this is the largest, most recent review incorporating all available evidence from RCTs on the impact of PCI on the prevention of BM in NSCLC, there are also limitations. Egger's test and visual inspection of the funnel plot indicated the presence of publication bias. However, sensitivity analysis showed that excluding smaller studies from the meta-analysis did not much alter the results. Furthermore, assessment of the methodological quality of the included studies showed that for some items risk of bias was high. Nevertheless, most of these high bias risk items could be found in the studies (7, 9, 10) that were excluded in the sensitivity analysis, and results remained largely similar to the original results.

The meta-analysis showed that the BM incidence was lower in patients who received PCI, but few trials also reported that PCI could cause toxicity resulting in a decline in QoL. Most occurring acute toxicities were fatigue, skin-related toxicity, and nausea or vomiting. Toxicities occurring on longer term were headache, dyspnea, and lethargy. In addition, the study of De Ruysscher et al. (14) also reported low-grade memory and cognitive functioning impairments. Therefore, the indications of PCI should be considered in the light of its potential (neuro)toxicity. QoL data were limited and not significantly different between the groups, no short-term OS benefit was shown, and the influence of PCI on long-term OS should be further investigated. It is necessary to further study the role of PCI in relation to neurocognitive decline and thus deterioration of QoL, and whether PCI could improve patients' long-term OS. In the era of more effective targeted therapy and immunotherapy, when extracranial disease is better controlled and patients are living longer, there may be increased importance of PCI. Moreover, hippocampal sparing techniques and medications such as memantine could be interesting future areas of research as alternatives to reduce toxicity and thus loss of QoL. Other areas of future research might include the role of MRI surveillance in combination with radical local treatment such as stereotactic radiosurgery or whole-brain radiotherapy. However, studies of the EORTC and RTOG showed that cure remains elusive in the overwhelming majority of these patients (20, 21).

CONCLUSION

The risk of developing BM was reduced in patients who received PCI compared to observation. To implement PCI as the standard treatment for patients with NSCLC, the impact of PCI on toxicity and QoL should be further investigated, as well as the impact on long-term OS. A future individual patient data meta-analysis with updated long-term OS could potentially produce definitive answers to these clinical questions.

AUTHOR CONTRIBUTIONS

WW wrote the initial draft of this review, with edits and revisions from all other authors, and especially BR and DR.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at https://www.frontiersin.org/articles/10.3389/fonc.2018.00241/full#supplementary-material.

REFERENCES

1. Vansteenkiste J, De Ruysscher D, Eberhardt WEE, Lim E, Senan S, Felip E, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2013) 24(Suppl 6):vi89–98. doi:10.1093/annonc/mdt241
2. Peters S, Bexelius C, Munk V, Leighl N. The impact of brain metastasis on quality of life, resource utilization and survival in patients with non-small-cell lung cancer. *Cancer Treat Rev* (2016) 45:139–62. doi:10.1016/j.ctrv.2016.03.009
3. Rangachari D, Yamaguchi N, VanderLaan PA, Folch E, Mahadevan A, Floyd SR, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer* (2015) 88:108–11. doi:10.1016/j.lungcan.2015.01.020
4. Sun D-S, Hu L-K, Cai Y, Li X-M, Ye L, Hou H-Y, et al. A systematic review of risk factors for brain metastases and value of prophylactic cranial irradiation in non-small cell lung cancer. *Asian Pac J Cancer Prev* (2014) 15:1233–9. doi:10.7314/APJCP.2014.15.3.1233
5. Auperin A, Arriagada R, Pignon JP, Le Pechoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* (1999) 341:476–84. doi:10.1056/NEJM199908123410703
6. Cox JD, Stanley K, Petrovich Z, Paig C, Yesner R. Cranial irradiation in cancer of the lung of all cell types. *JAMA* (1981) 245:469–72. doi:10.1001/jama.1981.03310300023013
7. Umsawasdi T, Valdivieso M, Chen TT, Barkley HTJ, Booser DJ, Chiuten DF, et al. Role of elective brain irradiation during combined chemoradiotherapy for limited disease non-small cell lung cancer. *J Neurooncol* (1984) 2:253–9. doi:10.1007/BF00253278
8. Russell AH, Pajak TE, Selim HM, Paradelo JC, Murray K, Bansal P, et al. Prophylactic cranial irradiation for lung cancer patients at high risk for development of cerebral metastasis: results of a prospective randomized trial conducted by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* (1991) 21:637–43. doi:10.1016/0360-3016(91)90681-S
9. Mira JG, Miller TP, Crowley JJ. Chest irradiation vs. chest irradiation plus chemotherapy with or without prophylactic brain radiotherapy in localized nonsmall lung cancer: a Southwest Oncology Group Study. *Int J Radiat Oncol Biol Phys* (1990) 19:145. doi:10.1016/0360-3016(90)90693-E
10. Miller TP, Crowley JJ, Mira J, Schwartz JG, Hutchins L, Baker L. A randomized trial of chemotherapy and radiotherapy for stage III non-small cell lung cancer. *Cancer Ther* (1998) 1:229–36.
11. Gore EM, Bae K, Wong SJ, Sun A, Bonner JA, Schild SE, et al. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of Radiation Therapy Oncology Group study RTOG 0214. *J Clin Oncol* (2011) 29:272–8. doi:10.1200/JCO.2010.29.1609
12. Pottgen C, Eberhardt W, Grannass A, Korfee S, Stuben G, Teschler H, et al. Prophylactic cranial irradiation in operable stage IIIA non small-cell lung cancer treated with neoadjuvant chemoradiotherapy: results from a German multicenter randomized trial. *J Clin Oncol* (2007) 25:4987–92. doi:10.1200/JCO.2007.12.5468
13. Li N, Zeng Z-F, Wang S-Y, Ou W, Ye X, Li J, et al. Randomized phase III trial of prophylactic cranial irradiation versus observation in patients with fully resected stage IIIA-N2 nonsmall-cell lung cancer and high risk of cerebral metastases after adjuvant chemotherapy. *Ann Oncol* (2015) 26:504–9. doi:10.1093/annonc/mdu567
14. De Ruysscher D, Dingemans A-MC, Praag J, Belderbos J, Tissing-Tan C, Herder J, et al. Prophylactic cranial irradiation versus observation in radically treated stage III non-small-cell lung cancer: a randomized phase III NVALT-11/DLCRG-02 study. *J Clin Oncol* (2018) JCO2017775817. doi:10.1200/JCO.2017.77.5817
15. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration; (2011) [updated March 2011]. Available from: www.handbook.cochrane.org (Accessed: January 30, 2018).
16. StataCorp. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP (2015).
17. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* (2001) 54:1046–55. doi:10.1016/S0895-4356(01)00377-8
18. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* (1997) 315:629–34. doi:10.1136/bmj.315.7109.629
19. Xie S, Li M, Zhou C, Song X, Wang C. Prophylactic cranial irradiation may impose a detrimental effect on overall survival of patients with nonsmall cell lung cancer: a systematic review and meta-analysis. *PLoS One* (2014) 9:e103431. doi:10.1371/journal.pone.0103431
20. Kocher M, Soffietti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* (2011) 29:134–41. doi:10.1200/JCO.2010.30.1655
21. Sperduto PW, Wang M, Robins HI, Schell MC, Werner-Wasik M, Komaki R, et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. *Int J Radiat Oncol Biol Phys* (2013) 85:1312–8. doi:10.1016/j.ijrobp.2012.11.042

Conflict of Interest Statement: LH: Consulting or Advisory Role: Boehringer Ingelheim and BMS. Fees for lectures: MSD, Astra Zeneca, Roche. Research grant: Roche. A-MD: Consulting or Advisory Role: Genentech (Inst), MSD Oncology (Inst), AstraZeneca (Inst), Pfizer, Eli Lilly (Inst), Boehringer Ingelheim (Inst), Bristol-Myers Squibb, Clovis Oncology (Inst). DR: Consulting or Advisory Role: Bristol-Myers Squibb (Inst), Genentech (Inst), Merck Serono (Inst), AstraZeneca (Inst), Celgene (Inst). Research Funding: Bristol-Myers Squibb (Inst).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

CASE REPORT
published: 05 June 2018
doi: 10.3389/fonc.2018.00188

Invasive Aspergillosis Mimicking Metastatic Lung Cancer

Michiel J. E. G. W. Vanfleteren[1,2,3], Anne-Marie C. Dingemans[2], Veerle F. Surmont[1], Karim Y. Vermaelen[1], Alida A. Postma[4], Astrid M. L. Oude Lashof[5], Cordula C. M. Pitz[6] and Lizza E. L. Hendriks[2]*

[1] Department of Respiratory Medicine, University Hospital Ghent, Ghent, Belgium, [2] Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, Netherlands, [3] Department of Respiratory Medicine, Sint-Jozefskliniek Izegem, Izegem, Belgium, [4] Department of Radiology and Nuclear Medicine, Maastricht University Medical Centre (MUMC +), Maastricht, Netherlands, [5] Department of Medical Microbiology, Section Infectious Diseases, Maastricht University Medical Centre (MUMC +), Maastricht, Netherlands, [6] Department of Respiratory Medicine, Laurentius Hospital Roermond, Roermond, Netherlands

In a patient with a medical history of cancer, the most probable diagnosis of an ^{18}FDG-avid pulmonary mass combined with intracranial abnormalities on brain imaging is metastasized cancer. However, sometimes a differential diagnosis with an infectious cause such as aspergillosis can be very challenging as both cancer and infection are sometimes difficult to distinguish. Pulmonary aspergillosis can present as an infectious pseudotumour with clinical and imaging characteristics mimicking lung cancer. Even in the presence of cerebral lesions, radiological appearance of abscesses can look like brain metastasis. These similarities can cause significant diagnostic difficulties with a subsequent therapeutic delay and a potential adverse outcome. Awareness of this infectious disease that can mimic lung cancer, even in an immunocompetent patient, is important. We report a case of a 65-year-old woman with pulmonary aspergillosis disseminated to the brain mimicking metastatic lung cancer.

Keywords: lung cancer, lung neoplasms, brain metastasis, brain neoplasms, brain abscess, aspergillosis, differential diagnosis

OPEN ACCESS

Edited by:
Marco Lucchi,
Università degli Studi di Pisa, Italy

Reviewed by:
Christopher William Seder,
Rush University Medical Center, United States
Janaki Deepak,
University of Maryland, Baltimore, United States

****Correspondence:***
Michiel J. E. G. W. Vanfleteren
michielvanfleteren@msn.com

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *18 February 2018*
Accepted: *11 May 2018*
Published: *05 June 2018*

Citation:
Vanfleteren MJEGW, Dingemans A-MC, Surmont VF, Vermaelen KY, Postma AA, Oude Lashof AML, Pitz CCM and Hendriks LEL (2018) Invasive Aspergillosis Mimicking Metastatic Lung Cancer. Front. Oncol. 8:188. doi: 10.3389/fonc.2018.00188

CASE DESCRIPTION

A 65-year-old woman, never-smoker, was referred for a second opinion in January 2014 because of an abnormal computed tomography (CT) of the chest with a mass in the right lower lobe. Extensive evaluation in the referring hospital had not revealed a diagnosis. A clear overview of the medical disease history is demonstrated in a timeline (**Figure 1**). Her medical history consisted of a right-sided mastectomy for breast cancer in 2006, with no adjuvant treatment indicated. On the staging 18-fluordeoxyglucose positron emission tomography-computed tomography (^{18}FDG-PET-CT) for the breast cancer in 2006 an asymptomatic, 30-mm diameter, lobulated ^{18}FDG-negative solitary mass was seen in the right lower lobe. Bronchoscopic sampling for cytology and microbiological cultures showed neither proof of malignancy nor infection, and follow-up was chosen. Serial follow-up chest CTs up to December 2011 (total follow-up of 5 years) showed no change and follow-up was ended.

In August 2013, she was seen in the referring hospital because of a productive cough, dyspnea on exertion, tiredness, and weight loss since the last 3 months. There was no fever nor night sweats. ^{18}FDG-PET-CT revealed an intense ^{18}FDG-avid mass in the right lower lobe, just next to the old pulmonary lesion, with intense hilar lymphadenopathy (**Figure 2**). Differential diagnosis consisted of malignancy (metastatic breast cancer or primary lung cancer) or infection. Bronchoscopic

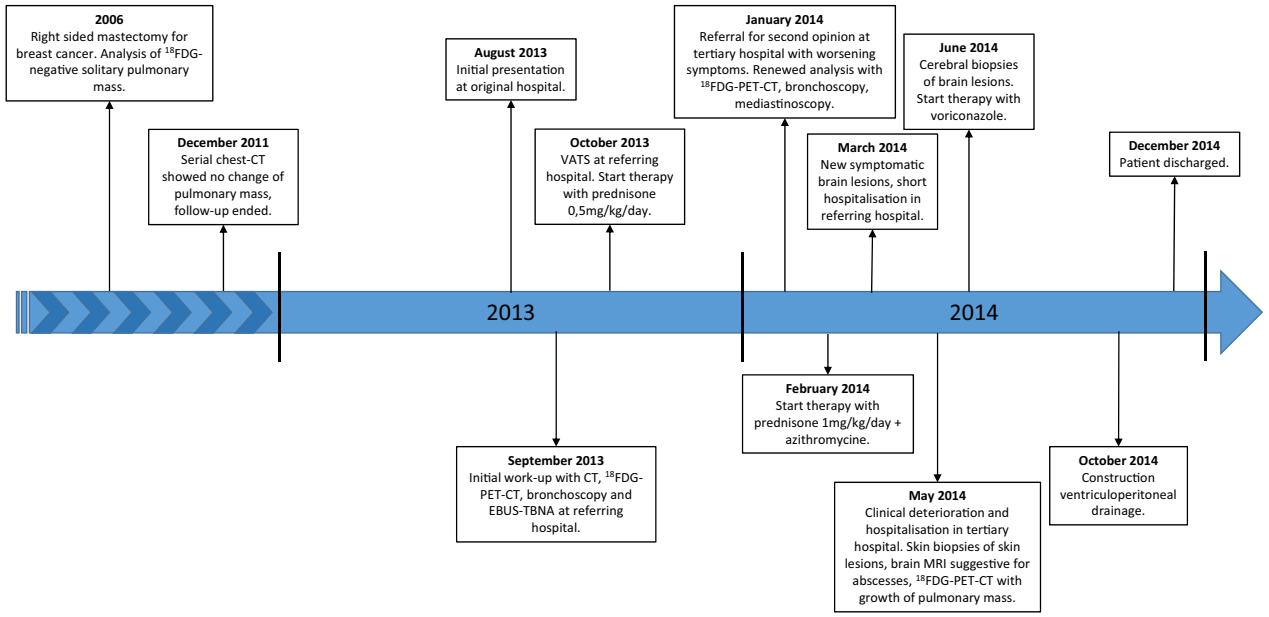


FIGURE 1 | Timeline. Abbreviations: ^{18}FDG, 18-fluordeoxyglucose; CT, computed tomography; VATS, video assisted thoracic surgery; ^{18}FDG-PET-CT, 18-fluordeoxyglucose positron emission tomography-computed tomography; EBUS-TBNA, endobronchial ultrasound with transbronchial needle aspiration; MRI, magnetic resonance imaging.

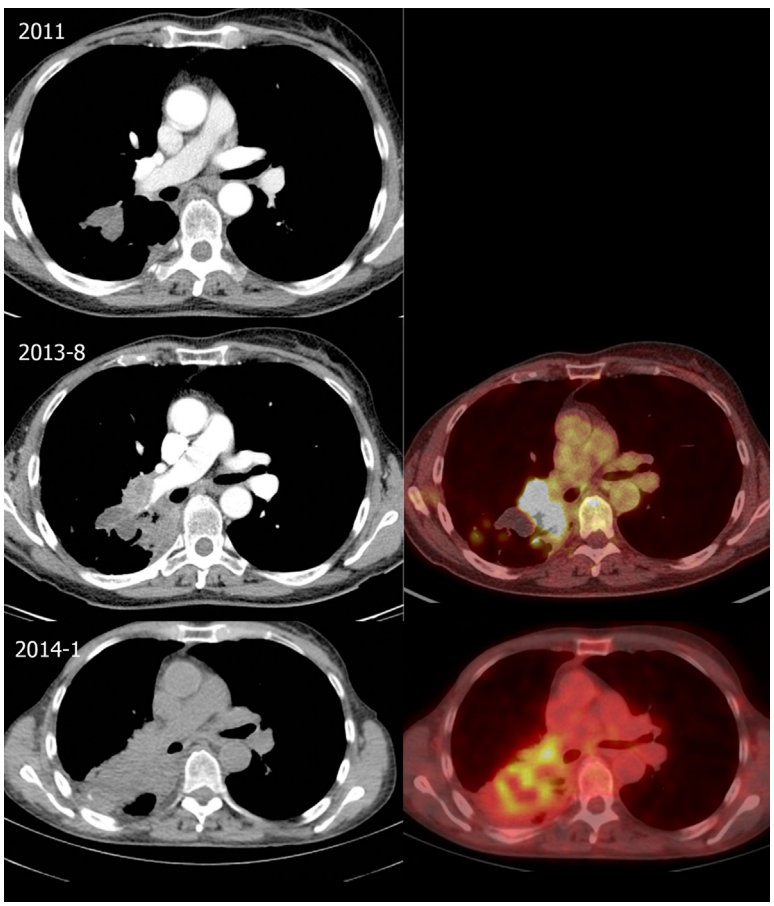


FIGURE 2 | Continued

FIGURE 2 | Evolution of thoracic lesions. Top: Follow-up chest computed tomography (CT) in 2011 showing a right-sided lobulated pulmonary mass at the right lower lobe (3.0-cm diameter). Middle: CT (left) and fusion 18-fluordeoxyglucose positron emission tomography-computed tomography (^{18}FDG-PET-CT) (right) in August 2013 shows an increase at the medial side of the mass and right hilar lymphadenopathy, with intense 18-fluordeoxyglucose (^{18}FDG) uptake. Bottom: CT (left) and fusion ^{18}FDG-PET-CT (right) in January 2014 showing further growth of the ^{18}FDG-avid mass in the right lower lobe with hilar invasion and a mild ^{18}FDG-avid subcarinal lymph node.

TABLE 1 | Diagnostic test results.

Date	Specimen	Microbiological test results	Pathological test results
2006	Bronchial washing right lower lobe	Culture negative for bacteria and fungi Auramine-rhodamine stain negative	No arguments for malignancy
August 15, 2013	Bronchial (brushing and) washing right lower lobe	Culture negative for bacteria and fungi Auramine-rhodamine stain negative	Active inflammation No arguments for malignancy
September 03, 2013	Computed tomography-guided biopsy right lower lobe	NA	Fibrosis with anthracosis and chronic inflammation No arguments for malignancy
September 23, 2013	EBUS 10R	NA	Representative specimen of reactive lymph node without arguments for malignancy
October 29, 2013	Wedge resection apical segment right lower lobe	Culture negative for bacteria	Fibrotic node with extensive chronic inflammation and bronchialization of the alveoli No arguments for malignancy No arguments for actinomyces infection
October 29, 2013	Urine	Culture negative for bacteria and fungi	NA
November 04, 2013	Blood	Culture negative for bacteria and fungi	NA
November 07, 2013	Urine	Culture negative for bacteria and fungi	NA
November 07, 2013	Wound fluid chest drain entrance	Sporadic *S. aureus*	NA
January 20, 2014	Bronchial washing right lower lobe	Bacterial culture with commensal throat flora Culture negative for fungi Culture negative for actinomyces Culture negative for nocardia Auramine-rhodamine stain negative Culture negative for mycobacteria	Active inflammation, sparse fungal hyphae and bacteria No arguments for malignancy
January 30, 2014	Mediastinoscopy 4L and 7	NA	Lymph node tissue without evidence of malignancy Extensive sinushistiocytosis at lymph node station 7
March 31, 2014	Cerebrospinal tap	NA	No arguments for malignancy or infection
May 02, 2014	Skin biopsy	Bacterial culture with coagulase-negative staphylococci Fungal culture with *Verticillium* species and *Aspergillus fumigatus*	Extensive active inflammation with a lobular panniculitis and localization of fungal hyphae No arguments for malignancy
May 02, 2014	Wound fluid skin biopsy	Fungal culture with *A. fumigatus*	NA
May 13, 2014	Serum	Galactomannan negative HIV 1 and HIV 2 antigen and immunoglobulin negative *Toxoplasma gondii* IgG positive, IgM negative *Treponema pallidum* immunoglobulin negative	NA
May 13, 2014	Blood (x2)	Culture negative for bacteria and fungi	NA
May 13, 2014	Urine	Culture negative for bacteria and fungi	NA
May 19, 2014	Serum	*Cryptococcus neoformans* antigen negative	NA
May 26, 2014	Serum	Interferon-gamma release assay negative	NA
June 02, 2014	Cerebral biopsy	*Aspergillus fumigatus*	Cerebral material with lytic cell remnants, active inflammation and presence of fungi (preference for *Aspergillus*)

NA, not available.

sampling, CT-guided biopsy, and endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) revealed no malignancy and cultures were negative (**Table 1**). Transthoracic biopsy of the mass showed fibrosis and a chronic inflammation with histiocytic reaction. A video-assisted thoracoscopy with partial wedge resection of the pulmonary nodule was performed to obtain a definitive diagnosis and to rule out or confirm malignancy. Pathologic analysis of the resection specimen showed fibrosis with bronchiectasis, focal inflammation, and bronchiolisation of the alveoli, but no malignancy or microorganisms (**Table 1**). With a diagnosis suggestive of cryptogenic organizing pneumonia, prednisone 0.5 mg/kg/day was initiated,

although, due to steroid side-effects, limited in dose and duration (prednisone 0.5 mg/kg/day for 3 weeks followed by gradual tapering of the dose, total duration of prednisone treatment was 2 months). Despite the steroids, her complaints worsened and the patient was referred to our tertiary center in January 2014. A new ^{18}FDG-PET-CT showed progression of the ^{18}FDG-avid lesion with extension into the mediastinum and lymph node station 4R, with also mass effect on the right pulmonary artery and invasion of the left superior pulmonary vein (**Figure 2**). There was no evidence of extrathoracic lesions. Because of the invasive growth, malignancy was again in the differential diagnosis. In our hospital, renewed analysis was performed with bronchoscopy and mediastinoscopy, both without evidence of malignancy or infection (**Table 1**). Cytology of the bronchial aspirate showed sporadic hyphae (most probable *Aspergillus*), but without growth on culture and these were considered contamination or colonization. In March 2014, a multidisciplinary decision was made for a treatment with a higher dose of prednisone 1 mg/kg/day in combination with macrolide antibiotic treatment for 3 months (with slow tapering of the steroids) under suspicion of cryptogenic organizing pneumonia, but without clinical or radiologic response. Additional diagnostics were considered for the growing part of the lesion, but a CT-guided biopsy and surgical sampling were both not possible because of the risk of a massive bleeding. A follow-up ^{18}FDG-PET-CT was scheduled to evaluate whether in the follow-up lesions would become better accessible for further diagnostic work-up. During the pulmonary work-up, in March 2014, the patient developed new complaints of progressive muscle weakness and sensibility loss of the right upper arm. She was hospitalized in the referring hospital. Additional brain imaging with magnetic resonance imaging (MRI) revealed multiple brain lesions in the cortex and watershed region, in the left corpus callosum, the left thalamus and partially in the right semioval center, which were considered brain metastases by the referring hospital (**Figure 3**). The MRI was revised by an experienced neuro-radiologist in our hospital who withheld a differential diagnosis of ischemia and metastasis. The brain lesions were not accessible for a biopsy because of the location and small size. Because of a poor clinical condition combined with a differential diagnosis of ischemia, no brain radiation was initiated. Patient was discharged after 1½-week hospitalization in the referring hospital. The neuro-oncology multidisciplinary team advised follow-up MRI 3 months later. On this MRI (May 2014), two lesions had enlarged significantly with marked perilesional edema but other lesions showed shrinkage (**Figure 4**). The radiologic appearance with restrictive diffusion of these lesions on diffusion-weighted images was suggestive for (atypical) cerebral abscesses rather than metastases. The ^{18}FDG-PET-CT showed further growth of the mass in the right lower lobe but without distant lesions. At the same time, the patient developed multiple ill-defined skin lesions. Because of her worse clinical condition, she was hospitalized in our tertiary hospital and cerebral and skin biopsies were performed: both showed marked inflammation and fungal hyphae with dichotomous branching, suggestive for *Aspergillus*, there was no evidence for malignancy (**Table 1**; **Figures 5** and **6**). Cultures of the wound fluid after skin biopsy also revealed *Aspergillus* (**Table 1**). The definitive diagnosis of proven invasive aspergillosis with pulmonary, mediastinal, cerebral, and skin involvement was made. Treatment with voriconazole was initiated with monitoring of serum and cerebral spinal fluid (CSF) voriconazole levels. Because of progressive somnolence caused by hydrocephalus, repeated CSF drainage was necessary. Eventually, five neurosurgical procedures were needed for effective control of the infection and adequate drainage of the CSF, with in the end placement of an internal ventriculo-peritoneal drain. During treatment with voriconazole, there was a slow clinical recovery. Additional immunological analysis did not reveal an immunity disorder; there were normal titers of total IgG, IgM, IgG, and IgA, there were no complement abnormalities, screening for antinuclear antibodies and antineutrophil cytoplasmic antibodies was negative. Only the use of prednisone could be identified as immunosuppressant factor which aided the further dissemination of this opportunistic infection. MRI of the brain performed after 6 months of treatment showed marked improvement without evidence of hydrocephalus, the chest CT also improved. Patient was discharged in December 2014, 7 months after admission. She rehabilitated and made a near complete recovery.

DISCUSSION

We report our experience of the diagnostic dilemma in this patient with disseminated aspergillosis mimicking metastatic cancer. The

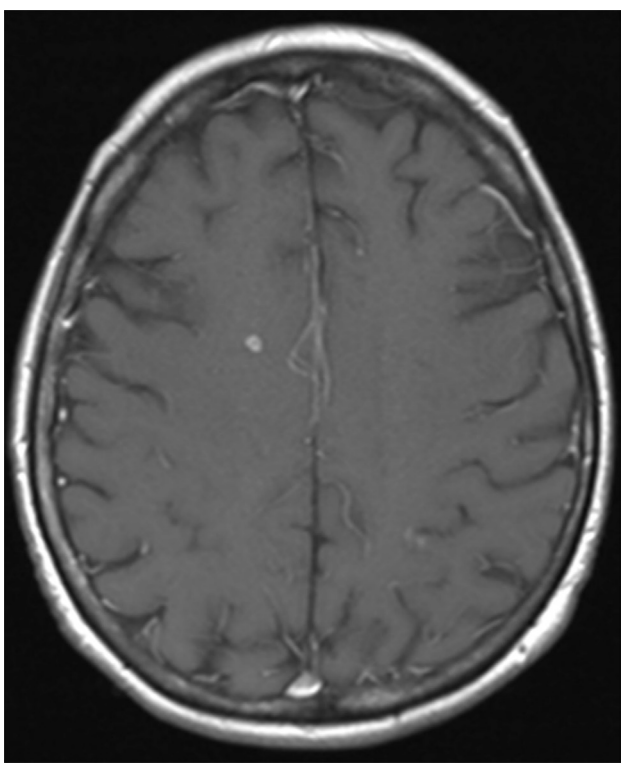


FIGURE 3 | Brain magnestic resonance imaging in March 2014. T1-weighted image after gadolinium of the brain shows a small right frontal enhancing cerebral lesion.

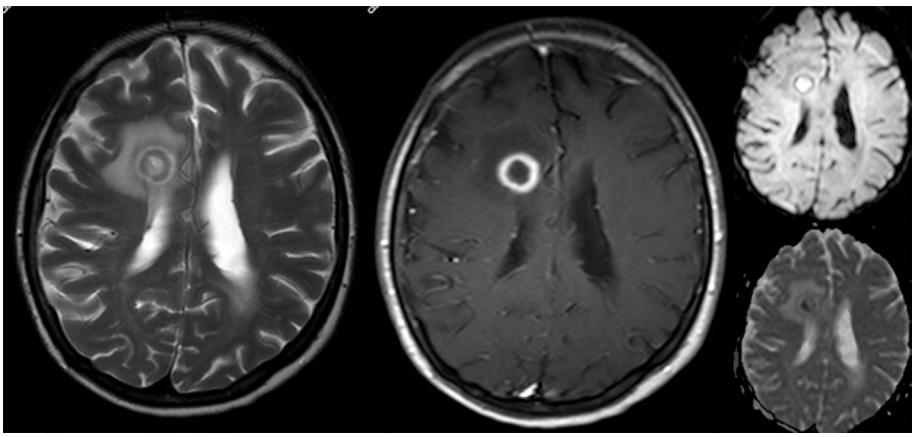


FIGURE 4 | Brain magnetic resonance imaging in May 2014. There is an increase in size of the right frontal lesion with surrounding perilesional edema. T2-weighted image (left) demonstrates a hypo-intense rim with ring-enhancement after gadolinium (contrast-enhanced T1-weighted middle). At diffusion imaging (right panels) there is restricted diffusion in a part of the central area.

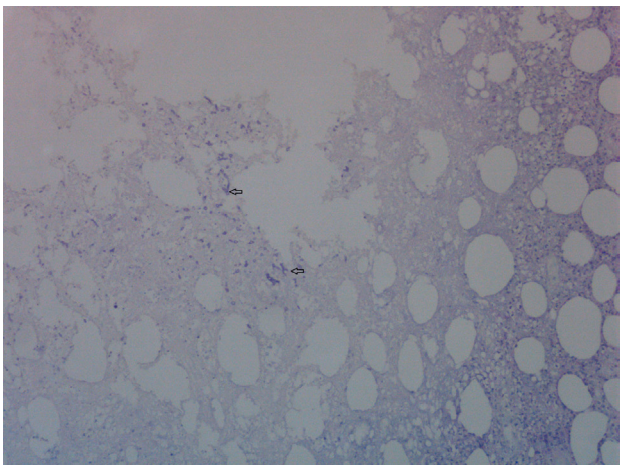


FIGURE 5 | Skin biopsy with presence of fungal hyphae. Periodic Acid Schiff stain on skin biopsy with fungal hyphae stained purple. Two fungal hyphae with dichotomous branching (diagnostic of *Aspergillus*) are depicted (arrows).

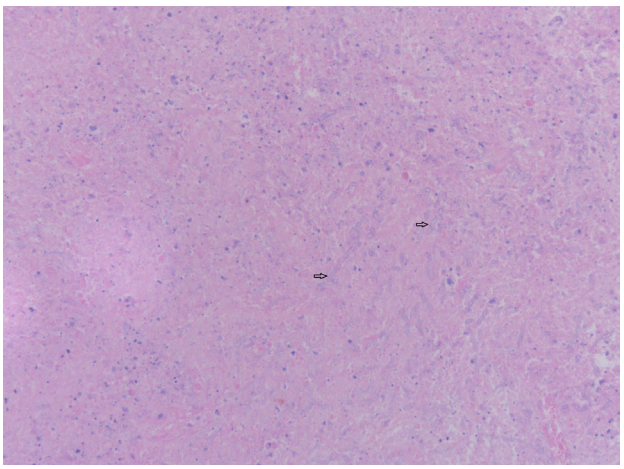


FIGURE 6 | Cerebral biopsy with presence of fungal hyphae. Hematoxylin and eosin stain on cerebral biopsy showing nectrotic tissue with moderate numbers of septate fungal hyphae with parallel walls. Two fungal hyphae with dichotomous branching (diagnostic of *Aspergillus*) are depicted (arrows).

^{18}FDG-avid pulmonary lesions were highly suspicious for malignancy, especially in a patient with a history of breast cancer. Even in the presence of brain lesions, this suspicion remained high, as these brain lesions were first thought to be of metastatic origin. Eventually skin and cerebral biopsies and wound cultures did reveal the definitive diagnosis of disseminated invasive aspergillosis.

As a tertiary center, patients are frequently referred to our center with presumed lung cancer. In a retrospective analysis of a tertiary US hospital, the majority of such patients were proven to have a neoplastic process, only 1.3% had an infection (1). Pulmonary aspergillosis mimicking lung malignancy remains rare and only sporadic case reports are available in literature (1–7). In addition, symptoms (such as malaise, weight loss, cough, and hemoptysis) are non-specific and are overlapping those of a pulmonary neoplasm. Moreover, pulmonary aspergillosis can present as an infectious pseudotumour with radiological appearance and features similar and indistinguishable from lung cancer. When clinical and radiological features are suspected for malignancy, it is of utmost importance to strive for a definitive histopathological diagnosis. Many minimal invasive techniques such as bronchoscopy, CT-guided biopsy or EBUS-TBNA are available today to obtain this histopathological diagnosis. If not amenable or feasible or histopathological diagnosis cannot be obtained, a surgical approach might be necessary. The differential diagnosis can be very challenging and perseverance for diagnostic accuracy can be a hard and exhaustive exercise, which is demonstrated in our case. Despite several attempts with noninvasive and invasive procedures to obtain a histopathological diagnosis, there was no clear evidence for malignancy or infection. Maybe in retrospect, the hyphae in the bronchial aspirate could have raised the suspicion for invasive aspergillosis, although this is very rare

in an immunocompetent host such as our patient. In retrospective studies with immunocompromised patients with a diagnosis of invasive aspergillosis, cytological examination of bronchial washings had a sensitivity of 64.0%, specificity of 99.1%, and positive predictive value of 88.9% (8), However, predictive values depend upon the prevalence of disease in the population tested and our patient did not have an impaired immunity. Moreover, various species of *Aspergillus* spp. can colonize the airways, especially in patients with a chronic pulmonary disease, without any pathogenic consequences (as was thought to be the case in our patient), but they are also capable of causing several and severe types of disease as has been described in patients with bronchiectasis (9). Pathological features in the surgical specimen suggestive for cryptogenic organizing pneumonia made this case more complex. Furthermore, the suspicion of malignancy remained high, with further growth of her thoracic disease and development of brain lesions, suspicious for brain metastasis. Indeed, cerebral abscesses caused by *Aspergillus* spp. can also mimic cerebral metastasis. Contrast-enhanced CT and MRI are the modalities of choice for imaging of the brain when brain metastasis is suspected, with MRI more appropriate in characterizing lesions (10–13). Although many MR features have been described, the differentiation between abscesses and necrotic brain tumors cannot be made in many cases with conventional MR imaging since its signal appearance can be similar to that of a cystic or necrotic tumor on conventional series (14, 15). A combination with diffusion-weighted MRI has been shown to be useful in the diagnosis of acute cerebral ischemia, malignancy, abscesses, cysts, and various forms of white matter disorders (16). In our case, the dissociated response, the hypo-intense rim at T2-weighted imaging and the diffusion-weighted MRI aided toward an infectious diagnosis. Previous reports in literature of a cerebral *Aspergillus* abscess mimicking a solid tumor are sparse; we could only identify two case resports (15, 17).

Coexistence of infectious pseudotumours and solid tumors at initial diagnosis have previously been reported (18), but are rather rare, especially in an immunocompetent patient. However, an endobronchial aspergilloma is thought to be able to infect endobronchial cancer lesions (19, 20). In general, most cases of coexisting infectious pseudotumours and lung cancer are rather a consequence of treatments with corticosteroids and/or chemotherapy.

CONCLUSION

Pulmonary aspergillosis, even in the presence of cerebral abscesses, can present as an infectious pseudotumour with clinical and imaging characteristics resembling lung malignancy. These clinical and radiological similarities can cause significant diagnostic difficulties, with a subsequent therapeutic delay and a potential adverse outcome. A definitive histopathological diagnosis should always be strived for when malignancy is suspected, but awareness that this infectious disease can mimic lung cancer even in immunocompetent patients is of great diagnostic and prognostic importance.

ETHICS STATEMENT

Patient gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

Conception and design and drafting of the manuscript: MV, AD, and LH. Drafting the manuscript for important intellectual content: all authors. All co-authors critically revised the article and gave final approval of this version to be published.

ACKNOWLEDGMENTS

The authors wish to thank C. J. Kootstra, department of Pathology, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands, for the selection and preparation of artwork.

REFERENCES

1. Rolston KV, Rodriguez S, Dholakia N, Whimbey E, Raad I. Pulmonary infections mimicking cancer: a retrospective, three-year review. *Support Care Cancer* (1997) 5(2):90–3. doi:10.1007/BF01262563
2. Baxter CG, Bishop P, Low SE, Baiden-Amissah K, Denning DW. Pulmonary aspergillosis: an alternative diagnosis to lung cancer after positive [18F]FDG positron emission tomography. *Thorax* (2011) 66(7):638–40. doi:10.1136/thx.2010.155515
3. Sanchez-Alarcos JM, Martínez-Cruz R, Ortega L, Calle M, Rodríguez-Hermosa JL, Alvarez-Sala JL. ABPA mimicking bronchogenic cancer. *Allergy* (2001) 56(1):80–1. doi:10.1034/j.1398-9995.2001.00840.x
4. Schweigert M, Dubecz A, Beron M, Ofner D, Stein HJ. Pulmonary infections imitating lung cancer: clinical presentation and therapeutical approach. *Ir J Med Sci* (2013) 182(1):73–80. doi:10.1007/s11845-012-0831-8
5. Stern JB, Wyplosz B, Validire P, Angoulvant A, Fregeville A, Caliandro R, et al. Bulky mediastinal aspergillosis mimicking cancer in an immunocompetent patient. *Ann Thorac Surg* (2014) 98(4):1472–5. doi:10.1016/j.athoracsur.2013.11.055
6. Takeuchi Y, Shirai T, Sakurai S, Mikamo M, Fujii M, Suda T. Allergic bronchopulmonary aspergillosis presenting with a pulmonary mass mimicking lung cancer. *Respirol Case Rep* (2013) 1(1):5–7. doi:10.1002/rcr2.4
7. Yasuda M, Nagashima A, Haro A, Saitoh G. Aspergilloma mimicking a lung cancer. *Int J Surg Case Rep* (2013) 4(8):690–2. doi:10.1016/j.ijscr.2013.02.028
8. Levy H, Horak DA, Tegtmeier BR, Yokota SB, Forman SJ. The value of bronchoalveolar lavage and bronchial washings in the diagnosis of invasive pulmonary aspergillosis. *Respir Med* (1992) 86(3):243–8. doi:10.1016/S0954-6111(06)80062-4
9. Maiz L, Nieto R, Cantón R, Gómez de la Pedrosa GE, Martinez-García MÁ. Fungi in bronchiectasis: a concise review. *Int J Mol Sci* (2018) 19(1):E142. doi:10.3390/ijms19010142
10. Yokoi K, Kamiya N, Matsuguma H, Machida S, Hirose T, Mori K, et al. Detection of brain metastasis in potentially operable non-small cell lung cancer: a comparison of CT and MRI. *Chest* (1999) 115(3):714–9. doi:10.1378/chest.115.3.714
11. Suzuki K, Yamamoto M, Hasegawa Y, Ando M, Shima K, Sako C, et al. Magnetic resonance imaging and computed tomography in the diagnoses of brain metastases of lung cancer. *Lung Cancer* (2004) 46(3):357–60. doi:10.1016/j.lungcan.2004.05.011
12. Seute T, Leffers P, ten Velde GP, Twijnstra A. Detection of brain metastases from small cell lung cancer: consequences of changing imaging techniques (CT versus MRI). *Cancer* (2008) 112(8):1827–34. doi:10.1002/cncr.23361

13. Hendriks LE, Bootsma GP, de Ruysscher DK, Scheppers NA, Hofman PA, Brans BT, et al. Screening for brain metastases in patients with stage III non-small cell lung cancer: Is there additive value of magnetic resonance imaging above a contrast-enhanced computed tomography of the brain? *Lung Cancer* (2013) 80(3):293–7. doi:10.1016/j.lungcan.2013.02.006
14. Yikilmaz A, Durak AC, Mavili E, Donmez H, Kurtsoy A, Kontas O. The role of diffusion-weighted magnetic resonance imaging in intracranial cystic lesions. *Neuroradiol J* (2009) 21(6):781–90. doi:10.1177/197140090802100605
15. Patiroglu T, Unal E, Yikilmaz A, Koker MY, Ozturk MK. Atypical presentation of chronic granulomatous disease in an adolescent boy with frontal lobe located aspergillus abscess mimicking intracranial tumor. *Childs Nerv Syst* (2010) 26(2):149–54. doi:10.1007/s00381-009-1003-7
16. Baehring JM, Fulbright RK. Diffusion-weighted MRI in neuro-oncology. *CNS Oncol* (2012) 1(2):155–67. doi:10.2217/cns.12.28
17. Sidani C, Freiser ME, Saigal G, Sklar E. Unusual case of cerebral aspergillosis with clinical and imaging findings mimicking lymphoma. *Neuroradiol J* (2013) 26(3):290–6. doi:10.1177/197140091302600306
18. Nilsson JR, Restrepo CS, Jagirdar J. Two cases of endobronchial carcinoid masked by superimposed aspergillosis: a review of the literature of primary lung cancers associated with aspergillus. *Ann Diagn Pathol* (2013) 17(1):131–6. doi:10.1016/j.anndiagpath.2011.06.005
19. Hirano T, Yamada M, Igusa R, Tanno A, Numakura T, Sakamoto K, et al. Two cases of endobronchial aspergilloma complicated with primary and metastatic lung cancer: a case report and literature review. *Respir Investig* (2016) 54(3):211–5. doi:10.1016/j.resinv.2015.12.005
20. Zhou XM, Li P, Zhao L, Shi WJ. Lung carcinosarcoma masked by tracheo-bronchial aspergillosis. *Intern Med* (2015) 54(15):1905–7. doi:10.2169/internalmedicine.54.3945

Conflict of Interest Statement: MV has nothing to disclose. AD: none related to current manuscript. Outside of the submitted work: advisory boards: Roche, Pfizer, Eli Lilly Boehringer Ingelheim, MSD, Astra Zeneca, BMS; fees for lectures: BMS, Roche, Ely Lilly. VS: none related to current manuscript. KV: none related to current manuscript. AP: none related to current manuscript. Outside of the submitted work: fees for lectures: Bayer. AL: none related to current manuscript. CP has nothing to disclose. LH: none related to current manuscript. Outside of the submitted work: advisory boards: Boehringer Ingelheim and BMS; fees for lectures: MSD, Astra Zeneca, Roche, research grant: Roche.

frontiers in Oncology

REVIEW
published: 09 May 2018
doi: 10.3389/fonc.2018.00154

Stereotactic Radiosurgery in the Management of Patients With Brain Metastases of Non-Small Cell Lung Cancer: Indications, Decision Tools and Future Directions

*Dianne Hartgerink[1], Britt van der Heijden[1], Dirk De Ruysscher[1,2], Alida Postma[3], Linda Ackermans[4], Ann Hoeben[5], Monique Anten[6], Philippe Lambin[1], Karin Terhaag[1], Arthur Jochems[1], Andre Dekker[1,2], Janna Schoenmaekers[7], Lizza Hendriks[7] and Jaap Zindler[1,2]**

[1] Department of Radiation Oncology (MAASTRO Clinic), GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, Netherlands, [2] Proton Therapy Department South-East Netherlands (ZON-PTC), Maastricht, Netherlands, [3] Department of Radiology, Maastricht University Medical Centre, Maastricht, Netherlands, [4] Department of Neurosurgery, Maastricht University Medical Centre, Maastricht, Netherlands, [5] Department of Medical Oncology, Maastricht University Medical Centre, Maastricht, Netherlands, [6] Department of Neurology, Maastricht University Medical Centre, Maastricht, Netherlands, [7] Department of Pulmonary Diseases, Maastricht University Medical Centre, Maastricht, Netherlands

Brain metastases (BM) frequently occur in non-small cell lung cancer (NSCLC) patients. Most patients with BM have a limited life expectancy, measured in months. Selected patients may experience a very long progression-free survival, for example, patients with a targetable driver mutation. Traditionally, whole-brain radiotherapy (WBRT) has been the cornerstone of the treatment, but its indication is a matter of debate. A randomized trial has shown that for patients with a poor prognosis, WBRT does not add quality of life (QoL) nor survival over the best supportive care. In recent decades, stereotactic radiosurgery (SRS) has become an attractive non-invasive treatment for patients with BM. Only the BM is irradiated to an ablative dose, sparing healthy brain tissue. Intracranial recurrence rates decrease when WBRT is administered following SRS or resection but does not improve overall survival and comes at the expense of neurocognitive function and QoL. The downside of SRS compared with WBRT is a risk of radionecrosis (RN) and a higher risk of developing new BM during follow-up. Currently, SRS is an established treatment for patients with a maximum of four BM. Several promising strategies are currently being investigated to further improve the indication and outcome of SRS for patients with BM: the effectivity and safety of SRS in patients with more than four BM, combining SRS with systemic therapy such as targeted agents or immunotherapy, shared decision-making with SRS as a treatment option, and individualized isotoxic dose prescription to mitigate the risk of RN and further enhance local control probability of SRS. This review discusses the current indications of SRS and future directions of treatment for patients with BM of NSCLC with focus on the value of SRS.

Keywords: brain metastases, non-small cell lung cancer, stereotactic radiosurgery, isotoxic dose prescription, shared decision

OPEN ACCESS

Edited by:
Yanis Boumber, Fox Chase Cancer Center, United States

Reviewed by:
Gregory Gan, University of New Mexico, United States
Michael T. Milano, University of Rochester, United States
Stephanie Elizabeth Weiss, Fox Chase Cancer Center, United States
Rachel E. Sanborn, Providence Cancer Center, United States

****Correspondence:***
Jaap Zindler
jaap.zindler@maastro.nl

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *30 January 2018*
Accepted: *24 April 2018*
Published: *09 May 2018*

Citation:
Hartgerink D, van der Heijden B, De Ruysscher D, Postma A, Ackermans L, Hoeben A, Anten M, Lambin P, Terhaag K, Jochems A, Dekker A, Schoenmaekers J, Hendriks L and Zindler J (2018) Stereotactic Radiosurgery in the Management of Patients With Brain Metastases of Non-Small Cell Lung Cancer: Indications, Decision Tools and Future Directions. Front. Oncol. 8:154. doi: 10.3389/fonc.2018.00154

INTRODUCTION

Brain metastases (BM) are the most frequent intracranial malignancies and originate mainly from lung cancer (1). In patients with driver mutations of non-small cell lung cancer (NSCLC), systemic therapies have become more effective in patients with metastatic disease, resulting in longer overall survival (OS). Due to the screening for BM, the longer OS, and the often poor drug penetration through the blood–brain barrier (BBB), more and more patients are diagnosed with BM. BM may cause neurologic symptoms, a decrease in quality of life (QoL), and are often associated with poor OS (2).

Overall, patients with BM are treated with the intention to maintain QoL during their remaining lifespan. Traditionally, the treatment consists predominately of radiotherapy, mainly whole-brain radiotherapy (WBRT), but in selected patients, surgery, systemic therapy, or a combination of treatment modalities is used. Depending on the prognostic subgroups, the OS after WBRT in patients with BM of NSCLC without systemic treatment remains poor with an estimated survival of weeks or months (3–5). For instance, for patients treated with WBRT and optimal supportive care in the QUARTZ trial, the median survival was 8.5 weeks, and there was no OS benefit (4). Physicians are increasingly reluctant in the use of WBRT, as the results of the QUARTZ trial did not show a benefit of WBRT in NSCLC patients over steroids alone in patients with an intermediate or unfavorable prognosis [recursive partitioning analysis (RPA 2–3)] (4).

It is increasingly important to accurately estimate the prognosis after all treatment options, to support decision-making of both patients and physicians. OS of patients with BM of NSCLC ranges from several weeks to several years depending on relevant prognostic factors, such as performance status, age, control of extracranial disease, number of BM, and the presence of driver mutations. Gaspar et al. published a report in 1997 on a prognostic index for patients with BM, the RPA based on patients mainly treated with WBRT. The RPA was externally validated, and the favorable prognostic RPA score had a median survival of 7.1 months. The unfavorable RPA score had a survival of only 2.3 months (6, 7). The weakness of the RPA score is that the majority of the patients are classified into the intermediate prognostic class, and for clinical decision-making the favorable and unfavorable prognostic classes are the most important ones Also, the RPA score was developed in the pre-immunotherapy era, and cancers other than NSCLC were included into this score which limits its utility in patients with BM of NSCLC. Therefore, the Graded Prognostic Assessment (GPA) was developed from a database of almost 2,000 patients with BM, validated and refined with diagnosis-specific (DS) indices based on a second retrospective analysis of 4,259 patients with BM (8–10). For patients with BM of NSCLC and an unfavorable DS GPA score, the median survival time is 3 vs 15 months for patients with a favorable DS-GPA score (11). Recently, a refined Lung-molGPA score was developed and validated specifically for patients with BM of NSCLC. molGPA integrates molecular features such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) alterations (12, 13). The overall median survival for the cohort was 12 months, and those patients with a Lung-molGPA score of 3.5–4.0 had a median survival of almost 4 years. It is for these reasons that lung-moGPA is the most useful prognostic tool for clinical practice in the era of personalized medicine and targeted agents.

In the last decades, a local alternative treatment became widely available, stereotactic radiosurgery (SRS). SRS has the advantage of achieving higher local tumor control while sparing healthy brain tissue, which results in less severe side effects such as neurocognitive damage and hair loss (14). SRS is currently a well-established treatment modality for patients with a maximum of four BM. SRS is also a more complex and costly treatment which may not be available in every radiotherapy department. Other disadvantages of SRS compared with WBRT are a higher risk of new BM during follow-up (e.g., distant brain recurrences), and an increased risk of radionecrosis (RN) depending on the volume of healthy brain tissue which is irradiated to a relatively high dose, tumor biology factors, and the location of the tumor. RN is focal damage of the nearby brain tissue caused by a high dose of radiation. The result of RN can be temporary or permanent neurologic symptoms. These symptoms can be treated with steroids, but steroids have several side effects such as obesity, sleeping disorders, hyperglycemia, and muscle weakness (15–17). The risk of RN is mainly correlated with the SRS dose in the brain and the size of the lesion, for example, if the volume of brain tissue which receives $\geq$12 Gy is more than 10 cm^3, the risk of RN increases to above 10% and can go as high as 25%. However, other factors may contribute. The risk of distant brain recurrences is mainly correlated with the number of SRS treated BM and varies between 40 and 90% if SRS is applied as a single treatment modality (14, 18). From all patients treated with SRS as a single treatment modality for a maximum of three BM, 25% of patients will receive WBRT, because a significant proportion of patients die from extra cranial disease progression. It should be stated that almost all long-term survivors will undergo WBRT at some time point (14, 19, 20).

For small BM, SRS is equally effective as surgical resection (21). SRS is typically delivered in one to five fractions of multiple photon beams, but more recently even multiple, i.e., more than four, BM can be treated with a single fraction (22). For patients with more than four BM, the current Dutch guidelines advises WBRT as standard of care, but trials are ongoing and already conducted to investigate the value of SRS in patients with more than three BM (23–26).

The aim of this review is to discuss the current evidence of SRS for BM of NSCLC, potential improvements in patient information with focus on shared decision-making (SDM), and promising future treatment strategies to improve the clinical outcome.

CURRENT EVIDENCE FOR SRS AS A SINGLE TREATMENT MODALITY

As mentioned previously, the indication of WBRT is currently a matter of debate: according to the QUARTZ trial, there was no beneficial effect of WBRT over steroids, in NSCLC patients, most with an RPA class 2–3, with respect to QoL or survival (4). There are several remarks with respect to clinical application of the results: patients were only included if the patient or the

multidisciplinary team had doubts if WBRT should be applied, favorable prognostic patients (RPA class I) did have a survival benefit of WBRT, and the effect on symptom control such as seizures or headache were not described in detail. The latter is relevant, because the reason for applying WBRT is sometimes symptom control, prevention of neurologic symptom progression, or prevention of dying due to a neurologic cause. The availability of drugs used to target different areas for these patients is constantly increasing which may influence their outcome. Taking into account the limitations of the study which is conducted in a poor prognostic population, physicians should be more reluctant to apply WBRT (RPA class 3).

As an alternative to SRS, patients with small asymptomatic BM of NSCLC can be treated with systemic therapy (chemotherapy, targeted therapy, or immunotherapy in the second line). Targeted therapy can be considered if there is a driver mutation (27, 28). Cranial radiation can be considered if a low response rate is to be expected from systemic treatment or if neurological symptoms are to be expected in the event of disease progression.

Nowadays, the preference for either SRS or WBRT depends on the size and number of BM, but only if patients are in a good physical condition (Karnofsky performance status 70 or more). Patients with a maximum of four BM are usually treated with SRS, and patients with more than four BM are treated with WBRT. The size and location of the lesions are decisive factors: a very large BM with a diameter of 6 cm is inappropriate for treatment with SRS or a large brainstem metastasis, whereas five minor lesions located in the cerebral hemispheres are technically less challenging for treatment with SRS. In patients with a poor performance status (Karnofsky performance status of less than 70) are usually treated with supportive care. Patients treated with SRS despite a poor physical condition still have a very poor prognosis with a median survival of around 3 months (2).

The treatment of patients with asymptomatic BM from non-squamous NSCLC depends on molecular diagnostics, but primary systemic treatment with deferral of radiotherapy is a treatment option that could be considered (29, 30). For NSCLC, Lim et al. randomized 105 patients with 1–4 asymptomatic BM to receive SRS followed by chemotherapy or upfront chemotherapy alone (31). The trial closed early due to slow recruitment and was therefore underpowered. SRS followed by chemotherapy did not improve the OS compared with upfront chemotherapy (14.6 vs 15.3 months, $p = 0.418$). The time to central nervous system (CNS) progression was not significant different between the two arms [9.4 months (SRS) vs 6.6 months (upfront chemotherapy), $p = 0.248$].

Also for patients with asymptomatic BM SRS is an attractive first line of treatment. Approximately 25% of the patients with an EGFR-mutated NSCLC have BM at first presentation. For patients with an EGFR targetable mutated NSCLC, an alternative first line of treatment consists of an EGFR inhibitor like erlotinib, gefitinib, osimertinib, or afatinib with a response rate of approximately 60–70% (30, 32). Only a small percentage passes through the BBB and the penetration is different between the treatment options whereas osimertinib has a greater penetration. However, the response probability is equal to the extra-cerebral response probability (33, 34). Approximately 24% of ALK translocated NSCLC patients have BM at presentation (35). In case of an ALK translocation the treatment consists of alectinib, ceritinib, or crizotinib, with an expected response rate of approximately 50–60%, whereas alectinib has a superior CNS activity compared with crizotinib (36). If cerebral progression occurs during treatment with an EGFR or ALK inhibitor, SRS is considered, or a second line of systemic therapy. A recent study provides evidence for upfront SRS in patients with asymptomatic BM. Patients who are tyrosine kinase inhibitors (TKI) naïve and have an EGFR mutation had a better survival than patients who were treated with primary systemic therapy (37). This study was limited by its retrospective nature. Prospective randomized studies are needed to investigate if upfront SRS without TKI, directly followed by TKI or even concurrent, is beneficial over primary systemic treatment without SRS in TKI naïve patients.

SRS for a Maximum of Four BM

The definition of limited BM traditionally consisted of patients presenting with a single BM, often treated with surgery. This definition has evolved to encompass patients presenting with up to three metastasis for treatment with SRS (38–41). The management of patients presenting with a limited number of BM and a good performance status has developed from WBRT alone to a more aggressive approach consisting of WBRT in combination with SRS (41–43). The necessity of WBRT was evaluated *via* clinical trials, which compared SRS alone to SRS with adjuvant WBRT (44–48).

Aoyama et al. reported the first randomized control trial comparing SRS alone with SRS plus WBRT, randomizing 132 patients with 1–4 BM from histologically confirmed systemic cancer, mainly NSCLC (67%) (46). The primary endpoint was cranial recurrence. Although the 1-year local control rate was higher in the SRS plus WBRT group (88.7 vs 72.5%, $p = 0.002$), there was no OS difference between the two study arms (trial was underpowered for the secondary endpoint survival). There was also no advantage with respect to cognition based on Mini-Mental Status Exam (MMSE) for patients receiving SRS plus WBRT. It should be taken into account that the MMSE is a crude measurement for neurocognition compared with a standardized test such as the Hopkins Verbal Learning Test (HVLT) or other neurocognitive tests proposed by the European Organization for Research and Treatment of Cancer (EORTC), for example (49–51). A secondary analysis of the JROSG 99-1 randomized clinical trial investigated the feasibility of SRS alone for patients with different prognoses defined by the DS-GPA (24). Significantly better OS was observed in the DS-GPA favorable group (scores 2.5–4.0) in WBRT + SRS vs SRS alone. However, it is questionable if the side effects of adding WBRT to SRS, justify a potential limited survival benefit in favorable prognostic patients.

Chang et al. also randomized patients into SRS alone or SRS plus WBRT treatment arms, but they took a different approach by evaluating patients' neurocognition using the HVLT-revised (HVLT-R) as the primary endpoint (47). Patients presenting with 1–3 BM from different primary cancers, mainly NSCLC (55%), were randomized, 30 patients to SRS alone and 28 to SRS plus WBRT. The trial was prematurely stopped because at the interim analysis, patients in the SRS plus WBRT arm were more likely to

have a decline in neurocognitive function 4 months posttreatment. They found an unexpected survival advantage (secondary endpoint) in the SRS alone arm, with an OS of 15.2 vs 5.7 months in the in the SRS alone, and SRS plus WBRT arms, respectively. The reasons for higher survival rates in the SRS alone arm were unclear. It may be explained by a higher rate of salvage cranial treatment. Moreover, chemotherapy was administered to more patients with a longer duration in the SRS group compared with the SRS plus WBRT group (52). The authors concluded that the management for patients presenting with one to three BM with SRS alone is the optimal treatment.

The EORTC evaluated SRS alone vs SRS plus WBRT with the primary endpoint of functional outcomes, using the World Health Organization (WHO) performance status scale, in patients with one to three BM from mainly NSCLC (53%) (44). They concluded that WBRT did not improve the duration of functional independence (WHO $\leq$ 2, SRS alone 10.0 months vs SRS plus WBRT 9.5 months). SRS plus WBRT reduced the incidence of radiological endpoints, such as distant brain failure and 2-year local control failure rate (radiosurgery group: 31–19%, $p = 0.040$). Despite the secondary outcomes, the QoL was worse in several domains for patients who received WBRT (31, 44). A secondary analysis of the EORTC 22952-26001 trial investigated the impact of WBRT on patients with a favorable GPA prognostic score. The primary endpoint was OS (45). There was no significant survival benefit for NSCLC patients with a favorable GPA score of WBRT + SRS over SRS alone. There was also no survival benefit for patients with controlled extracranial disease. This secondary analysis supports the practice of treatment with SRS alone for patient with limited BM.

Recently, Brown et al. reported the results of the North Coast Cancer Treatment Group (NCCTG) phase III study in patients with one to three BM, mainly from lung cancer, treated with SRS alone or SRS plus WBRT (53). Regarding the primary endpoint of neurocognitive function, the trial is comparable with Chang et al., except that Brown et al. randomized 208 patients (47). Cognitive progression, defined as a decline of >1 SD from baseline on $\geq$1 of the cognitive tests 3 months post-SRS, was higher in the SRS plus WBRT arm compared with SRS alone (91.7 vs 63.5%, $p < 0.001$), and cognitive deterioration was more frequent in long-term survivors (living 12 months or more) receiving WBRT plus SRS compared with SRS alone (94.4 vs 60%). The 1-year intracranial disease control was 50.5% in the SRS alone arm and almost 85% in the SRS plus WBRT arm. The secondary survival analysis showed a median OS of 10.4 months for SRS alone vs 7.4 months for SRS plus WBRT. The authors concluded that SRS alone is preferred for patients presenting with one to three BM, supporting the results of Chang et al.

A secondary analysis of the NCCTG randomized control trial from Brown et al. was performed by Churilla et al. to determine whether WBRT is associated with improved OS among NSCLC patients with favorable prognoses (DS-GPA $\geq$ 2.0 or $\geq$2.5) at diagnosis (53, 54). They used two separate cut-points of DS-GPA, $\geq$2.0 vs <2.0 and $\geq$2.5 vs <2.5 in a study population consisting of 126 NSCLC patients with 1–3 BM. For patients with DS-GPA $\geq$ 2.0 treated with SRS alone, the median survival was 17.9 vs 11.3 months in the SRS plus WBRT arm ($p = 0.63$), and 6.6 vs 3.7 months for patients with DS-GPA < 2.0 ($p = 0.85$). They observed no significant differences in survival analysis in favorable-prognosis NSCLC patients treated with SRS, with or without WBRT, which further supports the approach of SRS alone. The above trials, summarized in **Table 1**, demonstrate that adjuvant WBRT results in reduced QoL and neurocognitive function without improvement of OS.

TABLE 1 | Summary of selected trials evaluating the role of SRS ± WBRT for patients with limited brain metastases.

Trial	Patient selection	Primary endpoint	Local control	OS	Functional outcome
Aoyama et al. (46) SRS *N* = 67 WBRT + SRS *N* = 65	1–4 metastases, KPS ≥ 70, lesion diameter <3 cm	Cranial recurrence	1 year: 72.5 vs 88.7% ($p = 0.002$)	1 year: 28.4 vs 38.5% ($p = 0.42$)	No difference in cognition based on MMSE
Aoyama et al. (24) SRS *N* = 45 WBRT + SRS *N* = 43	1–4 metastases, NSCLC patients	OS according DS-GPA score	–	DS-GPA favorable: 10.6 vs 16.7 months ($p = 0.04$) DS-GPA unfavorable: 6.5 vs 4.75 months	No difference in neurocognitive function based on MMSE
Chang et al. (47) SRS *N* = 30 WBRT + SRS *N* = 28	1–3 metastases, KPS ≥ 70	Neurocognition (using HVLT-R)	1 year: 67 vs 100% ($p = 0.012$)	15.2 vs 5.7 months	HVLT-R decline 52 vs 24%
Kocher et al. (44) SRS *N* = 100 WBRT + SRS *N* = 99	1–3 metastases, WHO ≤ 2	Functional independence (WHO ≥ 2)	2 year: 69 vs 81% ($p = 0.04$)	10.9 vs 10.7 months ($p = 0.89$)	No difference 10.0 vs 9.5 months
Brown et al. (51) SRS *N* = 111 WBRT + SRS *N* = 102	1–3 metastases, diameter < 3 cm, ECOG performance score ≤2	Cognitive deterioration	3 months: 75.3 vs 93.7% ($p< 0.001$)	10.4 vs 7.4 months ($p = 0.92$)	Higher deterioration in verbal fluency and delayed/immediate memory in SRS + WBRT arm
Churilla et al. (53) SRS WBRT + SRS	1–3 metastases, NSCLC patients	OS according DS-GPA score	–	10.8 vs 7.5 months	No difference in survival in favorable-prognosis NSCLC patient

KPS, Karnofsky performance status; WBRT, whole-brain radiotherapy; SRS, stereotactic radiosurgery; WHO, World Health Organization; HVLT-R, Hopkins Verbal Learning Test revised; OS, overall survival. NSCLC, non-small cell lung cancer. MMSE, Mini-Mental State Examination; DS-GPA; diagnosis-specific Graded Prognostic Assessment.

The current available evidence supports the use of SRS as a single treatment modality in patients with a maximum of three BM. This is supported by the American Society for Therapeutic Radiation Oncology (ASTRO).

SRS for More Than Four BM

For patients presenting with >4 metastases, traditionally WBRT has been the standard of care. In patients with >4 metastases, the application of SRS is controversial, because the currently discussed randomized trials were done in patients with a limited number of BM. The additional palliative value of SRS over WBRT in patients with four or more BM remains to be determined. An international practice survey reported in 2010 showed the difference in consensus on SRS. In a responder-population consisting of SRS-specialists, 83% would consider patients >4 brain metastasis as potential candidate for SRS. By contrast, only 7% of a responder-population consisting of radiation oncologists agreed for SRS in patients with >4 BM (55). Physicians that support SRS in patients with >4 metastases indicate that in the past there where technical issues concerning the long treatment times and safety of the radiation doses (56–59).

The multi-institutional prospective study from Yamamoto et al. was the first evaluating SRS alone for four and more BM (22). The trial population consisted of favorable prognostic patients with low volume BM, three-quarters originate from primary lung cancer, the majority had an RPA 2 and KPS ≥ 80 (largest tumor <10 mL in volume, <3 cm in longest diameter; total cumulative volume ≤15 mL). This study included 1,194 patients with 1–10 metastases and where treated with SRS, split in to three cohorts: 208 patients with 5–10 metastases, 531 patients with 2–4 metastases, and 455 patients with a single metastasis. The intention was to determine non-inferiority in the cohort with 5–10 BM compared with 2–4 BM with OS as the primary endpoint. The OS did not differ between patients with 5–10 BM or 2–4 BM (HR 0.97, $p = 0.78$). As well as local control rates, distant brain relapses were not significantly different between both cohorts. This suggests that SRS without WBRT in patients with 5–10 BM is non-inferior to patients with 2–4 BM. SRS may be an alternative for WBRT as SRS is minimally invasive and has fewer side effects.

A second case-matched, retrospective cohort trial from Yamamoto et al. compared treatment results for patients with 10 or more BM vs 2–9 metastases (60). The primary endpoint was OS, whereas the secondary endpoints consisted of neurological death and deterioration, local recurrence and repeat SRS, and major complications of SRS. The median survival time between the two arms did not differ significantly, 6.8 months for patients with 2–9 BM vs 6.0 months for patients ≥10 BM ($p = 0.10$). Considering the incidence of neurological deterioration (defined as any brain disease-caused neurological worsening), there was no difference between the groups, including radiation-related complications. They concluded that treatment results after SRS were not inferior for patients with 10 or more BM than for patients with 2–9 metastases.

Serizawa et al. conducted a small retrospective study to compare the effectiveness of SRS ($N = 62$) with WBRT ($N = 34$) for multiple cranial metastases from non-small-cell lung cancer (61). They included patients with 1–10 BM with a life expectancy of more than 2 months, lesions >3 cm were surgically removed. The OS time and the neurological survival in the SRS arm were significantly longer. The risk of neurologically impaired QoL was also lower in the SRS arm.

The results of these studies support the hypothesis that SRS is a viable treatment option in patients with four or more BM. The main question if SRS is beneficial over WBRT with respect to QoL, survival, and maintenance of neurocognitive function, needs to be answered in randomized trials (25).

There are no published randomized trials evaluating the role of SRS in patients with ≥4 BM. In the Netherlands a randomized phase III trial (NCT02353000, https://clinicaltrials.gov/show/NCT02353000) is enrolling patients with 4–10 BM, KPS ≥ 70, and any primary solid tumor including NSCLC. The standard treatment WBRT is compared with SRS for all lesions, with the primary endpoint being of QoL at 3 months after radiotherapy (25). Another randomized phase III trial (NCT01592968) at the MD Anderson Cancer Center is randomizing patients with 4–15 BM to SRS alone vs WBRT alone. The primary endpoints are cognitive function and local tumor control at 4 months. If these trials are successful, SRS will replace WBRT as the standard treatment for patients with more than four BM. Several other trials are currently being initiated to evaluate the role of SRS in patients with multiple BM, such as Heidelberg (NCT0329778) and Boston (NTC03075072), among others.

Another treatment option for patients with multiple BM, especially in patients with asymptomatic BM of a driver mutation, is to only treat the larger and worrisome BM with SRS (**Figure 1**). This strategy is of specific interest in subgroups of patients who may survive over several years due in part to several lines of targeted agents and to postpone the radiotherapy (either SRS or WBRT) until progression of intracranial disease.

IMPROVING INDICATION OF CRANIAL IRRADIATION AS A TREATMENT OPTION FOR PATIENTS WITH BM DURING SDM

Especially in the palliative setting of BM, it will be increasingly important to better inform the patient about the available treatment options, such as SRS, to individualize the multimodality treatment of patients with BM of NSCLC.

Shared decision-making is based on the principle of the person's autonomy and to improve the participation of patients in making decision concerning their personal health and treatment. It can be divided into four parts: the health-care professional needs to inform the patient that a decision needs to be made and that the opinion of the patient also important is, the explanation from the health-care professional to the patient about the different options inclusive of advantages and disadvantages of the different treatment options, a discussion between the health-care professional and the patient about their preferences, and finally to make a decision about the chosen treatment (62).

Traditionally, physicians had a more paternalistic approach with respect to treatment choices based on national guidelines. However, for patients with BM with incurable cancer, it is of

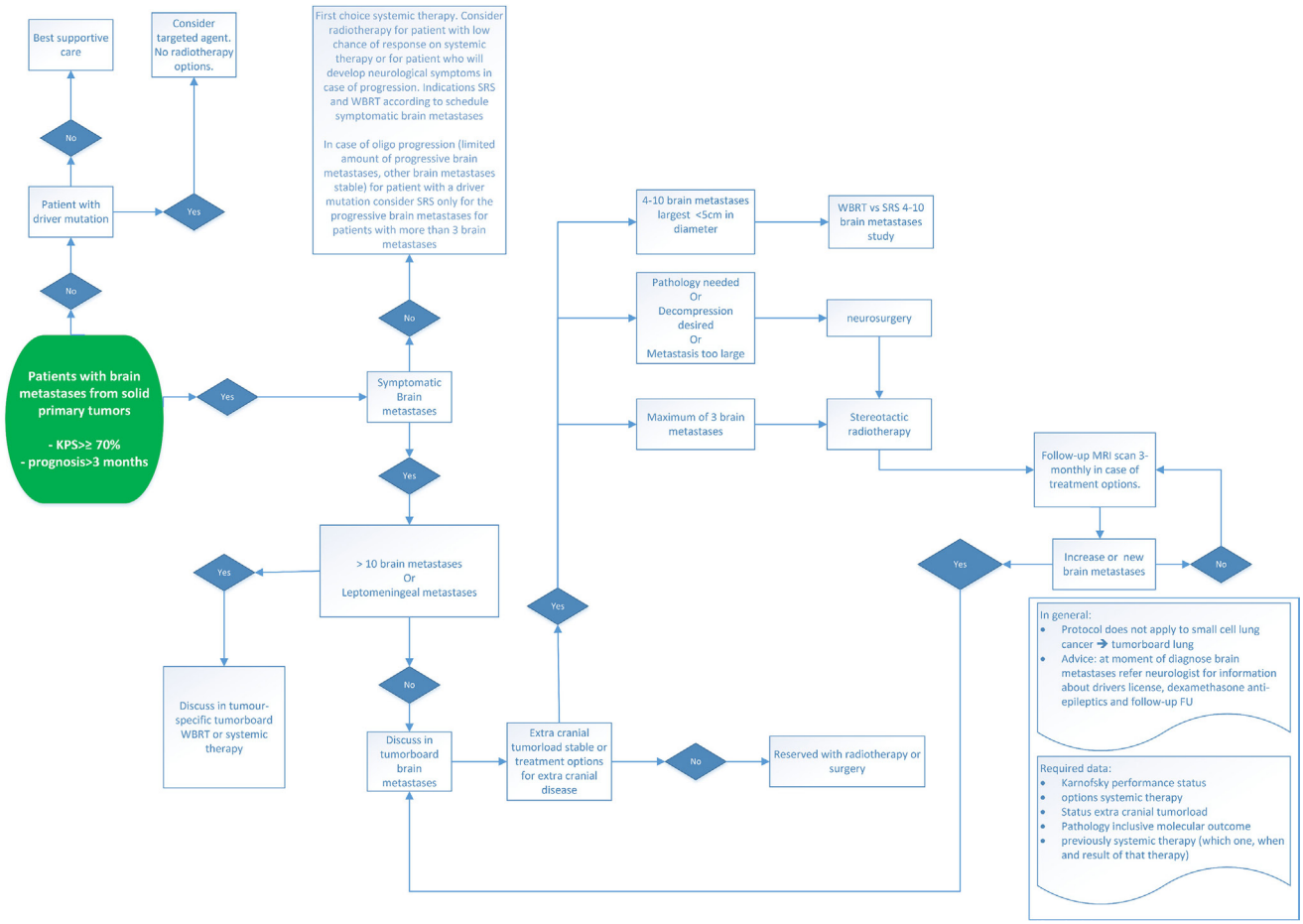


FIGURE 1 | Treatment options for BM of NSCLC. Abbreviations: KPS, Karnofsky performance status; WBRT, whole-brain radiotherapy; SRS, stereotactic radiosurgery; BM, brain metastases; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer.

specific relevance to consciously make choices between treatment options taking into account all advantages and disadvantages. With the availability of an increasing number of treatment options, SDM is challenging and complex, and work is in progress to make SDM tools available for the patient and caretakers.

Decision Support Systems (DSSs) Including SRS as a Treatment Option

A DSS is a direct aid in clinical decision-making, in which characteristics of individual patients are used to generate patient-specific assessments or recommendations that are then presented to clinicians for consideration (63).

In radiotherapy oncology, the DSSs use advanced and innovative information technology, combined with available medical data to achieve the highest possible accuracy in the prediction of everything from the response of the tumor, to the treatment response and toxicity of normal tissue (64). The base of SDM is individualized prognostic models for outcome prediction per patient. Individualized prognostic models use machine learning algorithms to learn from patients treated in the past to make predictions for patients we currently see in the clinic. Traditionally, outcome was calculated per group of patients, such as the RPA (65).

Recently, individualized prognostic models became available for patients treated with SRS for a limited number of BM of NSCLC (66). These two models can predict individualized chances of both early death (<3 months), and long-term survival (>12 months), after SRS for BM of NSCLC, with an area under the curve (AUC) for early death of 0.79 with a 95% confidence interval (CI) of 0.72–0.86, and an AUC for long-term survival of 0.77 with a 95% CI of 0.70–0.84. The nomograms were more accurate in the prediction of early death and long-term survival than commonly used prognostic scores after SRS for a limited number of brain metastasis of NSCLC. Examples of commonly used prognostic scores are the RPA, the Golden Grading System, DS-GPA, and Score Index for Radiosurgery in brain metastasis (SIR) (66). Other than the increased accuracy of prediction, these nomograms are also easy to use in routine clinical practice and are available at www.predictcancer.org (66). Other tumor-specific individualized models are necessary for more relevant clinical endpoints, such as the occurrence of distant brain recurrences, local control probability, and the risk of RN or cognitive toxicity. The current individualized prognostic models are relatively

simple and may become more accurate in outcome prediction if more patient-, treatment-, and tumor characteristics are added into these models. With respect to the latter genomic and radiological factors with biomarkers, radiomics, and deep learning are of specific interest (64, 67–70). Model performance is in part, dependent on the volume of patient data used on which to base these models (71). Unfortunately, sharing of data between hospitals is hampered by ethical, political, administrative, and legal barriers (72). Efforts have been made to learn from multiple hospitals while avoiding the hurdles associated with sharing data. The EuroCAT project is an example of one such effort, in which the distributed learning approach is championed (see the animation at https://www.youtube.com/watch?v=nQpqMIuHyOk) (73). Distributed learning is defined as learning from data stored at the hospital without the data leaving the hospital. As only model coefficients are transmitted, patient privacy is preserved while the data can still be used for teaching models. Models for survival and treatment-related side effects have been learned using this approach (64, 73–75).

Patient Decision Aids Including SRS as a Treatment Option

Patient decision aids are based on prognostic models which can be individually adapted to the characteristics of the patient and their disease. The model consists of two key steps: information exchange and deliberation between the health-care professional and the patient (76). The goal of these tools is to achieve an optimal individualized treatment strategy. The patient benefits of SDM have been proven with level 1 evidence on more than 30,000 patients, and yet clinical decision-making remains complex; patients must not only weigh several treatment options in terms of benefits and harms but also absorb a large amount of technical information while dealing with the emotional burden of their disease (25, 77). Lack of awareness about treatment options can lead patients to choose treatments that are more expensive or not aligned with their values. To improve patients' QoL, health-care quality, and to reduce unnecessary procedures, it is crucial to empower patients with solid decision support. Evidence shows that patients who use decision aids are better informed about their treatment options, and experience less decisional conflict, and less anxiety about their care. Despite the evidence, patient decision aids are not routinely applied in practice (77). The shared decision tools are focused on the patient, which means that the level of these tools is also adjusted to the average patient. Medically complicated terms will be avoided as much as possible (78). An example of a potential patient decision aid is a tool which will be designed for SRS treatment in NSCLC patients consists of several headings: who is the main health-care professional during the treatment, what is the path during the diagnosis to brain metastasis, what makes the treatment eligible for the patient, what does the treatment consist of, what are the advantages of the treatment, what are the disadvantage of the treatment including possible adverse events, what is the influence of the treatment on the life of the patient, and what does the follow-up consist of. Ideally, every treatment option will be incorporated within this decision aid.

When the patient has run through this decision tool, the patient and the health-care professional will discuss this tool, and the patient has the opportunity to ask questions about the content and the information in this tool. After this discussion, the patient and the health-care professional will determine, together, if the SRS treatment is the best treatment option for this patient. The goal of this SDM is to obtain an optimal individualized treatment strategy by making use of the shared decision tool in which there is a deliberation between the health-care professional and the patient (78).

FUTURE DIRECTIONS OF SRS FOR BM OF NSCLC TO FURTHER IMPROVE OUTCOME

Combining Systemic Therapy With SRS for BM of NSCLC

To further improve the clinical outcome of SRS in patients with BM of NSCLC, it can be considered to combine targeted therapies with either SRS or WBRT. The hypothesis is that systemic therapies have a superior penetration through the BBB after radiotherapy leading to a better response in the brain of the systemic agent. Considering multiple reports on the efficacy of targeted therapy on BM, it is interesting to investigate if the combination of SRS with systemic treatment improves efficacy above systemic treatment only (79, 80).

A few trials combined cranial radiation with targeted therapies in patients with BM from primary NSCLC. Lee et al. randomized 80 NSCLC patients with KPS $\geq$ 70 and multiple BM to erlotinib or placebo arms, both concurrent with WBRT (81). Patients continued with treatment of erlotinib or placebo until progression of disease. The neurological progression-free survival (nPFS) and median OS are not significantly different with an equal nPFS in both treatment arms of 1.6 ($p = 0.84$), and a median OS of 2.9 and 3.4 months in the placebo and erlotinib arms, respectively ($p = 0.83$). More grade 3/4 toxicity was found in the erlotinib arm compared with the placebo arm for fatigue and rash and there was no reported difference in the QoL. They concluded that there was no improvement of nPFS or OS for erlotinib concurrent to WBRT for patients with EGFR wild-type NSCLC and multiple BM.

A phase III trial from Sperduto et al. randomized 126 NSCLC patients with 1–3 BM into WBRT plus SRS vs WBRT plus SRS plus erlotinib or temozolomide (82). Erlotinib or temozolomide could be continued up to 6 months after radiation. The trial closed early because of slow accrual. There was no statistically difference between the groups concerning OS and time to CNS progression. The performance status was inferior in the group with erlotinib or temozolomide compared with the group treated with WBRT plus SRS. They found more grade 3–5 toxicity in the patients treated with targeted therapy concurrent with radiation. The trial did not support the concurrent use of systemic treatment with WBRT plus SRS. The question remains if SRS only combined with erlotinib or temozolomide provides benefit over either SRS or systemic treatment only, in these patients.

Another phase II trial from Welsh et al. enrolled patients with BM from NSCLC who received erlotinib concurrently

with WBRT, followed by maintenance erlotinib (83). The overall radiologic response rate was 86% and there was no increase in neurotoxicity and no grade ≥4 toxicity. The median survival was 9.3 months for EGFR wild-type patients and 19.1 months for patients with an EGFR mutation. The addition of erlotinib to cranial radiation was well tolerated, but there was no control arm.

Magnuson et al. preformed a multi-institutional analysis with 351 EGFR-mutant NSCLC patients who developed BM with no prior treatment with EGFR-TKI (37). Patients received EGFR-TKI followed by SRS or WBRT at intracranial progression ($N = 131$), WBRT followed by EGFR-TKI ($N = 120$), or SRS followed by EGFR-TKI ($N = 100$). The analysis demonstrated that the use of upfront EGFR-TKI, and deferral or radiotherapy is associated with inferior OS. SRS followed by EGFR-TKI resulted in the longest OS (46 vs 25 months for the EGFR-TKI arm). The high effective doses of SRS may ablate BM, whereas systemic therapy simultaneously controls the extracranial diseases and possibly intracranial micro metastatic disease. A prospective trial comparing SRS followed by EGFR-TKI vs EGFR-TKI only is urgently needed.

Hendriks et al. published a systematic review to address the toxicity of combining cranial radiotherapy (SRS, WBRT, or SRS + WBRT) with TKI such as erlotinib and gefitinib, focusing on neurological toxicity (84). Fifteen articles were included, with only one phase III randomized trial. The authors concluded that there are arguments that TKI can safely be combined with WBRT, lacking high-level evidence. Grade 3 or higher toxicity may increase combining TKI with SRS and WBRT. The systematic review emphasizes the need for further investigation. Two retrospective studies analyzed patients with concurrent crizotinib, an ALK inhibitor, and SRS for cranial and extracranial metastatic NSCLC patients. They concluded that SRS can be used safely in patients receiving crizotinib. When SRS was administered to the patient, crizotinib could be longer admitted to the patient, leading to a longer 2-year OS (72% duration of crizotinib >12 months vs 12% when duration of crizotinib <12 months) (85, 86). For ALK-rearranged patients, minimal data are available, further high quality studies evaluating the use of ALK inhibitors concurrent with SRS are needed.

Combining SRS With Immunotherapy

A potential radiobiological advantage of SRS is an enhanced antitumor immune response after radiation of the tumor as mediator of systemic effects, better known as the abscopal effect (87, 88). Radiotherapy changes the tumor environment resulting in the release of tumor antigens and therefore increases the antitumor effect of immunotherapy. For example, IL2 is a cytokine, which plays a role in the activation of the immune response against tumor cells. L19 targets the extra domain B of fibronectin, which is a marker for tumor neoangiogenesis and is, among others, overexpressed in NSCLC. L19 can significantly increase the immune response. Zegers et al. provide evidence for an increased therapeutic potential due to the combination of radiation therapy with L19-IL2 (89).

Reynders et al. published an overview of preclinical and clinical data about the abscopal effect, resulting in 37 articles. They found a median time to abscopal effect of 5 months, and an ongoing median time of abscopal response of 13 months before disease progression (88). The included data point toward a synergy between immune treatment and radiotherapy, but further research is needed before the abscopal effect can become relevant in clinical practice.

The abscopal effect is well discussed in the literature concerning patients with BM of metastatic melanoma. Schoenfeld et al. reviewed 16 patients with BM of melanoma treated with ipilimumab and cranial radiation to evaluate the abscopal effect. They found a superior OS for patients who received SRS before ipilimumab compared with patients receiving ipilimumab before SRS (26 vs 6 months, $p < 0.001$) (90). Also, Knisely et al. found an increased survival rate for patients with BM of melanoma treated with SRS in addition to ipilimumab, with a median survival of 21.3 months in the SRS plus ipilimumab group vs 4.9 months in the ipilimumab group and a 2-year survival of 47.2 vs 19.7% (91). Both trials suggesting a role for radiation therapy in enhancing immunotherapy.

This phenomenon was also demonstrated in a case report regarding a patient with metastatic lung adenocarcinoma treated with ipilimumab concurrent with radiation (92). A complete response was received at the initial site and all metastatic sites. Posttreatment, an increase in tumor-infiltrating cytotoxic lymphocytes and tumor regression was seen. They concluded that this approach in NSCLC may establish clinical trials for patients with advanced metastatic disease in the future. Combining immunotherapy with SRS in patients with BM of NSCLC to induce an abscopal effect and improve outcome is a strategy which is currently being investigated in clinical trials, NTC02086721, for example.

Individualized Isotoxic Dose Prescription (IDP) With SRS for Avoidance of RN and Improvement of Local Control

A disadvantage of SRS is the risk of RN with current SRS dose prescription. The SRS dose is prescribed based on the size of the planning target volume (PTV) of the BM and ranges between 15 and 27 Gy in one or three fractions. In larger BM, the dose is hypofractionated and lowered to avoid the risk of RN. Despite this strategy, the risk of RN is still increased in BM with a diameter of more than 2 cm as the volume of healthy brain tissue which is irradiated to a high dose remains relatively high (93).

A relatively new possible strategy to mitigate the risk of RN and to increase the local control probability is *IDP* (94). The idea of IDP is to prescribe the dose based on the normal tissue tolerance level instead of the size of the PTV so that the risk of complications is always minimized or even avoided. The dose in the PTV is escalated until the highest dose which is technically achievable. If the local control probability is unsatisfactory for the patient, the number of fractions can be increased to compensate. In the literature fractionated stereotactic radiotherapy (FSRT), approaches have been described to improve the local control in large BM (95, 96). These studies use a fixed prescribed dose, for example, 25 Gy in five fractions. FSRT has the increased risk of observing RN with increasing size of the BM due to the fixed prescribed dose, while IDP has the advantage that the

tolerance level of the healthy brain tissue is always respected. IDP will increase the local control probability of patients with a diameter of less than 2 cm compared with current SRS dose prescription and decrease the risk of RN in BM with a diameter of more than 2 cm. IDP, therefore has the potential to increase the therapeutic ratio, e.g., ratio local control/RN, for all sizes of BM (94). IDP is expected to yield the best results as the margins used are minimized or even avoided, with an optimal beam arrangement (non-coplanar vs coplanar SRS beams). Predictive studies for IDP have already been published, such as an *in silico* study for NSCLC patients (97). Individualized IDP, compared with conventionally prescribed fractionated radiotherapy, enabled a therapeutic gain in almost 80% of the patients. In a predictive modeling study, a 25% increase in the estimated tumor control probability was expected with IDP for patients with NSCLC (98). Nowadays IDP is not yet in active clinical use, clinical studies are needed to validate the results achieved with this *in silico* study.

CONCLUSION

In recent years, the management of lung cancer has changed dramatically. At present, patients having NSCLC with driver mutations are treated with multiple lines of systemic therapy leading to an increasing importance of the management of BM. The indication of WBRT is a matter of debate because of its side effects and relatively poor outcome in terms of QoL and survival after treatment. SRS is an emerging strategy for patients with BM of NSCLC and the standard treatment for patients with a maximum of three BM. SRS is also a promising treatment option for patients with four or more BM and randomized trials are ongoing to determine its value. Promising future strategies include combining SRS with systemic treatments, for example, upfront TKIs to improve survival by destruction of the BBB and better penetration of SRS. The combination of SRS with immunotherapy is promising to induce an abscopal effect. Finally, a promising strategy is the potential improvement of outcome of SRS in large BM by individualized IDP. With this strategy, the risk of RN is minimized or even avoided with a simultaneous improvement of the local control probability.

AUTHOR CONTRIBUTIONS

DH and BH have written the manuscript with input from all the authors.

ACKNOWLEDGMENTS

The authors would like to thank Mark Podesta, PhD, MAASTRO Clinic for the language correction.

REFERENCES

1. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer* (2002) 94(10):2698–705. doi:10.1002/cncr.10541
2. Zindler JD, Rodrigues G, Haasbeek CJ, De Haan PF, Meijer OW, Slotman BJ, et al. The clinical utility of prognostic scoring systems in patients with brain metastases treated with radiosurgery. *Radiother Oncol* (2013) 106(3):370–4. doi:10.1016/j.radonc.2013.01.015
3. Hendriks LE, Troost EG, Steward A, Bootsma GP, De Jaeger K, van den Borne BE, et al. Patient selection for whole brain radiotherapy (WBRT) in a large lung cancer cohort: impact of a new Dutch guideline on brain metastases. *Acta Oncol* (2014) 53(7):945–51. doi:10.3109/0284186X.2014.906746
4. Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet* (2016) 388(10055):2004–14. doi:10.1016/S0140-6736(16)30825-X
5. Jeene PM, de Vries KC, van Nes JGH, Kwakman JJM, Wester G, Rozema T, et al. Survival after whole brain radiotherapy for brain metastases from lung cancer and breast cancer is poor in 6325 Dutch patients treated between 2000 and 2014. *Acta Oncol* (2017) 57(5):637–43. doi:10.1080/0284186X.2017.1418534
6. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* (1997) 37(4):745–51. doi:10.1016/S0360-3016(96)00619-0
7. Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. *Int J Radiat Oncol Biol Phys* (2000) 47:1001–6. doi:10.1016/S0360-3016(00)00547-2
8. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys* (2008) 70:510–4. doi:10.1016/j.ijrobp.2007.06.074
9. Sperduto CM, Watanabe Y, Mullan J, Hood T, Dyste G, Watts C, et al. A validation study of a new prognostic index for patients with brain metastases: the graded prognostic assessment. *J Neurosurg* (2008) 109:87–9. doi:10.3171/JNS/2008/109/12/S14
10. 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) 77:655–61. doi:10.1016/j.ijrobp.2009.08.025
11. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary report of the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patient with brain metastases. *J Clin Oncol* (2011) 30:419–25. doi:10.1200/JCO.2011.38.0527
12. Sperduto PW, Yang J, Beal K, Pan H, Brown PD, Bangdiwala A, et al. Estimating survival in patients with lung cancer and brain metastases. An update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). *JAMA Oncol* (2017) 3(6):827–31. doi:10.1001/jamaoncol.2016.3834
13. Nieder C, Hintz M, Oehlke O, Bilger A, Grosu AL. Validation of the graded prognostic assessment for lung cancer with brain metastases using molecular markers (lung-molGPA). *Radiat Oncol* (2017) 12:107. doi:10.1186/s13014-017-0844-6
14. Zindler JD, Slotman BJ, Lagerwaard FJ. Patterns of distant brain recurrences after radiosurgery alone for newly diagnosed brain metastases: implications for salvage therapy. *Radiother Oncol* (2014) 112(2):212–6. doi:10.1016/j.radonc.2014.07.007
15. Le Rhun E, Dhermain F, Vogin G, Reyns N, Metellus P. Radionecrosis after stereotactic radiotherapy for brain metastases. *Expert Rev Neurother* (2016) 8:903–14. doi:10.1080/14737175.2016.1184572
16. Minniti G, Clarke E, Lanzetta G, Osti MF, Trasimeni G, Bozzao A, et al. Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. *Radiat Oncol* (2011) 6:48. doi:10.1186/1748-717X-6-48
17. Zhao B, Wen N, Chetty IJ, Huang Y, Brown SL, Snyder KC, et al. A prediction model of radiation-induced necrosis for intracranial radiosurgery based on target volume. *Med Phys* (2017) 44(8):4360–7. doi:10.1002/mp.12360
18. Rodrigues G, Warner A, Zindler J, Slotman B, Lagerwaard F. A clinical nomogram and recursive partitioning analysis to determine the risk of regional failure after radiosurgery alone for brain metastases. *Radiother Oncol* (2014) 111(1):52–8. doi:10.1016/j.radonc.2013.11.015

19. Ayala-Peacock DN, Peiffer AM, Lucas JT, Isom S, Kuremsky JG, Urbanic JJ, et al. A nomogram for predicting distant brain failure in patients treated with gamma knife stereotactic radiosurgery without whole brain radiotherapy. *Neuro Oncol* (2014) 16(9):1283–8. doi:10.1093/neuonc/nou018
20. Ayala-Peacock DN, Attia A, Braunstein SE, Ahluwalia MS, Hepel J, Chung C, et al. Prediction of new brain metastases after radiosurgery: validation and analysis of performance of a multi-institutional nomogram. *J Neurooncol* (2017) 135(2):403–11. doi:10.1007/s11060-017-2588-4
21. Sneed PK, Suh JH, Goetsch SJ, Sanghavi SN, Chappell R, Buatti JM, et al. A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. *Int J Radiat Oncol Biol Phys* (2002) 53(3):519–26. doi:10.1016/S0360-3016(02)02770-0
22. Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol* (2014) 15:387–95. doi:10.1016/S1470-2045(14)70061-0
23. Lippitz B, Lindquist C, Paddick I, Peterson D, O'Neill K, Beaney R. Stereotactic radiosurgery in the treatment of brain metastases: the current evidence. *Cancer Treat Rev* (2014) 40(1):48–59. doi:10.1016/j.ctrv.2013.05.002
24. Aoyama H, Tago M, Shirato H, et al. Japanese Radiation Oncology Study Group 99-1 (JROSG 99-1) investigators. Stereotactic radiosurgery with or without whole-brain radiotherapy for brain metastases: secondary analysis of the JROSG 99-1 randomized clinical trial. *JAMA Oncol* (2015) 1(4):457–64. doi:10.1001/jamaoncol.2015.1145
25. Zindler JD, Bruynzeel AME, Eekers DBP, Hurkmans CW, Swinnen A, Lambin P. Whole brain radiotherapy versus stereotactic radiosurgery for 4-10 brain metastases: a phase III randomised multicentre trial. *BMC Cancer* (2017) 17:500. doi:10.1186/s12885-017-3494-z
26. Gijtenbeek JMM, Ho VKY, Heesters MAAM, Lagerwaard FJF, de Graeff A, Boogerd W, et al. Richtlijn 'Hersenmetastasen' (Revisie). *Ned Tijdschr Geneeskd* (2011) 155:A4294.
27. Besse B, Le Moulec S, Mazières J, Senellart H, Barlesi F, Chouaid C, et al. Bevacizumab in patients with nonsquamous non-small cell lung cancer and asymptomatic untreated brain metastases (BRAIN): a nonrandomized, phase II study. *Clin Cancer Res* (2015) 21(8):1896–903. doi:10.1158/1078-0432.CCR-14-2082
28. Barlesi F, Gervais R, Lena H, Hureaux J, Berard H, Paillotin D, et al. Pemetrexed and cisplatin as first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) with asymptomatic inoperable brain metastases: a multicenter phase II trial (GFPC07-01). *Ann Oncol* (2011) 22(11):2466–70. doi:10.1093/annonc/mdr003
29. Wong A. The emerging role of targeted therapy and immunotherapy in the management of brain metastases in non-small-cell lung cancer. *Front Oncol* (2017) 7(33). doi:10.3389/fonc.2017.00033
30. Sekina A, Satoh H. Paradigm shift of therapeutic management of brain metastases in EGFR-mutant non-small cell lung cancer in the era of targeted therapy. *Med Oncol* (2017) 34:121. doi:10.1007/s12032-017-0978-2
31. Lim SH, Lee JY, Lee MY, Kim SH, Lee J, Sun JM, et al. A randomized phase II trial of stereotactic radiosurgery (SRS) versus observation for patients with asymptomatic cerebral oligo-metastases in non-small-cell lung cancer. *Ann Oncol* (2014) 26:762–8. doi:10.1093/annonc/mdu584
32. Wu YL, Zhou C, Cheng Y, Lu S, Chen GY, Huang C, et al. Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: a phase II study (CTONG-0803). *Ann Oncol* (2013) 24:993–9. doi:10.1093/annonc/mds529
33. Broniscer A, Panetta JC, O'Shaughnessy M, Fraga C, Bai F, Krasin MJ, et al. Plasma and cerebrospinal fluid pharmacokinetics of erlotinib and its active metabolite OSI-420. *Clin Cancer Res* (2007) 13(5):1511–5. doi:10.1158/1078-0432.CCR-06-2372
34. Fan Y, Xu X, Xie C. EGFR-TKI therapy for patients with brain metastases from non-small-cell lung cancer: a pooled analysis of published data. *Onco Targets Ther* (2014) 7:2075–84. doi:10.2147/OTT.S67586
35. Rangachari D, Yamaguchi N, VanderLaan PA, Folch E, Mahadevan A, Floyd SR, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer* (2015) 88(1):108–11. doi:10.1016/j.lungcan.2015.01.020
36. Thai AA, Solomon BJ. Treatment of ALK-positive nonsmall cell lung cancer: recent advances. *Curr Opin Oncol* (2018) 30:84–91. doi:10.1097/CCO.0000000000000431
37. Magnuson WJ, Lester-Coll NH, Wu AJ, Yang TJ, Lockney NA, Gerber NK, et al. Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. *J Clin Oncol* (2017) 35(10):1070–7. doi:10.1200/JCO.2016.69.7144
38. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* (1998) 280(17):1485–9. doi:10.1001/jama.280.17.1485
39. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* (1990) 332(8):494–500. doi:10.1056/NEJM199002223220802
40. Soliman H, Das S, Larson DA, et al. Stereotactic radiosurgery (SRS) in the modern management of patients with brain metastases. *Oncotarget* (2016) 7:12318–12330. doi:10.18632/oncotarget.7131
41. Tsao M, Xu W, Sahgal A. A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. *Cancer* (2012) 118(9):2486–93. doi:10.1002/cncr.26515
42. Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American society for radiation oncology evidence-based guideline. *Pract Radiat Oncol* (2012) 2:210–25. doi:10.1016/j.prro.2011.12.004
43. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patient with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* (2004) 363:1665–72. doi:10.1016/S0140-6736(04)16250-8
44. Kocher M, Soffietti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* (2011) 29:134–41. doi:10.1200/JCO.2010.30.1655
45. Churilla TM, Handorf E, Collette S, Collette L, Dong Y, Aizer AA, et al. Whole brain radiotherapy after stereotactic radiosurgery or surgical resection among patients with one to three brain metastases and favorable prognoses: a secondary analysis of EORTC 22952-26001. *Ann Oncol* (2017) 28(1):2588–94. doi:10.1093/annonc/mdx332
46. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* (2006) 295:2483–91. doi:10.1001/jama.295.21.2483
47. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* (2009) 10:1037–44. doi:10.1016/S1470-2045(09)70263-3
48. Sahgal A, Aoyama H, Kocher M, Neupane B, Collette S, Tago M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys* (2015) 91(4):710–7. doi:10.1016/j.ijrobp.2014.10.024
49. Aoyama H, Tago M, Kato N, Toyoda T, Kenjyo M, Hirota S, et al. Neurocognitive function of patients with brain metastases who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys* (2007) 68(5):1388–95. doi:10.1016/j.ijrobp.2007.03.048
50. Meyers CA, Smith JA, Bezjak A, Mehta MP, Liebmann J, Illidge T, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J Clin Oncol* (2004) 22:157–65. doi:10.1200/JCO.2004.05.128
51. Leung A, Lien K, Zeng L, Nguyen J, Caissie A, Culleton S, et al. The EORTC QLQ-BN20 for assessment of quality of life in patients receiving treatment of prophylaxis for brain metastases: a literature review. *Expert Rev Pharmacoecon Outcomes Res* (2011) 11(6):693–700. doi:10.1586/erp.11.66
52. Weiss DS, Kelly PJ. Neurocognitive function after WBRT plus SRS or SRS alone. *Lancet Oncol* (2010) 11(3):220–1. doi:10.1016/S1470-2045(09)70387-0
53. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, 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):401–9. doi:10.1001/jama.2016.9839

54. Churilla TM, Ballman KV, Brown PD, Twohy EL, Jaeckle K, Farace E, et al. Stereotactic radiosurgery with or without whole-brain radiation therapy for limited brain metastases: a secondary analysis of the North Central Cancer Treatment Group N0574 (Alliance) randomized controlled trial. *Int J Radiat Oncol Biol Phys* (2017) 99(5):1173–8. doi:10.1016/j.ijrobp.2017.07.045
55. Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Vichare A, et al. International practice survey on the management of brain metastases: third international consensus workshop on palliative radiotherapy and symptom control. *Clin Oncol* (2012) 24(6):e81–92. doi:10.1016/j.clon.2012.03.008
56. Terahara A, Machida T, Kubo T, Aoki Y, Ohtomo K. Analysis of dose distribution in gamma knife radiosurgery for multiple targets. *Int J Radiat Oncol Biol Phys* (2000) 47(5):1431–4. doi:10.1016/S0360-3016(00)00483-1
57. Nath SK, Lawson JD, Simpson DR, Vanderspek L, Wang JZ, Alksne JF, et al. Single-isocenter frameless intensity-modulated stereotactic radiosurgery for simultaneous treatment of multiple brain metastases: clinical experience. *Int J Radiat Oncol Biol Phys* (2010) 78(1):91–7. doi:10.1016/j.ijrobp.2009.07.1726
58. Thomas EM, Popple RA, Wu X, Clark GM, Markert JM, Guthrie BL, et al. Comparison of plan quality and delivery time between columetric arc therapy (RapidArc) and Gamma Knife radiosurgery for multiple cranial metastases. *Neurosurgery* (2014) 75:409–17. doi:10.1227/NEU.0000000000000448
59. Sahgal A, Ma L, Chang E, Shiu A, Larson DA, Laperriere N, et al. Advances in technology for intracranial stereotactic radiosurgery. *Technol Cancer Res Treat* (2009) 8:271–80. doi:10.1177/153303460900800404
60. Yamamoto M, Kawabe T, Sato Y, Higuchi Y, Nariai T, Watanabe S, et al. Stereotactic radiosurgery for patients with multiple brain metastases: a case-matched study comparing treatment results for patients with 2-9 versus 10 or more tumors. *J Neurosurg* (2014) 121:16–25. doi:10.3171/2014.8.GKS141421
61. Serizawa T, Iuchi T, Ono J, Saeki N, Osato K, Odaki M, et al. Gamma knife treatment for multiple metastastic brain tumors compared with whole-brain radiation therapy. *J Neurosurg* (2000) 93(Suppl 3):32–6. doi:10.3171/jns.2000.93.supplement
62. Stiggelbout AM, Pieterse AH, De Haes JCJM. Shared decision making: concepts, evidence, and practice. *Patient Educ Couns* (2015) 98(10):1172–9. doi:10.1016/j.pec.2015.06.022
63. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. *BMJ* (2005) 330(7494):765. doi:10.1136/bmj.38398.500764.8F
64. Lambin P, Zindler J, Vanneste BG, De Voorde LV, Eekers D, Compter I, et al. Decision support systems for personalized and participative radiation oncology. *Adv Drug Deliv Rev* (2017) 109:131–53. doi:10.1016/j.addr.2016.01.006
65. Bright TJ, Wong A, Dhurjati R, Bristow E, Bastian L, Coeytaux RR, et al. Effect of clinical decision-support systems: a systematic review. *Ann Intern Med* (2012) 157(1):29–43. doi:10.7326/0003-4819-157-1-201207030-00450
66. Zindler JD, Jochems A, Lagerwaard FJ, Beumer R, Troost EGC, Eekers DBP, et al. Individualized early death and long-term survival prediction after stereotactic radiosurgery for brain metastases of non-small cell lung cancer: two externally validated nomograms. *Radiother Oncol* (2017) 123(2):189–94. doi:10.1016/j.radonc.2017.02.006
67. Lambin P, Roelofs E, Reymen B, Velazquez ER, Buijsen J, Zegers CM, et al. 'Rapid Learning health care in oncology' – an approach towards decision support systems enabling customised radiotherapy'. *Radiother Oncol* (2013) 109(1):159–64. doi:10.1016/j.radonc.2013.07.007
68. Lambin P, van Stiphout RG, Starmans MH, Rios-Velazquez E, Nalbantov G, Aerts HJ, et al. Predicting outcomes in radiation oncology – multifactorial decision support systems. *Nat Rev Clin Oncol* (2013) 10(1):27–40. doi:10.1038/nrclinonc.2012.196
69. Lambin P, Leijenaar RTH, Deist TM, Peerlings J, de Jong EEC, van Timmeren J, et al. Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol* (2017) 14(12):749–62. doi:10.1038/nrclinonc.2017.141
70. Aerts HJ, Velazquez ER, Leijenaar RT, Parmar C, Grossmann P, Carvalho S, et al. Decoding tumour phenotype by non-invasive imaging using a quantitative radiomics approach. *Nat Commun* (2014) 5:4006. doi:10.1038/ncomms5006
71. Etheredge LM. A rapid-learning health system. *Health Aff (Millwood)* (2007) 26:107–18. doi:10.1377/hlthaff.26.2.w107
72. Doshi P, Jefferson T, Del Mar C. The imperative to share clinical study reports: recommendations from the Tamiflu experience. *PLoS Med* (2012) 9:e1001201. doi:10.1371/journal.pmed.1001201
73. Timo MD, Jochems A, van Soest J, Nalbantov G, Oberije C, Walsh S, et al. Infrastructure and distributed learning methodology for privacy-preserving multi-centric rapid learning health care: euroCAT. *Clin Transl Radiat Oncol* (2017) 4:24–31. doi:10.1016/j.ctro.2016.12.004
74. Jochems A, Deist TM, El Naqa I, Kessler M, Mayo C, Reeves J, et al. Developing and validating a survival prediction model for NSCLC patients through distributed learning across 3 countries. *Int J Radiat Oncol Biol Phys* (2017) 99(2):344–52. doi:10.1016/j.ijrobp.2017.04.021
75. Jochems A, Deist TM, van Soest J, Eble M, Bulens P, Coucke P, et al. Distributed learning: developing a predictive model based on data from multiple hospitals without data leaving the hospital – a real life proof of concept. *Radiother Oncol* (2016) 121(3):459–67. doi:10.1016/j.radonc.2016.10.002
76. O'Connor AM, Stacey D, Entwistle V, Llewellyn-Thomas H, Rovner D, Holmes-Rovner M, et al. *Decision Aids for People Facing Health Treatment or Screening Decisions (Cochrane Review)*. Chichester, UK: John Wiley & Sons, Ltd, The Cochrane Library (2004).
77. Stacey D, Légaré F, Col NF, Bennett CL, Barry MJ, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* (2014) (1):CD001431. doi:10.1002/14651858.CD001431.pub4
78. O'Connor AM, Stacey D, Légaré F, et al. Coaching to support patients in making decisions. *BMJ* (2008) 336:228–9. doi:10.1136/bmj.39435.643275.BE
79. Barani IJ, Larson DA, Berger MS. Future directions in treatment of brain metastases. *Surg Neurol Int* (2013) 4(Suppl 4):220–30. doi:10.4103/2152-7806.111299
80. Lin NU. Targeted therapies in brain metastases. *Curr Treat Options Neurol* (2014) 16(1):276. doi:10.1007/s11940-013-0276-z
81. Lee SM, Lewanski CR, Counsell N, Ottensmeier C, Bates A, Patel N, et al. Randomized trial of erlotinib plus whole-brain radiotherapy for NSCLC patients with multiple brain metastases. *J Natl Cancer Inst* (2014) 106:dju151. doi:10.1093/jnci/dju151
82. Sperduto PW, Wang M, Robins HI, Schell MC, Werner-Wasik M, Komaki R, et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. *Int J Radiat Oncol Biol Phys* (2013) 85:1312–8. doi:10.1016/j.ijrobp.2012.11.042
83. Welsh JW, Komaki R, Amini A, Munsell MF, Unger W, Allen PK, et al. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer brain metastases. *J Clin Oncol* (2013) 31:895–902. doi:10.1200/JCO.2011.40.1174
84. Hendriks LE, Schoenmaekers J, Zindler JD, Eekers DB, Hoeben A, De Ruysscher DK, et al. Safety of cranial radiotherapy concurrent with tyrosine kinase inhibitors in non-small cell lung cancer patients: a systematic review. *Cancer Treat Rev* (2015) 41(7):634–45. doi:10.1016/j.ctrv.2015.05.005
85. Gan GN, Weickhardt AJ, Scheier B, Doebele RC, Gaspar LE, Kavanagh BD, et al. Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. *Int J Radiat Oncol Biol Phys* (2014) 88(4):892–8. doi:10.1016/j.ijrobp.2013.11.010
86. Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene addicted non-small cell lung cancer. *J Thorac Oncol* (2012) 7(12):1807–14. doi:10.1097/JTO.0b013e3182745948
87. Kondziolka D, Shin SM, Brunswick A, Kim I, Silverman JS. The biology of radiosurgery and its clinical applications for brain tumors. *Neuro Oncol* (2015) 17(1):29–44. doi:10.1093/neuonc/nou284
88. Reynders K, Illidge T, Siva S, Chang JY, De Ruysscher D. The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant. *Cancer Treat Rev* (2015) 41(6):503–10. doi:10.1016/j.ctrv.2015.03.011
89. Zegers CM, Rekers NH, Quaden DH, Lieuwes NG, Yaromina A, Germeraad WT, et al. Radiotherapy combined with the immunocytokine L19-IL2 provides long-lasting antitumor effects. *Clin Cancer Res* (2015) 21(5):1151–60. doi:10.1158/1078-0432.CCR-14-2676
90. Schoenfeld JD, Mahadevan A, Floyd SR, Dyer MA, Catalano PJ, Alexander BM, et al. Ipilmumab and cranial radiation in metastatic melanoma patients: a case series and review. *J Immunother Cancer* (2015) 3:50. doi:10.1186/s40425-015-0095-8

91. Knisely JP, Yu JB, Flanigan J, Sznol M, Kluger HM, Chiang VL. Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival. *J Neurosurg* (2012) 117(2):227–33. doi:10.3171/2012.5.JNS111929
92. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An absocap response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. *Cancer Immunol Res* (2013) 1(6):365–72. doi:10.1158/2326-6066.CIR-13-0115
93. Zindler JD, Schiffelers J, Lambin P, Hoffmann AL. Improved effectiveness of stereotactic radiosurgery in large brain metastases by individualized isotoxic dose prescription: an in silico study. *Strahlenther Onkol* (2018). doi:10.1007/s00066-018-1262-x
94. Zindler JD, Thomas CR Jr, Hahn SM, Hoffmann AL, Troost EGC, Lambin P, et al. Increasing the therapeutic ratio for stereotactic ablative radiotherapy by individualized isotoxic dose prescription. *J Natl Cancer Inst* (2016) 108(2):djv305. doi:10.1093/jnci/djv305
95. Kim YJ, Cho KH, Kim JY, Lim YK, Min HS, Lee SH, et al. Single-dose versus fractionated stereotactic radiotherapy for brain metastases. *Int J Radiat Oncol Biol Phys* (2011) 81:483–9. doi:10.1016/j.ijrobp.2010.05.033
96. Al-Omair A, Soliman H, Xu W, Karotki A, Mainprize T, Phan N, et al. Hypofractionated stereotactic radiotherapy in five daily fractions for post-operative surgical cavities in brain metastases patients with and without prior whole brain radiation. *Technol Cancer Res Treat* (2013) 12:493–9. doi:10.7785/tcrt.2012.500336
97. Hoffmann AL, Troost EG, Huizenga H, Kaanders JH, Bussink J. Individualized dose prescription for hypofractionation in advanced non-small-cell lung cancer radiotherapy: an in silico trial. *Int J Radiat Oncol Biol Phys* (2012) 83(5):1596–602. doi:10.1016/j.ijrobp.2011.10.032
98. van Baardwijk A, Bosmans G, Bentzen SM, Boersma L, Dekker A, Wanders R, et al. Radiation dose prescription for non-small-cell lung cancer according to normal tissue dose constraints: an in silico clinical trial. *Int J Radiat Oncol Biol Phys* (2008) 71(4):1103–10. doi:10.1016/j.ijrobp.2007.11.028

Conflict of Interest Statement: MAASTRO Clinic has a research agreement with Varian Medical Systems, Palo Alto, CA, USA. DR: Advisory board of Merck/Pfizer, Roche/Genentech, Bristol Myers Squibb, Celgene.

The reviewer SW and handling Editor declared their shared affiliation.

frontiers in Oncology

MINI REVIEW
published: 05 September 2018
doi: 10.3389/fonc.2018.00336

Brain Radiation Necrosis: Current Management With a Focus on Non-small Cell Lung Cancer Patients

*Gokoulakrichenane Loganadane[1], Frédéric Dhermain[2], Guillaume Louvel[2], Paul Kauv[3], Eric Deutsch[2,4,5], Cécile Le Péchoux[2] and Antonin Levy[2,4,5]**

[1] Department of Radiation Oncology, AP-HP, CHU Henri Mondor, University of Paris-Est, Créteil, France, [2] Department of Radiation Oncology, Gustave Roussy, Université Paris-Saclay, Villejuif, France, [3] Department of Neuroradiology, AP-HP, CHU Henri Mondor, University of Paris-Est, Créteil, France, [4] INSERM U1030, Molecular Radiotherapy, Gustave Roussy, Université Paris-Saclay, Villejuif, France, [5] Université Paris-Sud, Université Paris-Saclay, Le Kremlin-Bicêtre, France

As the prognosis of metastatic non-small cell lung cancer (NSCLC) patients is constantly improving with advances in systemic therapies (immune checkpoint blockers and new generation of targeted molecular compounds), more attention should be paid to the diagnosis and management of treatments-related long-term secondary effects. Brain metastases (BM) occur frequently in the natural history of NSCLC and stereotactic radiation therapy (SRT) is one of the main efficient local non-invasive therapeutic methods. However, SRT may have some disabling side effects. Brain radiation necrosis (RN) represents one of the main limiting toxicities, generally occurring from 6 months to several years after treatment. The diagnosis of RN itself may be quite challenging, as conventional imaging is frequently not able to differentiate RN from BM recurrence. Retrospective studies have suggested increased incidence rates of RN in NSCLC patients with oncogenic driver mutations [epidermal growth factor receptor (EGFR) mutated or anaplastic lymphoma kinase (ALK) positive] or receiving tyrosine kinase inhibitors. The risk of immune checkpoint inhibitors in contributing to RN remains controversial. Treatment modalities for RN have not been prospectively compared. Those include surveillance, corticosteroids, bevacizumab and local interventions (minimally invasive laser interstitial thermal ablation or surgery). The aim of this review is to describe and discuss possible RN management options in the light of the newly available literature, with a particular focus on NSCLC patients.

Keywords: complication, stereotactic radiotherapy, radiosurgery, vascular endothelial growth factor (VEGF), lung cancer, immunotherapy

OPEN ACCESS

Edited by:
Deepa S. Subramaniam, MedStar Georgetown University Hospital, United States

Reviewed by:
Meng Xu Welliver, The Ohio State University, United States
David Ball, Peter MacCallum Cancer Centre, Australia

***Correspondence:**
Antonin Levy
antonin.levy@gustaveroussy.fr

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *24 January 2018*
Accepted: *02 August 2018*
Published: *05 September 2018*

Citation:
Loganadane G, Dhermain F, Louvel G, Kauv P, Deutsch E, Le Péchoux C and Levy A (2018) Brain Radiation Necrosis: Current Management With a Focus on Non-small Cell Lung Cancer Patients. Front. Oncol. 8:336. doi: 10.3389/fonc.2018.00336

INTRODUCTION

Due to its incidence and specific brain tropism, non-small cell lung cancer (NSCLC) represents the most common source of brain metastases (BM) (1). Given advances in systemic treatments with prolonged overall survival and better imaging [brain magnetic resonance imaging (MRI)] detection, BM incidence rate is increasing. The prognosis of BM NSCLC patients with targetable mutations has improved (2, 3), and recently available immune checkpoint blockers (ICI) provide promising prolonged outcome in non-mutated patients (4, 5). Altogether, up to 22% of NSCLC patients may have BM at the time of initial diagnosis, and BM will develop in approximately half of

patients during their disease (6, 7). The BM rate may then be even higher in molecularly selected groups, such as epidermal growth factor receptor (EGFR) mutated or anaplastic lymphoma kinase (ALK) positive NSCLC patients (8).

The main focal treatment options for BM include surgery, stereotactic radiosurgery (SRT), and whole brain radiation therapy (WBRT). In the past decade, SRT has become the most frequently delivered focal treatment in patients with good prognosis criteria, and a limited number (<4) of BM (9–11). Frameless SRT delivers "ablative" dose, in a single or multiple course, as a definitive or postoperative treatment (12, 13). Focal high dose irradiation, as compared with neurosurgery, has the ability to treat inoperable sites, several lesions, and has the advantage to be less invasive. WBRT alone or in combination with SRT has been challenged in randomized trial, and its role is now limited to selected patients with multiple BMs ineligible for SRT (12, 14, 15). SRT is now often favored over WBRT due to a lower rate of adverse neurocognitive side effects. It has also been suggested that SRT without WBRT was feasible as the initial treatment for patients with 5–10 BMs (16). Local control at 1 year is generally high (88% in recent series), and SRT is generally considered as a cost-effective treatment (12, 17).

However, rare but potentially debilitating secondary late effects (3 months to several years post-irradiation) have been described after SRT. The most common delayed complication SRT is brain radiation necrosis (RN). RN may be particularly challenging in terms of diagnosis and treatment. Few studies have highlighted that RN may be more frequent in NSCLC patients harboring an oncogenic driver mutation. Within this review we aimed to describe and discuss the current knowledge regarding RN, with a special attention to NSCLC patients.

PATHOBIOLOGY

The physiopathology of radiation necrosis is still elusive and several hypotheses have been proposed. Implicated mechanisms in delayed RN include vascular injury, immune-mediated mechanisms and direct neural effects.

The vasculature damages are characterized by an increased permeability and a disruption of the blood brain barrier (BBB). High dose focal radiotherapy induces an endothelial cell loss through acid sphingomyelinase-dependent apoptosis (18) leading to vasogenic edema and ischemia. Tissue ischemia and vasogenic edema induce hypoxia, leading to reactive oxygen species production, affecting many cellular functions, and produce an increase of the hypoxia inducible factor (HIF-1α). HIF-1α subsequently upregulates the vascular endothelial growth factor (VEGF) secreted by astrocytes and endothelial cells. Immunohistochemistry of surgical samples of RN showed increased levels of VEGF in reactive astrocytes surrounding the core of necrotic tissue. VEGF exacerbates edema by increase of vascular permeability (19). These data indicate a crucial role of VEGF in the development and progression of RN and its inhibition could decrease the vascular permeability and therefore edema. Following these observation, anti-VEGF therapy has been one of the most tested compounds in the preclinical setting, and the sole pharmacological agent translating to clinical efficacy in the treatment of RN (cf. below, chapter on VEGF inhibition) (20, 21).

The immune system and peri-necrotic inflammation are also implicated in RN formation. Local infiltration of immune cells likely aggravates RN. VEGF induces the expression of adhesion proteins such as ICAM-1 on endothelial cells, and trigger pro-inflammatory cytokines [e.g.,: interleukin (IL)-1α, IL-6 and tumor necrosis alpha (TNF)-α] in animal models (18). Yoritsune et al. have also shown in human RN specimens, that astrocyte cells expressing the chemokine CXCL12 might attract CXCR4-expressing immune cells into the perinecrotic area, which in turn aggravates the local hypoxia (18, 22). The introduction of ICIs has significantly modified the therapeutic landscape of advanced NSCLC. As those agents are immunostimulatory, they could potentially exacerbate a preexisting inflammatory reaction in the context of RN.

Radiation induces white matter necrosis and oligodendrocytes demyelination. In the periphery of this necrotic zone, astrocytes, microglial cells and oligodendrocytes produce factors promoting cytokine release. A decrease of oligodendrocytes with incomplete neural stem cells or neuroblasts repopulation has been described (23, 24). Remyelinisation after human embryonic stem cell-derived oligodendrocyte progenitors transplantation is subsequently also assessed in preclinical models (25). Following these observations, many other agents than anti-VEGF have been tested in the experimental setting, but without reported favorable clinical effects (18).

CLINICAL SPECIFICITIES OF BRAIN RADIONECROSIS

The diagnosis of RN may be challenging. The main issue is to distinguish between RN and local recurrence (LR). When analyzing epidemiology or predictive factors of RN, one should keep in mind the possible subsequent bias related to diagnosis difficulties, as described below.

Epidemiology and Predictive Factors

Reported clinical rate of RN is approximately 10%, with or without prior surgery (**Table 1**) (32, 35, 37). However, the rate of asymptomatic radiographical RN is higher: up to 25–30% in some series (29, 31). The cumulative incidence of RN is increasing over time after SRT. As an example, in a series from the Memorial Sloan Kettering, the actuarial incidence of RN was 5.2% at 6 months, 17.2% at 12 months, and 34% at 24 months (31). In another Japanese series, 16 patients with MRI contrast enhancement >18 months following SRT were identified. With a median follow-up of 48.2 months, 12 adverse radiation events (suspected radiological or pathological confirmed RN) occurred in a median follow-up of 33.2 months (38).

Predictive risk factors associated with the development of RN cited in the literature link to BM, and treatment characteristics. Main accepted ones are a larger BM size, reirradiation, and higher total delivered radiotherapy dose (39, 40). Others criteria including BM features (location and deepness), radiotherapy

TABLE 1 | Literature overview.

Series	Date	N. of pts	N. of lesions	N. of NSCLC pts *N* (%)	NSCLC histology *N* (%)	Mutation status *N* (%)	median FU (mo.)	Incidence radiog. RN *N* (%)	Incidence symptom. RN *N* (%)	Risk factors RN	Trt RN	Efficacy
Kim (26)	1997	77	91	77 (100)	ADK: 36 (47), SCC: 17 (22), LCC:13 (17), unclassified: 11 (14)	NM	8	NM	4 (4) lesions	NM	Surgery ($n = 1$)	NM
Saitoh (27)	2010	49	78	78 (100)	ADK: 36 (74), other: 13 (26)	NM	17.4	12.2 pts	6 (12) pts	NM	Steroids ($n = 5$), surgery ($n = 1$)	NM
Matsuyama (28)	2013	299	573	299 (100)	ADK: 210 (70), SCC: 34 (11), LCC: 5 (2), other: 10 (3), unknown: 40 (13)	NM	8,2		6 (2) pts	NM	HBOT ($n = 6$)	Improvement in all
Minniti (29)	2014	135	171	65 (48)	NM	NM	11.4	12 (9) pts	5 (6) pts	V18, V21	NM	NM
Won (30)	2015	64	123	64 (100)	ADK: 52 (82), SCC: 6 (9), LC: 4 (6), poorly diff. 2 (3)	NM	13.9	4 (6) pts	4 (6.1) pts	NM	Steroids ($n = 3$), surgery ($n = 1$)	NM
Kohutek (31)	2015	327	583	116 (43)	NM	NM	17.2	70 (26) lesions	47 (17) lesions	Maximal diameter	NM	NM
Miller (32)	2016	1939	5747	836 (43)	ADK: 530 (27), SCC: 97 (5), mixed/unknown: 209 (11)	EGFR+/ALK-: 35 (2), EGFR-/ALK+: 11 (1), EGFR-/ALK-: 104 (5)	12	427 (7) lesions	231 (4) lesions	Maximal diameter, heterogenity index	NM	NM
Ishihara (33)	2016	53	217	53 (100)	ADK: 29 (55), SCC:12 (23), others: 12 (23)	NM	8	20 (12) lesion)	6 (2.3) lesions	NM	Steroids ($n = 6$)	NM
Kim (34)	2017	1650	2843	699 (42)	NM	NM	NM	222 (8) lesions	120 (4) lesions	Targeted therapies (univ.) (anti VEGFR, anti EGFR, anti Her2), maximal diameter, heterogenity index	NM	NM
Keller^{+} (35)	2017	181	189	82 (45)	NM	NM	15	35 (19) pts	12 (7) pts	Infratentorial location	Surgery ($n = 7$)	NM
Martin (36)	2018	480	NM	294 (61)	NM	NM	23	48 (10) pts	48 (10) pts	ICI	Steroids ($n = 18$)	NM

N. of, number of; NSCLC, non-small cell lung cancer; pts, patients; FU, follow-up; RN, radionecrosis; Trt, treatment; ADK, adenocarcinoma; SCC, squamous cell carcinoma; mo., months; symptom., symptomatic; radiog., radiographic; LC, large cell carcinoma; NM, not mentioned; diff, differentiated; univ., univariate; HBOT, hyperbaric oxygen therapy; ICI, immune checkpoint inhibitors; V18, V21, volume of brain receiving 18 and 21 Gy; Univ, univariate; heterogeneity index = maximum dose/prescribed dose.

$^{+}$Postop hypofractionated stereotactic radiation therapy only.

parameters (high dose per fraction, volume of irradiated normal brain parenchyma [generally total volume of irradiated brain at a dose 12Gy or more]), and the use concurrent systemic therapy (including ICI) have been evocated but not systematically described (29, 41–45). In any case, fractionation (i.e., to increase the number of radiotherapy fractions), or the use of formulas for optimal individual SRT dose based on BM volume is encouraged to prevent RN (46).

Some authors advocated that RN occurrence might be more frequent in NSCLC patients (**Table 1**). In a NSCLC cohort of 836 patients (2,276 lesions), Miller et al. showed that lung adenocarcinoma histology (1-year incidence of 5.9% vs. 3.1–3.9% for other histologies), and ALK (HR 6.36, $p < 0.001$), but not EGFR lesions had increased rates of RN. The 1-year cumulative incidences of RN among EGFR+, ALK+, and ALK/EGFR wild-type lesions were 7.6, 17.3, and 3.7%, respectively. EGFR or ALK inhibitors, as compared to conventional treatments, were not associated with the occurrence of RN (32). Another series included 699/1,650 (42%) NSCLC patients who underwent SRS, with or without WBRT. Patients also received systemic treatments, including targeted therapies. NSCLC patients who received concurrent EGFR tyrosine kinase inhibitors (TKIs) had an increased of 12-month cumulative incidence of RN (15.6 vs. 6%, $p = 0.04$) as compared to other patients. This was more specifically observed in patients that received SRT+WBRT ($p = 0.02$) as compared with those receiving SRT without WBRT ($p = 0.45$) (34). It should anyway be emphasized that BM NSCLC patients with an oncogenic driver mutation generally receive more intensive local treatment, partly explaining the excess risk of toxicity (47).

The risk of ICI in contributing to RN is controversial. Prospective data is lacking and most retrospective series included melanoma patients (48). A retrospective SRT series reported a higher incidence of symptomatic RN for patients who received ICI as compared to those who did not. Among 480 patients with BM (289 [61%] of 480 NSCLC) who had been treated with SRT, 115 (24%) received an anti-PD1 (nivolumab or pembrolizumab) or an anti-cytotoxic T-lymphocyte associated protein 4 (ipilimumab). Patients treated with ICI had a significantly higher rate of symptomatic RN after adjustment for tumor type (HR: 2.6; $p = 0.004$). The risk of neurotoxicity was however highest for melanoma patients treated with ipilimumab (36). Other retrospective studies focusing on the outcome of patients with NSCLC with BM who received both cranial RT and an ICI did not report RN increase (49–52). However, it should be emphasized that pseudoprogression, observed with ICI may be difficult to be distinguished from RN or brain progression (53).

Challenges in RN Diagnosis

Radiographic changes (grade I, approximately 50%) from the symptomatic RN (grade II–IV) should be distinguished. In the latter case, an intervention may be required whereas a simple surveillance is sufficient for the former case. The symptoms depend on the location of the lesion, but manifest usually with focal neurologic signs and symptoms related to cerebral edema.

The main difficulty is to distinguish between RN and LR. Histology is the gold standard for a confirmed diagnostic. A recent series of BM patients who had a brain biopsy for RN or LR suspicion on MRI included 11/34 (31%) lung cancers patients. Most biopsies (24/35; 69%) showed RN only, and time from SRT to biopsy was significantly longer (>9 months) in the RN group ($p = 0.004$) as LR seemed to occur earlier than RN (54). On the other hand, brain biopsies are invasive and may not be accessible for all patients. Histopathologic interpretation of brain specimens could also be challenging due to heterogeneity of the lesion mixing irradiated residual tumor cells of indeterminate viability with RN that can be missed by the sampling, and some authors suggested that excision of the lesion only is able to determine its true histological nature (55).

More often, non-invasive (clinical and radiographic) criteria are used, but the distinction between the RN and tumor can be particularly challenging. In most cases, conventional MRI shows a contrast-enhancing mass lesion with central necrosis and reactive edema contiguous to the site of the initial BM. "T1/T2 mismatch" (i.e., larger mass lesion seen in T2 sequence as compares with the T1 contrast-enhanced residual lesion) may favor RN (56). Dynamic (perfusion- and diffusion-weighted) MRI (**Figure 1**), and spectro-MRI (or magnetic resonance spectroscopy: MRS) have extensively been assessed to differentiate RN from LR. Dynamic susceptibility contrast-enhanced (DSCE) MR perfusion decreased parameters such as relative cerebral blood volume (rCBV) and relative peak height (rPH) or percentage of signal-intensity recovery (PSR) increase correlate with RN (57). On diffusion-weighted MR, decreased signal on diffusion-weighted imaging (DWI) and increased apparent diffusion coefficient (ADC) maps values reflect tumor control (58). MRS is an analytical technique that can be used to complement MRI in the characterization of tissue. Low lipid peak or high choline-to-creatine ratio and high choline-to-N-acetylaspartate (NAA) ratio on MR spectroscopy suggest tumor recurrence (59). Regarding positron emission tomography (PET), lower uptake with various radiotracers [fluorodeoxyglucose (FDG), methionine, fluorodihydroxyphénylalanine (Fdopa), fluoroéthyl-L-tyrosine, fluorocholine or thallium chloride-201 single-photon emission computed tomography (SPECT)] suggests necrosis. FDG has been the most commonly studied radiotracers but specificity is low, and the use of the couple dynamic MRI/PET is encouraged (60–64). Altogether, these imaging studies underline the difficulties to diagnose RN. Finally, the beneficial effect of steroids has also been incorporated to the diagnosis strategy, as depicted in the existing proposed algorithm to diagnose and treat RN (37, 64).

TREATMENT OPTIONS OF RADIATION NECROSIS

RN can generally be managed conservatively without intervention. In symptomatic patients, moderate dose of glucocorticoids may produce prompt symptomatic improvement by reducing cerebral edema. Corticosteroids can then be gradually tapered. If not sufficient, RN management consists of VEGF inhibitors or laser interstitial thermal therapy (LITT).

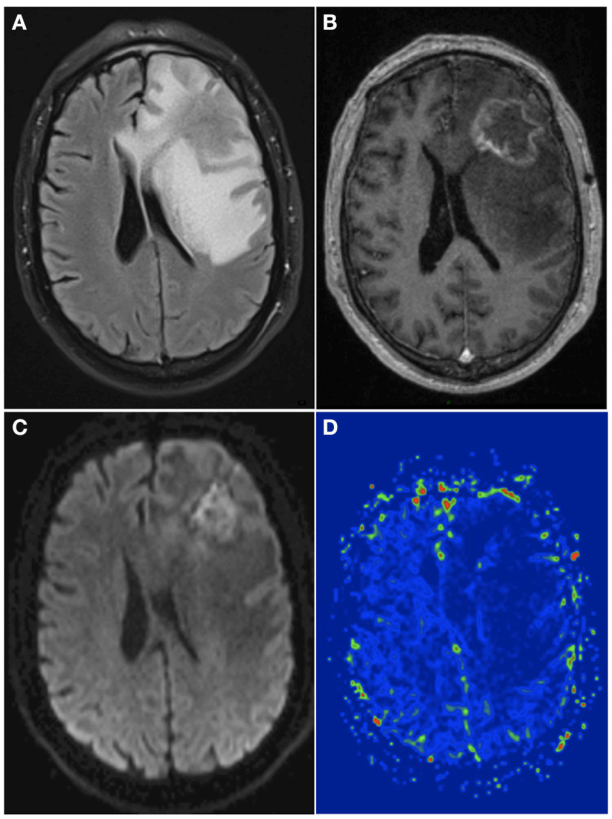


FIGURE 1 | A 66-year-old man with history of brain metastasis of non-mutated NSCLC and treated by surgical resection and postop SRT. **(A)** Axial T2w FLAIR sequence showed a hyperintense signal appeared around the treated region 13 months after SRT. **(B)** T1w contrast sequence showed an inhomogeneous ring enhancement within the treated region. **(C)** DWI showed a low signal within the enhanced margin, with a high ADC (not shown). **(D)** Dynamic susceptibility contrast-enhanced perfusion weighted imaging showed a low hyperperfusion with a relative cerebral blood volume of 1.5, suggesting absence of tumor recurrence. Surgical resection confirmed the diagnosis of cerebral RN.
NSCLC, non-small cell lung cancer; T2w, T2 weighted; T1w, T1 weighted; DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient; SRT, stereotactic radiotherapy; RN, radionecrosis.

Ultimately, surgery may be required in patients who are resistant to other treatments, and/or to obtain a definitive diagnosis if a LR is suspected. Alternative approaches have been reported in some cases (therapeutic anticoagulation, antiplatelet therapy, and hyperbaric oxygen therapy), but may not be currently recommended.

VEGF Inhibition

As previously described, VEGF plays a critical role in the RN pathogenesis. Bevacizumab is the most commonly used anti-VEGF monoclonal antibody, and was prospectively evaluated in only one small prospective trial in the context of RN. Fourteen patients were randomized 1:1 to receive four cycles of intravenous (IV) bevacizumab at a dose of 7.5 mg/kg every 3 weeks vs. IV saline placebo. The primary endpoint was the change in edema volume on MRI (T2 FLAIR images) from baseline to the first evaluation at 6 weeks. Of note, there were no BM patients included but only prior irradiated primary central nervous system or head and neck tumors. Crossover was permitted, and the sample size was estimated to 16 patients. The 7 patients in the bevacizumab arm had a decreased volume of FLAIR edema with clinical amelioration whereas placebo arm patients demonstrated an increase in the volume of T2 weighted FLAIR edema (−59 vs. +14%, respectively; $p = 0.01$). Similarly, in patients receiving bevacizumab, a median decrease in the T1 weighted gadolinium enhancement (−63 vs. +17%; $p = 0.006$), and of the endothelial transfer constant (K-trans; a measure of capillary permeability in DCE MRI; −99 vs. +49%; $p = 0.02$) were reported. Six of 11 patients receiving bevacizumab had adverse events, with 3 serious adverse events: one aspiration pneumonitis, one pulmonary embolism secondary to deep vein thrombosis and one superior sagittal sinus thrombosis (65). Other retrospective series also reported a clinical benefit of bevacizumab, including reduction in steroid requirement (66–68).

Those promising results should nevertheless be tempered. One should not forget that bevacizumab has a certain activity on BM in NSCLC patients, especially when we know that LR and RN can be associated in a significant proportion of cases (69). Development of RN was also observed among 24/271 (9%) patients receiving SRT with concurrent bevacizumab (31). Worsening of symptoms may occur, and RN recurrences after bevacizumab withdrawal have been described (70). In a series including a majority (11/14; 79%) of BM from primary lung cancer, clinical improvement was seen in 13/14 cases (92.9%), but the 10/13 responsive patients (76.9%) exhibited a recurrence of brain necrosis after bevacizumab discontinuation (71). Bevacizumab is a promising treatment option for RN, but needs to be validated in larger prospective studies.

Invasive Interventions

LITT is a stereotactic-guided minimally invasive ablative technique that generates high temperature, resulting in tissue coagulation necrosis, angiogenesis eradication, and cellular apoptosis. The use of LITT-guided MRI allows to control accurately the delivery, and to spare the surrounding healthy tissues. LITT has been used in several situations in neurology, including RN. Most of the available data come from small retrospective studies. Rao et al. reported the results of MRI-guided LITT for 12/15 (80%) NSCLC patients with suspected RN or LR after SRT for BM. On average, the lesion size measured 3.7 cm. Authors were able to perform 3.3 ablations per treatment, in a total ablation time of 7.5 min. The local control was high (76%) at a median follow-up of 6 months, with two patients experiencing recurrence at 6 and 18 weeks after the procedure (72). The largest series, from the University of Arizona, consisted of 25 patients with suspected RN, occurring after treatment for 18 primary brain tumors and 7 BM. Progression free and overall survival rates in patients with BM were 11.4 and 55.9 months, respectively. The quality of life analysis showed an improvement on mental health and vitality at 12 months (73). One of the advantages of this technique is the possibility to perform a biopsy prior to treatment to confirm the diagnosis of RN. Moreover,

LITT is a reasonable option in case of LR, considering the efficacy and secondary effects of other treatment modalities (i.e., reirradiation).

Surgery allows pathological confirmation, and the rapid relief from mass effect and brain edema. In a series of 15 patients with RN, the surgery improved the neurological symptoms in 14 cases. Pure RN was histologically determined for 50% of operated patients. In the algorithm proposed by the authors, patients with significant increased edema volume with mass effect, or becoming symptomatic despite steroids trial should undergo surgery (37). Another surgical series for patients with RN reported that 9 had a steroid dose reduction, 4 improved their performance status score (4 stable and 3 deterioration), and neurologic deficits were ameliorated in 4 (4 stable). Nonetheless, 2 worsened their neurologic deficit and one patient developed a new neurologic deficit after surgery. This study highlights the potential morbidity of surgical resections of RN, and suggests reserving surgery for symptomatic patients in whom medical treatment has failed (74).

PERSPECTIVES AND CONCLUDING REMARKS

Newer generation TKIs will possibly modify the therapeutic sequences in advanced mutated NSCLC patients. In retrospective studies, the deferral of radiation therapy (SRT or WBRT) was usually associated with inferior survival rates in oncogenic driver mutation patients (75, 76). However newer generation TKI such as first-line alectinib (*ALK*+ patients) and osimertinib (*EGFR* mutated patients) provided superior intracranial control compared to standard of care (2, 3). This, with the increased use of ICI, may then possibly lead to a decreased use of SRT, and subsequently change the RN rate occurrences in NSCLC patients. Moreover, NSCLC mutated patients have potentially an increased incidence of RN due to tumor biology or the use of concurrent TKI, but this remains to be confirmed.

An ongoing randomized phase II trial (BeSt Trial;Alliance A221208; NCT02490878) from the MD Anderson is investigating whether the addition of bevacizumab (10 mg/kg IV at day one and 15 for four cycles) to standard corticosteroid therapy could result in greater improvement of RN symptoms (primary endpoint: patient-reported outcome of RN up to 8 weeks). One hundred thirty patients should be included and eligibility criteria encompass perfusion-imaging parameters of RN susceptibility (high PSR and low rCBV). Another multicenter prospective French trial (CV-METANEC;NCT02636634) has recently been completed. It compared PET-FET (1-Fluoro-Ethyl-Tyrosine) and magnetic resonance spectroscopy to histological results in patients receiving brain biopsy for active persistent and increased brain lesion 4 months after SRT. The results of such studies should help to differentiate RN from LR after SRT, and help to guide clinicians to select an appropriate treatment for patients.

AUTHOR CONTRIBUTIONS

GL and AL designed and outlined structure and contents of the review. All authors contributed to the literature analysis, interpretation, and writing of the review.

REFERENCES

1. Davis FG, Dolecek TA, McCarthy BJ, Villano JL. Toward determining the lifetime occurrence of metastatic brain tumors estimated from 2007 United States cancer incidence data. *Neuro Oncol.* (2012) 4:1171–7. doi: 10.1093/neuonc/nos152
2. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. ALEX trial investigators. alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med.* (2017) 377:829–38 doi: 10.1056/NEJMoa1704795
3. Mok T, Ahn MJ, Han J, Han JY, Katakami N, Kim HR, et al. CNS response to osimertinib in patients (pts) with T790M-positive advanced NSCLC: data from a randomized phase III trial (AURA3). *J Clin Oncol.* (2017) 35(Suppl. abstr 9005):9005. doi: 10.1200/JCO.2017.35.15_suppl.9005
4. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol.* (2016) 17:976–83. doi: 10.1016/S1470-2045(16)30053-5
5. Levy A, Massard C, Soria JC, Deutsch E. Concurrent irradiation with the anti-programmed cell death ligand-1 immune checkpoint blocker durvalumab: single centre subset analysis from a phase 1/2 trial. *Eur J Cancer.* (2016) 68:156–62. doi: 10.1016/j.ejca.2016.09.013
6. Rangachari D, Yamaguchi N, VanderLaan PA, Folch E, Mahadevan A, Floyd SR, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer* (2015) 88:108–11. doi: 10.1016/j.lungcan.2015.01.020
7. Sahgal A, Aoyama H, Kocher M, Neupane B, Collette S, Tago M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys.* (2015) 91:710–17. doi: 10.1016/j.ijrobp.2014.10.024
8. Brambilla E, Travis WD. Lung cancer. In: Stewart BW, Wild CP, editors. *World Cancer Report*. Lyon: World Health Organization (2014)
9. Chargari C, Magne N, Guy JB, Rancoule C, Levy A, Goodman KA, et al. Optimize and refine therapeutic index in radiation therapy: overview of a century. *Cancer Treat Rev.* (2016) 45:58–67. doi: 10.1016/j.ctrv.2016.03.001
10. Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, et al. Estimating survival in patients with lung cancer and brain metastases: an update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). *J Am Med Assoc Oncol.* (2017) 3:827–831. doi: 10.1001/jamaoncol.2016.3834
11. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non- small-cell lung cancer: ESMO clinical practice guide- lines for diagnosis, treatment and follow-up. *Ann Oncol.* (2016) 27:v1–v27. doi: 10.1093/annonc/mdw326
12. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radi- osurgery alone vs radiosurgery with whole brain radia- tion therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *J Am Med Assoc.* (2016) 316:401–09. doi: 10.1001/jama.2016.9839
13. Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol.* (2017) 18:1040−8. doi: 10.1016/S1470-2045(17)30414-X

14. Loganadane G, Hendriks L, Le Péchoux C, Levy A. The current role of whole brain radiation therapy in non-small cell lung cancer patients. *J Thorac Oncol*. (2017) 12:1467–77. doi: 10.1016/j.jtho.2017.07.006
15. Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet* (2016) 388:2004–14. doi: 10.1016/S0140-6736(16)30825-X
16. Yamamoto M, Serizawa T, Shuto T, Higuchi Y, Sato Y4 Kawagishi J, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol*. (2014) 15:387–95. doi: 10.1016/S1470-2045(14)70061-0
17. Lester-Coll NH, Dosoretz AP, Magnuson WJ, Laurans MS, Chiang VL, Yu JB. Cost-effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for up to 10 brain metastases. *J Neurosurg*. (2016) 125:18–25. doi: 10.3171/2016.7.GKS161499
18. Soussain C, Ricard D, Fike JR, Mazeron JJ, Psimaras D, Delattre JY. CNS complications of radiotherapy and chemotherapy. *Lancet*. (2009) 374:1639–51. doi: 10.1016/S0140-6736(09)61299-X
19. Schmidt RE, Ackerman JJ, Garbow JR. Anti-VEGF antibodies mitigate the development of radiation necrosis in mouse brain. *Clin Cancer Res*. (2014) 20:2695–702. doi: 10.1158/1078-0432.CCR-13-1941
20. Nordal RA, Nagy A, Pintilie M, Wong CS, et al. Hypoxia and hypoxia-inducible factor-1 target genes in central nervous system radiation injury: a role for vascular endothelial growth factor. *Clin Cancer Res*. (2004) 10:3342–53. doi: 10.1158/1078-0432.CCR-03-0426
21. Perez-Torres CJ, Yuan L, Schmidt RE, Rich KM, Drzymala RE, Hallahan DE, et al. Specificity of vascular endothelial growth factor treatment for radiation necrosis. *Radiother Oncol*. (2015) 117:382–5. doi: 10.1016/j.radonc.2015.09.004
22. Yoritsune E, Furuse M, Kuwabara H, Miyata T, Nonoguchi N, Kawabata S, et al. Inflammation as well as angiogenesis may participate in the pathophysiology of brain radiation necrosis. *J Radiat Res*. (2014) 55:803–11. doi: 10.1093/jrr/rru017
23. Achanta P, Capilla-Gonzalez V, Purger D, Reyes J, Sailor K, Song H, et al. Subventricular zone localized irradiation affects the generation of proliferating neural precursor cells and the migration of neuroblasts. *Stem Cells*. (2012) 30:2548–60. doi: 10.1002/stem.1214
24. Panagiotakos G, Alshamy G, Chan B, Abrams R, Greenberg E, Saxena A, et al. Long-term impact of radiation on the stem cell and oligodendrocyte precursors in the brain. *PLoS ONE* (2007) 2:e588. doi: 10.1371/journal.pone.0000588
25. Piao J, Major T, Auyeung G, Policarpio E, Menon J, Droms L, et al. Human embryonic stem cell-derived oligodendrocyte progenitors remyelinate the brain and rescue behavioral deficits following radiation. *Cell Stem Cell*. (2015) 16:198–210. doi: 10.1016/j.stem.2015.01.004
26. Kim YS, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for patients with nonsmall cell lung carcinoma metastatic to the brain. *Cancer* (1997) 80:2075–83.
27. Saitoh J, Saito Y, Kazumoto T, Kudo S, Ichikawa A, Hayase N, et al. Therapeutic effect of linac-based stereotactic radiotherapy with a micro-multileaf collimator for the treatment of patients with brain metastases from lung cancer. *Jpn J Clin Oncol*. (2010) 40:119–24. doi: 10.1093/jjco/hyp128
28. Matsuyama T, Kogo K, Oya N. Clinical outcomes of biological effective dose-based fractionated stereotactic radiation therapy for metastatic brain tumors from non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. (2013) 85:984–90. doi: 10.1016/j.ijrobp.2012.09.008
29. Minniti G, Clarke E, Lanzetta G, Osti MF, Trasimeni G, Bozzao A, et al. Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. *Radiat Oncol*. (2011) 6:48. doi: 10.1186/1748-717X-6-48
30. Won YK, Lee JY, Kang YN, Jang JS, Kang JH, Jung SL, et al. Stereotactic radiosurgery for brain metastasis in non-small cell lung cancer. *Radiat Oncol J*. (2015) 33:207–16. doi: 10.3857/roj.2015.33.3.207
31. Kohutek ZA, Yamada Y, Chan TA, Brennan CW, Tabar V, Gutin PH, et al. Long-term risk of radionecrosis and imaging changes after stereotactic radiosurgery for brain metastases. *J Neurooncol*. (2015) 125:149–156. doi: 10.1007/s11060-015-1881-3
32. Miller JA, Bennett EE, Xiao R, Kotecha R, Chao ST, Vogelbaum MA, et al. Association between radiation necrosis and tumor biology after stereotactic radiosurgery for brain metastasis. *Int J Radiat Oncol Biol Phys*. (2016) 96:1060–69. doi: 10.1016/j.ijrobp.2016.08.039
33. Ishihara T, Yamada K, Harada A, Isogai K, Tonosaki Y, Demizu Y, et al. Hypofractionated stereotactic radiotherapy for brain metastases from lung cancer: evaluation of indications and predictors of local control. *Strahlenther Onkol*. (2016) 192:386–93. doi: 10.1007/s00066-016-0963-2
34. Kim JM, Miller JA, Kotecha R, Xiao R, Juloori A, Ward MC, et al. The risk of radiation necrosis following stereotactic radiosurgery with concurrent systemic therapies. *J Neurooncol*. (2017) 133:357–368. doi: 10.1007/s11060-017-2442-8
35. Keller A, Doré M, Cebula H, Thillays F, Proust F, Darié I, et al. Hypofractionated stereotactic radiation therapy to the resection bed for intracranial metastases. *Int J Radiat Oncol Biol Phys*. (2017) 99:1179–89. doi: 10.1016/j.ijrobp.2017.08.014
36. Martin AM, Cagney DN, Catalano PJ, Alexander BM, Redig AJ, Schoenfeld JD, et al. Immunotherapy and symptomatic radiation necrosis in patients with brain metastases treated with stereotactic radiation. *J Am Med Assoc Oncol*. (2018) 4:1123–24. doi: 10.1001/jamaoncol.2017.3993
37. Telera S, Fabi A, Pace A, Vidiri A, Anelli V, Carapella CM, et al. Radionecrosis induced by stereotactic radiosurgery of brain metastases: results of surgery and outcome of disease. *J Neurooncol*. (2013) 113:313–25. doi: 10.1007/s11060-013-1120-8
38. Fujimoto D, von Eyben R, Gibbs IC, Chang SD, Li G, Harsh GR, et al. Imaging changes over 18 months following stereotactic radiosurgery for brain metastases: both late radiation necrosis and tumor progression can occur. *J Neurooncol*. (2018) 136:207–12. doi: 10.1007/s11060-017-2647-x
39. Sneed PK, Mendez J, Vemer-van den Hoek JGM, et al. Adverse radi- ation effect after stereotactic radiosurgery for brain metastases: Incidence, time course, and risk factors. *J Neurosurg*. (2015) 123:373–86. doi: 10.3171/2014.10.JNS141610
40. Korytko T, Radivoyevitch T, Colussi V, Wessels BW, Pillai K, Maciunas RJ, et al. 12 Gy gamma knife radiosurgical volume is a predictor for radiation necrosis in non-AVM intracranial tumors. *Int J Radiat Oncol Biol Phys*. (2006) 64:419–24. doi: 10.1016/j.ijrobp.2005.07.980
41. Le Rhun E, Dhermain F, Vogin G, Reyns N, Metellus P. Radionecrosis after stereotactic radiotherapy for brain metastases. *Expert Rev Neurother*. (2016) 16:903–14. doi: 10.1080/14737175.2016.1184572
42. Ruben JD, Dally M, Bailey M, Smith R, McLean CA, Fedele P. Cerebral radiation necrosis: incidence, outcomes, and risk factors with emphasis on radiation parameters and chemotherapy. *Int J Radiat Oncol Biol Phys*. (2006) 65:499–508. doi: 10.1016/j.ijrobp.2005.12.002
43. Blonigen BJ, Steinmetz RD, Levin L, Lamba MA, Warnick RE, Breneman JC. Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* (2010) 7:996–1001. doi: 10.1016/j.ijrobp.2009.06.006
44. Colaco RJ, Martin P, Kluger HM, Yu JB, Chiang VL. Does immunotherapy increase the rate of radiation necrosis after radiosurgical treatment of brain metastases? *J Neurosurg* (2016) 125:17–23. doi: 10.3171/2015.6.JNS142763
45. Fang P, Jiang W, Allen P, Glitza I, Guha N, Hwu P, et al. Radiation necrosis with stereotactic radiosurgery combined with CTLA-4 blockade and PD-1 inhibition for treatment of intracranial disease in metastatic melanoma. *J Neurooncol*. (2017) 133:595–602. doi: 10.1007/s11060-017-2470-4
46. Bohoudi O, Bruynzeel AM, Lagerwaard FJ, Cuijpers JP, Slotman BJ, Palacios MA. Isotoxic radiosurgery planning for brain metastases. *Radiother Oncol*. (2016) 120:253–7. doi: 10.1016/j.radonc.2016.05.001
47. Levy A, Faivre-Finn C, Hasan B, De Maio E, Berghoff AS, Girard N, et al. Diversity of brain metastases screening and management in non-small cell lung cancer in Europe: results of the european organisation for research and treatment of cancer lung cancer group survey. *Eur J Cancer* (2018) 93:37–46. doi: 10.1016/j.ejca.2018.01.067
48. Hwang WL, Pike LRG, Royce TJ, Mahal BA, Loeffler JS. Safety of combining radiotherapy with immune-checkpoint inhibition. *Nat Rev Clin Oncol*. (2018) 15:477–94. doi: 10.1038/s41571-018-0046-7
49. Hubbeling HG, Schapira BA, Horick NK, Goodwin KEH, Lin JJ, Oh KS, et al. Safety of combined PD-1 pathway inhibition and intracranial radiation

therapy in non-small cell lung cancer. *J Thorac Oncol*. (2018) 13:553–61. doi: 10.1016/j.jtho.2018.01.012
50. Ahmed KA, Kim S, Arrington J, Naghavi AO, Dilling TJ, Creelan BC, et al. Outcomes targeting the PD-1/PD-L1 axis in conjunction with stereotactic radiation for patients with non-small cell lung cancer brain metastases. *J Neurooncol*. (2017) 133:331–38. doi: 10.1007/s11060-017-2437-5
51. Pike LRG, Bang A, Ott P, Balboni T, Taylor A, Catalano P, et al. Radiation and PD-1 inhibition: favorable outcomes after brain-directed radiation. *Radiother Oncol*. (2017) 124:98–103. doi: 10.1016/j.radonc.2017.06.006
52. Chen L, Douglass J, Kleinberg L, Ye X, Marciscano AE, Forde PM, et al. Concurrent immune checkpoint inhibitors and stereotactic radiosurgery for brain metastases in non-small cell lung cancer, melanoma, and renal cell carcinoma. *Int J Radiat Oncol Biol Phys*. (2018) 100:916–25. doi: 10.1016/j.ijrobp.2017.11.041
53. Levy A, Hendriks LE, Faivre-Finn C. Are we ready to safely combine anti-PD-1/PD-L1 with cranial irradiation in non-small cell lung cancer patients? *J Thorac Oncol*. (2018) 13:475–77. doi: 10.1016/j.jtho.2018.02.019
54. Narloch JL, Farber SH, Sammons S, McSherry F, Herndon JE, Hoang JK, et al. Biopsy of enlarging lesions after stereotactic radiosurgery for brain metastases frequently reveals radiation necrosis. *Neuro Oncol*. (2017) 19:1391–97. doi: 10.1093/neuonc/nox090
55. Nath SK, Sheridan AD, Rauch PJ, Yu JB, Minja FJ, Vortmeyer AO, et al. Significance of histology in determining management of lesions regrowing after radiosurgery. *J Neurooncol*. (2014) 117:303–10. doi: 10.1007/s11060-014-1389-2
56. Leeman JE, Clump DA, Flickinger JC, Mintz AH, Burton SA, Heron DE. Extent of perilesional edema differentiates radionecrosis from tumor recurrence following stereotactic radiosurgery for brain metastases. *Neuro Oncol* (2013) 15:1732–8. doi: 10.1093/neuonc/not130
57. Barajas RF, Chang JS, Sneed PK, Segal MR, McDermott MW, Cha S. Distinguishing recurrent intra-axial metastatic tumor from radiation necrosis following gamma knife radiosurgery using dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. *AJNR Am J Neuroradiol*. (2009) 30:367–72. doi: 10.3174/ajnr.A1362
58. Lee CC, Wintermark M, Xu Z, Yen CP, Schlesinger D, Sheehan JP. Application of diffusion-weighted magnetic resonance imaging to predict the intracranial metastatic tumor response to gamma knife radiosurgery. *J Neurooncol*. (2014) 118:351–61. doi: 10.1007/s11060-014-1439-9
59. Hollingworth W, Medina LS, Lenkinski RE, Shibata DK, Bernal B, Zurakowski D, et al. A systematic literature review of magnetic resonance spectro- scopy for the characterization of brain tumors. *AJNR Am J Neuroradiol* (2006) 27:1404–11.
60. Tomura N, Kokubun M, Saginoya T, Mizuno Y, Kikuchi Y. Differentiation between treatment-induced necrosis and recurrent tumors in patients with metastatic brain tumors: comparison among (11)C-Methionine-PET, FDG-PET, MR permeability imaging, and MRI-ADC-preliminary results. *AJNR Am J Neuroradiol*. (2017) 38:1520–27. doi: 10.3174/ajnr.A5252
61. Lohmann P, Stoffels G, Ceccon G, Rapp M, Sabel M, Filss CP, et al. Radiation injury vs. recurrent brain metastasis: combining textural feature radiomics analysis and standard parameters may increase (18)F-FET PET accuracy without dynamic scans. *Eur Radiol*. (2017) 27:2916–27. doi: 10.1007/s00330-016-4638-2
62. Ceccon G, Lohmann P, Stoffels G, Judov N, Filss CP, Rapp M, et al. Dynamic O-(2-18F-fluoroethyl)-L-tyrosine positron emission tomography differentiates brain metastasis recurrence from radiation injury after radiotherapy. *Neuro Oncol*. (2017) 19:281–88. doi: 10.1093/neuonc/now149
63. Hatzoglou V, Yang TJ, Omuro A, Gavrilovic I, Ulaner G, Rubel J, et al. A prospective trial of dynamic contrast-enhanced MRI perfusion and fluorine-18 FDG PET-CT in differentiating brain tumor progression from radiation injury after cranial irradiation. *Neuro Oncol*. (2016) 18:873–80. doi: 10.1093/neuonc/nov301
64. Chao ST, Ahluwalia MS, Barnett GH, Stevens GH, Murphy ES, Stockham AL, et al. Challenges with the diagnosis and treatment of cerebral radiation necrosis. *Int J Radiat Oncol Biol Phys*. (2013) 87:449–57. doi: 10.1016/j.ijrobp.2013.05.015
65. Levin VA, Bidaut L, Hou P, Kumar AJ, Wefel JS, Bekele BN, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiat Oncol Biol Phys*. (2011) 79:1487–95. doi: 10.1016/j.ijrobp.2009.12.061
66. Boothe D, Young R, Yamada Y, Prager A, Chan T, Beal K. Bevacizumab as a treatment for radiation necrosis of brain metastases post stereotactic radiosurgery. *Neuro Oncol*. (2013) 15:1257–63. doi: 10.1093/neuonc/not085
67. Remon J, Le Péchoux C, Caramella C, Dhermain F, Louvel G, Soria JC, et al. Brain radionecrosis treated with bevacizumab in a patient with resected squamous cell carcinoma of the lung. *J Thorac Oncol*. (2017) 12:e1–e3. doi: 10.1016/j.jtho.2016.08.124
68. Tye K, Engelhard HH, Slavin KV, Nicholas MK, Chmura SJ, Kwok Y, et al. An analysis of radiation necrosis of the central nervous system treated with bevacizumab. *J Neurooncol*. (2014) 117:321–7. doi: 10.1007/s11060-014-1391-8
69. Besse B, Le Moulec S, Mazières J, Senellart H, Barlesi F, Chouaid C, et al. Bevacizumab in patients with nonsquamous non-small cell lung cancer and asymptomatic, untreated brain metastases (BRAIN): a nonrandomized, phase ii study. *Clin Cancer Res*. (2015) 21:1896–903. doi: 10.1158/1078-0432.CCR-14-2082
70. Jeyaretna DS, Curry WT Jr, Batchelor TT, Stemmer-Rachamimov A, Plotkin SR. Exacerbation of cerebral radiation necrosis by bevacizumab. *J Clin Oncol*. (2011) 29:e159–62. doi: 10.1200/JCO.2010.31.4815
71. Zhuang H, Yuan X, Zheng Y, Li X, Chang JY, Wang J, et al. A study on the evaluation method and recent clinical efficacy of bevacizumab on the treatment of radiation cerebral necrosis. *Sci Rep*. (2016) 6:24364. doi: 10.1038/srep24364
72. Rao MS, Hargreaves EL, Khan AJ, Haffty BG, Danish SF. Magnetic resonance-guided laser ablation improves local control for postradiosurgery recurrence and/or radiation necrosis. *Neurosurgery*. (2014) 74:658–67. doi: 10.1227/NEU.0000000000000332
73. Smith CJ, Myers CS, Chapple KM, Smith KA. Long-term follow-up of 25 cases of biopsy-proven radiation necrosis or post-radiation treatment effect treated with magnetic resonance-guided laser interstitial thermal therapy. *Neurosurgery* (2016) 79 (Suppl. 1):S59-S72. doi: 10.1227/NEU.0000000000001438
74. McPherson CM, Warnick RE. Results of contemporary surgical management of radiation necrosis using frameless stereotaxis and intraoperative magnetic resonance imaging. *J Neurooncol*. (2004) 68:41–7 doi: 10.1023/B:NEON.0000024744.16031.e9
75. Magnuson WJ, Lester-Coll NH, Wu AJ, Yang TJ, Lockney NA, Gerber NK, et al. Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. *J Clin Oncol*. (2017) 35:1070–77. doi: 10.1200/JCO.2016.69.7144
76. Johung KL, Yeh N, Desai NB, Williams TM, Lautenschlaeger T, Arvold ND, et al. Extended survival and prognostic factors for patients with ALK-rearranged non-small-cell lung cancer and brain metastasis. *J Clin Oncol*. (2016) 34:123–9. doi: 10.1200/JCO.2015.62.0138

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

REVIEW
published: 03 July 2018
doi: 10.3389/fonc.2018.00208

Management of Brain Metastases in Epidermal Growth Factor Receptor Mutant Non-Small-Cell Lung Cancer

*William J. Kelly, Neil J. Shah and Deepa S. Subramaniam**

Division of Hematology-Oncology, Georgetown University, Washington, DC, United States

Lung cancer remains a leading cause of mortality with 1.69 million deaths worldwide. Activating mutations in epidermal growth factor receptor (EGFR), predominantly exon 19 deletions and exon 21 L858R mutations, are known oncogenic drivers identified in 20–40% of non-small-cell lung cancers (NSCLC). 70% of EGFR-mutant NSCLC patients develop brain metastases (BM), compared to 38% in EGFR wild-type patients. First-generation tyrosine kinase inhibitors (TKIs), such as erlotinib and gefitinib have proven to be superior to chemotherapy in the front-line treatment of EGFR-mutant NSCLC, as has afatinib, a second-generation TKI. The most common acquired resistance mechanism is the development of a gatekeeper mutation in exon 20 T790M. Osimertinib has emerged as a third-generation EGFR TKI with proven activity in the front-line setting as well as in patients with a T790M acquired resistance mutation with remarkable CNS activity. As long-term survival outcomes in EGFR-mutant NSCLC continue to improve, the burden of BM becomes a greater challenge. Here, we review the literature related to the management of BM in EGFR-mutant NSCLC including the role of the three generations of EGFR TKIs, immunotherapy, and brain radiation.

Keywords: epidermal growth factor receptor, non-small-cell lung cancer, brain metastases, targeted therapy, osimertinib

OPEN ACCESS

Edited by:
Miguel Angel Villalona, Baptist Health South Florida, United States

Reviewed by:
Joel W. Neal, Stanford University, United States
Rabab Mohamed Gaafar, Cairo University, Egypt
Gregory Alan Otterson, The Ohio State University, United States

***Correspondence:**
Deepa S. Subramaniam
dss26@gunet.georgetown.edu

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *01 February 2018*
Accepted: *22 May 2018*
Published: *03 July 2018*

Citation:
Kelly WJ, Shah NJ and Subramaniam DS (2018) Management of Brain Metastases in Epidermal Growth Factor Receptor Mutant Non-Small-Cell Lung Cancer. Front. Oncol. 8:208. doi: 10.3389/fonc.2018.00208

OVERVIEW OF BRAIN METASTASES IN EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTANT NON-SMALL-CELL LUNG CANCER (NSCLC)

Epidemiology and Molecular Alterations in EGFR Mutant NSCLC

Lung cancer remains a leading cause of mortality with 1.69 million deaths worldwide (1). An estimated 234,030 new cases will occur in the United States in 2018 with a median age at diagnosis of 70 and 64% predominance for males (2). Approximately 84% of these lung cancers are non-small cell lung cancers (NSCLC) (3). NSCLC has traditionally been classified by histology (adenocarcinoma, squamous, and large cell) but the classification paradigm has evolved to incorporate molecular subtypes that guide treatment decision making.

Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor which activates Jak, PI3K, ROS, and RAS pathways leading to cell survival (4, 5). The most common activating mutations are exon 19 deletions or point mutations in exon 21 *via* Leu858Arg (L858R) (6, 7). Reports of the prevalence of EGFR mutations in NSCLC ranges from 46.7% in the East Asian population as reported by Liu et al. (8) to 38.4% (range 36.5–40.3%) in China and 14.1% (range 12.7–15.5%) in Europe seen in Zhang et al. (9) and 22% in African Americans enrolled in the Lung Cancer Mutation Consortium (10). The landmark BR21 trial demonstrated the survival advantage in chemo-refractory NSCLC with the use erlotinib, a first-generation EGFR inhibitor (11).

Subsequently, three additional drugs (gefitinib, afatinib, and osimertinib) have now been approved to treat newly diagnosed EGFR-mutated advanced NSCLC. Among NSCLC patients who progress on first- or second-generation EGFR TKI therapy, most do so through a unique gatekeeper mutation, viz. the exon 20 point mutation Thr790Met (T790M) in the ATP-binding site of EGFR (12). Incidence of the T790 gatekeeper mutation has been reported to be between 49 and 63% (13, 14). The methionine side chain acts as a "gatekeeper" residue causing steric hindrance thus decreasing hydrophilicity and preventing tyrosine kinase binding (15). The T790M mutation also increases ATP affinity (16). Other rare mechanisms of TKI resistance include MET amplifications or mutations, HER2 amplifications, and rarely BRAF mutations (12). Additionally, transformation to small cell histology is another possible mechanism of EGFR TKI resistance (13).

Prevalence of Brain Metastases (BM) in EGFR-Mutant NSCLC

Among NSCLC patients, those with BM have an increased frequency of EGFR mutations than those without brain metastasis and conversely, among EGFR mutant NSCLC patients the incidence of BM (70%) greatly surpasses the incidence of BM in wild-type (wt) EGFR NSCLC patients (38%) (17). Approximately, one-third of EGFR-mutant NSCLC patients develop central nervous system (CNS) progression during the course of their illness (18). Among Asian populations, the prevalence of EGFR mutations in NSCLC BM ranges from 39 to 63% (19, 20). Among North American and European populations this ranges from 2 to 40% (21, 22). At initial diagnosis, EGFR mutation discordance estimates between primary and BM range are minimal (23). Prevalence of T790M mutations in CNS lesions among EGFR mutant NSCLC patients with TKI failure is much lower than anticipated at around 17% (24). This may reflect a pharmacokinetic failure of the first-generation EGFR TKIs to penetrate the brain and thus induced acquire resistance *via* the gatekeeper T790M mutation. Case reports have detailed patients on gefitinib and erlotinib, first-generation TKIs with modest brain penetrance, who have developed T790M-mediated resistance at primary tumor locations but not in the brain metastasis (25, 26). CNS progression appears to be higher in those with L858R point mutations (18). Interestingly, a retrospective radiologic analysis of 57 NSCLC patients suggested that exon 19 deleted patients may have more of a miliary pattern of BM (27). **Table 1** summarizes the prospective trials of three generations of EGFR tyrosine inhibitors in EGFR-mutant NSCLC with BM.

FIRST-GENERATION TYROSINE KINASE INHIBITORS (TKIs)

Erlotinib

Erlotinib is a first-generation (EGFR) tyrosine kinase inhibitor (TKI) (28). The drug reduces EGFR autophosphorylation in intact tumor cells at a median inhibitory concentration of 20 nM although this ranges from 5 (nM) and 6 (nM) in exon 19 deletion and L858R cell models respectively to >2,000 (nM) in T790M models (29, 30). High-performance liquid chromatography studies have shown that erlotinib penetrates the cerebrospinal fluid (CSF) at a rate of between 2 (67 nM) and 4% (31, 32). Radiolabeled ^{11}C-erlotinib injected to one NSCLC patient was shown to accumulate in brain metastasis (33). Additionally, the average concentrations of erlotinib in CSF appear to be higher in those with partial responses (PRs) (35 ng/ml) compared to those who have progressive disease (16 ng/ml) (32).

Several studies have evaluated the effect of erlotinib in NSCLC patients with BM. Deng et al. reported on six unselected NSCLC patients with BM treated with erlotinib and noted that four of the six harbored an EGFR mutation in the tumor; two PRs and two stable diseases (SD) were noted in EGFR mutant patients (32).

TABLE 1 | Prospective studies in epidermal growth factor receptor (EGFR) mutant non-small-cell lung cancers (NSCLC) patients with brain metastases (BM).

Study	Phase	Tyrosine kinase inhibitors therapy	EGFR mutant NSCLC patients with BM (unless specified)	Response rate (%)	Survival (months)
Park 2012	II	Erlotinib or gefitinib	28	Partial Response (PR): 83 Stable Disease (SD): 11	Progression-free survival (PFS): 6.6 Overall Survival (OS): 15.9
Yu 2017	I	Pulsatile erlotinib	34 (only 32% had brain mets)	Complete Response (CR): 2 PR: 70	PFS: 9.9
Iuchi 2013	II	Gefitinib	41	Objective response rate (ORR): 88	PFS: 14.5 OS: 21.9
Yang 2017 (BRAIN)	III	Icotinib	85	–	Intracranial PFS: 10.0
Schuler 2016 (LUX-Lung 3/6)	III	Afatinib	25/46	–	PFS: 11.1/8.2
Park 2016 (LUX-Lung 7)	II	Afatinib	26	–	8.4
Mok 2017 (AURA 3)	II	Osimertinib	144 (T790M mut)	–	PFS: 8.5
Goss 2017 (AURA/AURA2)	II	Osimertinib	50 (T790M mut)	Central nervous system (CNS) ORR: 54	–
Yang 2017 (BLOOM)	I	Osimertinib	32 (LM, 11 T790M mut)	ORR: 43	–
Soria 2017 (FLAURA)	III	Osimertinib	53	ORR: 75 CNS PD: 6	PFS: 15.2

Porta et al. retrospectively reviewed 69 NSCLC with BM patients treated with erlotinib (34). 17 patients had EGFR mutations, 82% of whom had an objective response rate (ORR) to erlotinib including eight complete responses (CRs) as well as a median time to progression of 11.7 months compared to 5.8 in EGFR wt patients and an overall survival of 12.9 months versus 3.1, respectively (34). Moreover, no patients without EGFR mutations had an objective response (34). A phase II study prospectively evaluated EGFR mutant NSCLC patients treated with erlotinib or gefitinib and noted that 83% achieved a PR and 11% SD without a statistically significant difference in progression-free survival (PFS) (6.6 months) or overall survival (OS) (15.9) between the two TKIs (35).

Dose escalation has also been examined as a potential strategy to increase CNS permeability and overcome resistance. In a small but compelling retrospective case series of nine EGFR mutant lung cancer patients with brain or leptomeningeal metastases that occurred despite conventional dosing of an EGFR inhibitor, patients were treated with high dose "pulsatile" erlotinib (1,500 mg weekly) and a CNS partial response rate of 67% (6 of 9 patients) was noted; however, median time to CNS progression was only 2.7 months (36). Following this, a phase 1 study in 34 patients with EGFR mutant lung cancer treated with escalating pulse doses of erlotinib found the maximum tolerated dose to be 1,200 mg given on days 1 and 2, with 50 mg given on days 3–7 weekly and it should be noted that 32% of patients had BM at study entry and none of these patients had progression of an untreated CNS metastasis or new CNS lesions while on study (37).

The role of erlotinib in leptomeningeal disease has also been examined. A retrospective review of 25 NSCLC (9 with exon 21 EGFR mutation and 8 with exon 19 deletion) patients with leptomeningeal (LM) carcinomatosis treated with either erlotinib or gefitinib demonstrated that those treated with erlotinib had a cytologic conversion rate of 64.3% compared to 9.1% with gefitinib (38), suggesting greater activity of erlotinib over gefitnib in the setting of LM disease. In another series of NSCLC patients with leptomeningeal metastasis who had failed gefitinib treatment, all 6 patients with an EGFR mutation-derived clinical benefit with 3 PRs and 3 with SD (39). 1 patient whose tumor did not harbor an EGFR mutation developed progressive disease as the best response.

Gefitinib

Gefitinib, another first-generation EGFR TKI, is a substrate for the *P*-glycoprotein efflux pumps and the drug has a brain penetration rate of only 1% (40, 41). There have been many retrospective reviews of NSCLC patients with BM treated with gefitinib. An old retrospective study of 14 NSCLC patients with BM observed 1 CR (6%) and 5 PRs (33%); this was done prior to the understanding of the role of EGFR mutation status on response to targeted therapies (42). Another report on 15 patients found an ORR of 60% (43). In 2009, a retrospective study of 23 Korean never-smoker patients with lung adenocarcinoma and brain metastasis without prior whole brain radiotherapy (WBRT) found that gefitinib or erlotinib without WBRT resulted in an intracranial response rate of 73.9%, noting that the prevalence of EGFR mutations in Korean non-smoker NSCLC population is high (44). Following this, Zhang et al. retrospectively reviewed 43 Chinese EGFR mutant NSCLC patients with BM treated with gefitinib or erlotinib until extracranial lesion progression; an intracranial lesion ORR of 57% and PFS of 9.3 months was observed, with no statistically significant difference in OS between gefitinib versus erlotinib (45).

Multiple prospective studies have also shown efficacy of gefitinib in NSCLC patients with BM. In 2004, Ceresoli reported on 41 NSCLC patients with BM treated with gefitinib including 18 patients with prior WBRT and observed a partial response rate of only 10% (46). Chiu et al. conducted a prospective study in 57 unselected NSCLC with BM patients observing an ORR of 33% and PFS of 5 months (47). Similarly, a 2007 study by Wu et al. examined 40 unselected NSCLC with BM patients (23 with prior WBRT) and found a 32% ORR and PFS of 9 months (48). However, a phase II study in 21 Chinese NSCLC patients with BM treated with prior WBRT reported a much higher 81% ORR and a PFS of 10 months (49).

Subsequent studies focused on gefitinib's efficacy in NSCLC with BM patients who harbored EGFR-activating mutations. Iuchi reported in 2013 on a phase II trial of 41 Japanese lung adenocarcinoma patients with BM showing a brain metastasis ORR of 87.8% with 13 CRs (50). Stereotactic radiation and WBRT were required in 20 patients (50). Patients with exon 19 deletions had a statistically significant PFS and OS advantage compared to L858R mutations (50). While the results of many of these studies appeared to be promising, the results and thus, the potential efficacy of first-generation EGFR TKIs in patient with BM, need to be interpreted with caution given the small numbers of patients in these predominantly retrospective reports.

Icotinib

Icotinib, a first-generation TKI approved in China, has a median CSF penetration rate of 6.1% (51). The BRAIN study was a multicenter, open-label, parallel randomized controlled trial of 176 Asian EGFR mutant NSCLC patients with at least three brain lesions; patients treated with icotinib had a median intracranial PFS of 10.0 months compared to 4.8 months in those treated with whole brain irradiation plus concurrent or sequential chemotherapy, translating to a 44% risk reduction from intracranial progression or death, and making this a potentially promising option (52).

SECOND-GENERATION TKIs

Afatinib

Afatinib is an oral second-generation TKI which selectively and irreversibly blocks EGFR, HER2, and HER4 kinase activity (53–55). The LUX-Lung 3 was a phase III trial of front-line afatinib in EGFR mutant advanced or metastatic NSCLC (56). Subgroup analysis of 35 patients with asymptomatic BM showed a PFS of 11.1 months versus 5.4 months with cisplatin and pemetrexed (57). The LUX-Lung 6 study was an open label randomized, multicenter phase III trial of Asian patients with EGFR mutant advanced or metastatic lung cancer (58). Prespecified subgroup analysis of 46 asymptomatic BM patients revealed that

PFS was improved from 8.2 to 4.7 months in those treated with gemcitabine and cisplatin (58). Those who received whole brain radiation therapy appeared to have better PFS benefit than those who did not receive radiation; however, among BM patients, rates of CNS progression were similar to chemotherapy in both the LUX-Lung 3 (45 vs 33% chemotherapy) and LUX-Lung 6 (21.4 vs 27.8%) (58).

Another study through the afatinib compassionate use program examined 100 NSCLC patients with BM and/or leptomeningeal disease who had progressed on platinum chemotherapy and a first-generation EGFR TKI, 74% of whom had a documented EGFR mutation (59). Median time to treatment failure was 3.6 months and was similar to a matched group of 100 patients without CNS metastasis; 35% had cerebral response and one heavily pretreated patient with impressive leptomeningeal response and neurological recovery had a CSF concentration of nearly 1 nM (59).

The LUX-Lung 7 study, which was an international, open label, randomized phase II trial comparing afatinib to gefitinib in EGFR mutant advanced or metastatic NSCLC patients, noted that PFS was longer with afatinib (11 months) than gefitinib (10.9 months) but not statistically significant among the subgroup of 26 patients (16%) with asymptomatic brain metastasis (60). Thus, despite its promise as a second-generation irreversible EGFR targeted agent, afatinib did not pan out to be significantly superior to the first-generation agents in systemic disease (or CNS disease) and its use is limited by its greater toxicity profile, except in some of the less common EGFR mutations where data suggest better efficacy.

Dacomitinib

Dacomitinib, another second-generation TKI with activity against EFGR, HER2, and HER4 was studied in two double blind, multicenter, randomized phase III trials: BR.26 and ARCHER 1009 (61, 62). In BR.26, dacomitinib did not improve OS in patients who had previously received gefitinib or erlotinib; routine brain imaging was not done in this study (61). Similarly, in Archer 1009, dacomitinib was not superior to erlotinib in advanced or metastatic NSCLC and only 2% of patients in this trial had brain metastasis at baseline (62).

THIRD-GENERATION TKIs

Osimertinib

Osimertinib is an oral, irreversible EGFR TKI that targets the classical activating mutations as well as the gatekeeper resistance mutation, i.e., T790M (63). Preclinical models showed that osimertinib had greater penetration of the murine blood–brain barrier (BBB) than gefitinib, rociletinib, or afatinib and increased exposure by labeled radiography in cynomolgus monkey brains (64).

AURA 3 was a randomized, international, open-label, phase II trial of T790M positive advanced NSCLC patients who had progressed on front-line EGFR TKI therapy (63). 144 patients had CNS metastases and those who received osimertinib had a longer median PFS (8.5 months) than platinum-pemetrexed chemotherapy (4.2 months) with a hazard ratio of 0.32 (63). A pooled analysis of AURA extension and AURA2 trials in 50 patients with asymptomatic BM found a CNS ORR of 54% to osimertinib treatment with 12% having complete CNS response, with benefit also noted in patients who had not received prior radiotherapy to the brain (65).

The BLOOM study was a phase I trial of patients with CSF cytology confirmed leptomeningeal disease (66). Preliminary results of 32 treated patients (23 evaluable) found 10 had radiographic improvement and 13 with SD; additionally 7 of 8 symptomatic patients improved and, the geometric mean decrease in CSF EGFRm DNA copy was 57% (66).

The FLAURA study is a phase III study in 556 EGFR mutant (exon 19 del or L858R) advanced NSCLC patients which randomized patients 1:1 to a standard of care EGFR TKI (erlotinib or gefitinib) or osimertinib (67). Patients with neurologically stable CNS metastases were allowed on this study, accounting for 21% of patients on this study (67). Front-line treatment with osimertinib resulted in improved median PFS (18.9 months) compared to standard EGFR TKI therapy with erlotinib or gefitinib (10.2 months); median OS data were not mature at the time of the PFS analysis (67). It should be noted that ORR of known/treated CNS metastasis at trial entry was 77% in the osimertinib-treated patients compared to 63% in the standard EGFR TKI patients (68). Response duration lasting >or = 6 months was noted in 88% of patients on the osimertinib arm, with a CR rate of 18%, while no CRs were observed in the arm with standard EGFR TKI. This has led to the FDA approval of osimertinib in the United States as an option for the front-line treatment of EGFR-mutated NSCLC harboring exon 19 deletions or exon 21 L858R mutations.

Rociletinib

Rociletinib (CO1686) was a unique, oral, irreversible TKI designed for NSCLC patients with activity against activating EGFR mutations (L858R and Del 19) and the gatekeeper resistance mutation T790M. The CNS activity of rociletinib was poor compared to systemic disease (69, 70). Camidge et al. reported that 22 of 42 patients continued rociletinib for an average of 120 days after CNS disease progression, treated with brain radiation (70). The development of this drug has since been halted given the high risk-to-benefit ratio related to the hyperglycemia resulting from blockade of the insulin growth factor receptor. Importantly, rociletinib appears to have poor brain penetration with most patients on rociletinib coming off the drug for CNS progression. In a study of the clinical activity of osimertinib in 45 EGFR-mutant NSCLC patients previously treated with rociletinib, subsequent treatment with osimertinib still achieved a brain disease control rate (response + SD) of 88% (71).

MISCELLANEOUS TKIs

AZD3759

AZD3759 in an oral EGFR TKI designed for CNS penetration with a ratio of unbound brain to unbound plasma concentration of 0.65 (72, 73). AZD3759 caused tumor regression in leptomeningeal and brain metastasis mouse models (73). Preliminary results

of the phase I BLOOM study of 38 EGFR-mutant NSCLC with BM or leptomeningeal metastasis (LM) treated with AZD3759 showed an intracranial ORR of 63% and extracranial ORR of 50% (74). Trough CSF concentrations were above the IC90 for pEGFR (74). Further development of this drug is on hold given the highly promising results with osimertinib in the FLAURA trial.

Tesevatinib

Tesevatinib (KD019) is a novel, oral, reversible TKI, which inhibits EGFR, HER2/neu, and Src family nonreceptor tyrosine kinases. Preclinical studies demonstrated good blood–brain penetration of tesevatinib with brain/blood radioactivity of 1 at 6–24 h and brain/plasma ratio of 2.3–4.4 from 1 to 24 h after a dose of tesevatinib (75). The studies also reported good anti-tumor activity with extended median survival time by 20% in preclinical mice models. Considering the preclinical results, Berz D et al. enrolled NSCLC pts with EGFR activating mutation and BM ($n = 4$) or leptomeningeal metastases (LM) ($n = 3$) which had progressed after prior EGFR TKI therapy (76). The authors used RECIST 1.1 for BM measurement and response evaluation. Symptomatic LM disease was diagnosed with CSF cytology or MRI finding and response was measured by improvement in symptoms, CSF cytology, and/or MRI findings. One patient with BM had 19% reduction of target lesion on day 23, and another patient had 57% reduction of target BM with resolution of LM symptoms and MRI findings on day 41. Grade ≥ 3 AEs were QTc prolongation, hypokalemia, dehydration, UTI, and ALT elevation.

COMBINATORIAL/ALTERNATIVE TREATMENT APPROACHES

Combination EGFR TKI and Radiotherapy

Brain metastasis are resistant to systemic chemotherapy due to the BBB which restricts passage of small, non-polar molecules, or those with receptor-mediated transport (77). Thus research has investigated whether radiation can enhance TKI efficacy. In preclinical models, EGFR TKIs have been shown to increase radiation responses by promoting radiation-induced apoptosis as well as inhibiting cellular cycling, DNA damage repair, accelerated repopulation, and angiogenesis (78–80).

Concurrent use of EGFR TKIs during radiotherapy remains in question. A retrospective study of 44 EGFR-mutant NSCLC treated with concurrent radiotherapy evaluated adverse events (AEs) (81). The most common AEs were rash (50%), anorexia (18%), and diarrhea (15%) with two patients having grade ≥ 3 rash (81). Radiation-related AEs included hydrocephalus (2 patients), pneumonitis (3 patients, one grade ≥ 3), myocarditis (1 patient), radiodermatitis (3 patients), laryngopharyngitis (2 patients), esophagitis (2 patients), and enteritis (1 patient) (81). A meta-analysis of 9 retrospective studies and 1 randomized controlled trial examining WBRT with EGFR TKI versus WBRT alone or EGFR TKI therapy alone included 1,041 unselected NSCLC patients with BM (82). In comparing combination therapy versus EGFR TKI alone the hazard ratios showed improved intracranial PFS with EGFR TKI alone (82). In comparing combination therapy versus WBRT alone the combination therapy had significantly improved OS (HR 0.52), intracranial PFS (HR 0.36), and extracranial PFS (HR0.52) (82). In addition, another meta-analysis of 15 studies including 3 phase II and 1 phase II trials in 1,552 unselected NSCLC patients with BM found that combination radiotherapy and EGFR TKI had improved response rate and disease control rate than radiotherapy alone or chemotherapy (83). Combination therapy significantly prolonged time to CNS progression (HR 0.56) and median OS (HR 0.58) but increased AE including rash (83).

A 2015 meta-analysis examined 12 observational studies that exclusively included EGFR-mutant NSCLC patients with brain metastasis (84). The analysis found that upfront cranial radiation improved intracranial PFS and 2-year OS but more neurological AEs were noted (84). One retrospective review by Gerber et al. examined 222 EGFR-mutant NSCLC BM patients treated with erlotinib, or WBRT or stereotactic radiation (SRS) (85). Patients treated with SRS had an OS of 64 months which was statistically significantly longer than the erlotinib group with median OS of 26 months (85). The results are likely biased due to the selection of patients with lower intracranial disease burden for the SRS approach. The median time to intracranial progression was understandably longer in the WBRT arm than the upfront erlotinib arm (24 vs 16 months; $p = 0.04$) (85). Another multi-institutional analysis of 351 EGFR-mutant NSCLC patients with BM compared treatment with SRS followed by EGFR TKI, WBRT followed by EGFR TKI, or EGFR TKI followed by radiotherapy (SRS or WBRT) at intracranial progression (86). Those receiving SRS upfront had improved OS (46 months) compared to those receiving upfront WBRT followed by TKI (30 months), or upfront EGFR TKI (25 months) (86).

Immunotherapy

PD-1 blockade has revolutionized the treatment of lung cancer and has been shown to have intracranial responses. However, many of the landmark immunotherapy studies have excluded EGFR-mutant NSCLC patients or patients with BM. Early analysis from a non-randomized, open-label, phase II trial showed 33% brain metastasis response rate among 18 NSCLC with BM (87). However, only one patient in this study had EGFR mutation (87). *In vitro* studies have shown that PD-L1 protein expression is higher in EGFR-mutant NSCLC cell lines than in EGFR wt and expression of mutated EGFR can induce PD-L1 expression (88, 89). In NSCLC, estimates of brain metastasis PDL1 positivity (PDL1 tumor cell expression exceeding 5%) have ranged from 12 to 52% (90–92) but this has not been well characterized in the EGFR-mutant population.

Given the potential for intracranial activity the question may arise if checkpoint inhibition has a role in EGFR-mutant NSCLC with BM. While there is a paucity of data for checkpoint inhibitors in this population, some extrapolation from EGFR-mutant NSCLC is possible. A meta-analysis of Checkmate 057 (nivolumab), Keynote 010 (pembrolizumab), and POPLAR (atezolizumab) showed that immune checkpoint inhibition prolonged OS over docetaxel in EGFR wt but not EGFR-mutant NSCLC (93). As checkpoint inhibition does not appear superior to chemotherapy EGFR-mutant NSCLC, immunotherapies use in

the EGFR-mutant NSCLC with BM population is likely equally reserved. Nevertheless, one should consider immunotherapy in later lines of therapy.

Combinational EGFR TKI and Anti-Angiogenic Therapy

Several studies have looked at combining EGFR TKI with vascular endothelial growth factor directed monoclonal antibody therapy (94). The BELIEF trial was an international, multicenter, single-arm phase II trial of 109 treatment-naïve, advanced or metastatic, EGFR-mutant, lung adenocarcinoma patients treated with the combination erlotinib and bevacizumab (95). 37 patients (33%) harbored T790M mutations and 21 (19%) had brain metastasis; the median PFS was 13.2 months overall and 8.8 months for patients with brain metastasis (95). One of the greatest concerns with bevacizumab use among brain metastatic patients has been CNS hemorrhage. While CNS hemorrhage carries high morbidity and mortality, the incidence of CNS hemorrhage among bevacizumab-treated patients is less than 0.2% (96). Ongoing studies are investigating the combination of osimertinib and bevacizumab in EGFR-mutant NSCLC with BM (NCT02971501).

CONCLUSION

In conclusion, patients with EGFR-mutant NSCLC are continuing to live longer with median overall survival of 30.9 months and nearly 15% of patients are alive at 5 years (97). As patients live longer, most of these patients are likely to develop BM and we will need optimal therapies with low toxicity to manage the BM. Based on the summary of literature to date (**Table 1**), it is the expert opinion of the authors that a CNS-active TKI such as osimertinib is the EGFR TKI of choice in newly diagnosed advanced NSLC harboring exon 19 deletions or exon 21 L858R mutations, given not only its CNS response rate but the durability of the CNS control, in addition to compelling data with tripling of the median PFS. It would be hard to argue against our opinion that osimertinib is the drug of choice in patients with and without BM. That said, the data regarding the use of upfront SRS followed by EGFR TKI needs to be taken into account in personalizing treatment options for patients with EGFR-mutant NSCLC and BM. The EGFR-mutant NSCLC patient who presents with a solitary brain metastasis should still be considered for surgical resection followed by CNS-active EGFR TKI therapy such as osimertinib. Selected patients with CNS oligometastatic disease with large volume BM that are symptomatic may benefit from the Magnuson approach of using upfront SRS while those with military or multiple, small, and especially asymptomatic BM may be able to delay the need for radiation with the use of upfront EGFR TKIs such as osimertinib. Whole brain radiation should be an option that is reserved for refractory BM that have progressed beyond SRS and systemic therapies, thus delaying the onset of neurocognitive decline that almost inevitably follows such an approach. Novel WBRT techniques such as hippocampal sparing (RTOG 0933) or use of drugs such as memantine (RTOG 0614) may further help to reduce the long-term neurotoxicity of WBRT in these patients (98).

AUTHOR CONTRIBUTIONS

WK drafted epidemiology, prevalence, TKI, radiotherapy, immunotherapy, and anti-angiogenic therapy sections. NS provided literature review and drafted TKI sections. DS provided concept, design for paper, scientific review, and interpretation of data. All authors contributed to manuscript revision, read, and approved the submitted version.

REFERENCES

1. World Health Organization. *Cause-Specific Mortality, 2000-2016. Global Summary Statistics*. Available from: http://www.who.int/healthinfo/global_burden_disease/estimates/en/ (Accessed: June 19, 2018).
2. NCI Surveillance, Epidemiology, and End Results Program. *Cancer Stat Facts: Lung and Bronchus Cancer*. Available from: https://seer.cancer.gov/statfacts/html/lungb.html (Accessed: June 19, 2018).
3. American Cancer Society. *Cancer Facts & Figures 2017*. Atlanta, Ga: American Cancer Society (2017).
4. Zheng HC. The molecular mechanism of chemoresistance in cancers. *Oncotarget* (2017) 8(35):59950–64. doi:10.18632/oncotarget.19048
5. Sordella R, Bell DW, Haber DA, Settleman J. Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. *Science* (2004) 305(5687):1163–7. doi:10.1126/science.1101637
6. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* (2004) 304(5676):1497–1450. doi:10.1126/science.1099314
7. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* (2004) 350(21):2129–39. doi:10.1056/NEJMoa040938
8. Liu L, Liu J, Shao D, Deng Q, Tang H, Liu Z, et al. Comprehensive genomic profiling of lung cancer using a validated panel to explore therapeutic targets in East Asian patients. *Cancer Sci* (2017) 108(12):2487–94. doi:10.1111/cas.13410
9. Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget* (2016) 7(48):78985–93. doi:10.18632/oncotarget.12587
10. Steuer CE, Behera M, Berry L, Kim S, Rossi M, Sica G, et al. Role of race in oncogenic driver prevalence and outcomes in lung adenocarcinoma: results from the Lung Cancer Mutation Consortium. *Cancer* (2016) 122(5):766–72. doi:10.1002/cncr.29812
11. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* (2005) 353:123–32. doi:10.1056/NEJMoa050753
12. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR TKI therapy in 155 patients with EGFR mutant lung cancers. *Clin Cancer Res* (2013) 19(8):2240–7. doi:10.1158/1078-0432.CCR-12-2246
13. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* (2011) 3(75):75ra26. doi:10.1126/scitranslmed.3002003
14. Kuiper JL, Heideman DA, Thunnissen E, Paul MA, van Wijk AW, Postmus PE, et al. Incidence of T790M mutation in (sequential) rebiopsies in EGFR-mutated NSCLC-patients. *Lung Cancer* (2014) 85(1):19–24. doi:10.1016/j.lungcan.2014.03.016
15. Kobayashi S, Boggon TJ, Dayaram T, Janne PA, Kocher O, Meyerson M, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med* (2005) 352(8):786–92. doi:10.1056/NEJMoa044238

16. Yun CH, Mengwasser KE, Toms AV, Woo MS, Grulich H, Wong KK, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci U S A* (2008) 105(6):2070–5. doi:10.1073/pnas.0709662105
17. Ge M, Zhuang Y, Zhou X, Huang R, Lian X, Zhan Q. High probability and frequency of EGFR mutations in in non-small cell lung cancer with brain metastases. *J Neuroncol* (2017) 135(2):413–8. doi:10.1007/s11060-017-2590-x
18. Heon S, Yeap BY, Britt GJ, Costa DB, Rabin MS, Jackman DM, et al. Development of central nervous system metastases in patients with advanced non-small cell lung cancer and somatic EGFR mutations treated with gefitinib or erlotinib. *Clin Cancer Res* (2010) 16(23):5873–82. doi:10.1158/1078-0432.CCR-10-1588
19. Gow CH, Chang YL, Hsu YC, Tsai MF, Wu CT, Yu CJ, et al. Comparison of epidermal growth factor receptor mutations between primary and corresponding metastatic tumors in tyrosine kinase inhibitor-naïve non-small-cell lung cancer. *Ann Oncol* (2009) 20(4):696–702. doi:10.1093/annonc/mdn679
20. Matsumoto S, Takahashi K, Iwakawa R, Matsuno Y, Nakanishi Y, Kohno T, et al. Frequent EGFR mutations in brain metastases of lung adenocarcinoma. *In J Cancer* (2006) 119(6):1491–4. doi:10.1002/ijc.21940
21. Sun M, Behrens C, Feng L, Ozburn N, Tang X, Yin G, et al. HER family receptor abnormalities in lung cancer brain metastases and corresponding primary tumors. *Clin Cancer Res* (2009) 15(15):4829–37. doi:10.1158/1078-0432.CCR-08-2921
22. Daniele L, Cassoni P, Bacillo E, Cappia S, Righi L, Volante M, et al. Epidermal growth factor receptor gene in primary tumor and metastatic sites from non-small cell lung cancer. *J Thorac Oncol* (2009) 4(6):684–8. doi:10.1097/JTO.0b013e3181a52359
23. Burel-Vandenbos F, Ambrosetti D, Coutts M, Pedeutour F. EGFR mutation status in brain metastases of non-small cell lung carcinoma. *J Neurooncol* (2013) 111(1):1–10. doi:10.1007/s11060-012-0990-5
24. Hata A, Katakami N, Yoshioka H, Takeshita J, Tanaka K, Nanjo S, et al. Rebiopsy of non-small cell lung cancer patients with acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitor: comparison between T790M mutation-positive and mutation-negative populations. *Cancer* (2013) 119(24):4325–32. doi:10.1002/cncr.28364
25. Jackman DM, Holmes AJ, Lindeman N, Wen PY, Kesari S, Borras AM, et al. Response and resistance in a non-small-cell lung cancer patient with epidermal growth factor receptor mutation and leptomeningeal metastases treated with high-dose gefitinib. *J Clin Oncol* (2006) 24(27):4517–20. doi:10.1200/JCO.2006.06.6126
26. Clarke JL, Pao W, Wu N, Miller VA, Lassman AB. High dose weekly erlotinib achieves therapeutic concentrations in CSF and is effective in leptomeningeal metastases from epidermal growth factor receptor mutant lung cancer. *J Neurooncol* (2010) 99(2):283–6. doi:10.1007/s11060-010-0128-6
27. Sekine A, Kato T, Haqiwara E, Shinohara T, Komagata T, Iwasawa T, et al. Metastatic brain tumors from non-small cell lung cancer with EGFR mutations: distinguishing influence of exon 19 deletion on radiographic features. *Lung Cancer* (2012) 77(1):64–9. doi:10.1016/j.lungcan.2011.12.017
28. Dempke WC, Edvardsen K, Lu S, Reinmuth N, Reck M, Inoue A. Brain metastases in NSCLC-are TKIs changing the treatment strategy? *Anticancer Res* (2015) 35(11):5797–806.
29. Moyer JD, Barbacci EG, Iwata KK, Arnold L, Boman B, Cunningham A, et al. Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase. *Cancer Res* (1997) 57(21):4838–48.
30. Kancha RK, von Bubnoff N, Peschel C, Duyster J. Functional analysis of epidermal growth factor receptor (EGFR) mutations and potential implications for EGFR targeted therapy. *Clin Cancer Res* (2009) 15(2):460–7. doi:10.1158/1078-0432.CCR-08-1757
31. Toagashi Y, Masago K, Masuda S, Mizuno T, Fukudo M, Ikemi Y, et al. Cerebrospinal fluid concentration of gefitinib and erlotinib inpatients with non-small cell lung cancer. *Cancer Chemother Pharmacol* (2012) 70(3):399–405. doi:10.1007/s00280-012-1929-4
32. Deng Y, Feng W, Wu J, Chen Z, Tang Y, Zhang H, et al. The concentration of erlotinib in the cerebrospinal fluid of patients with brain metastasis from non-small-cell lung cancer. *Mol Clin Oncol* (2014) 2(1):116–20. doi:10.3892/mco.2013.190
33. Weber B, Winterdahl M, Memon A, Sorensen BS, Keiding S, Sorensen L, et al. Erlotinib accumulation in brain metastases from non-small cell lung cancer: visualization by positron emission tomography in a patient harboring a mutation in the epidermal growth factor receptor. *J Thorac Oncol* (2011) 6(7):1287–9. doi:10.1097/JTO.0b013e318219ab87
34. Porta R, Sanchez-Torres JM, Paz-Ares L, Massuti B, Requart N, Mayo C, et al. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. *Eur Respir J* (2011) 37(3):624–31. doi:10.1183/09031936.00195609
35. Park SJ, Kim HT, Lee DH, Kim KP, Kim SW, Suh C, et al. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. *Lung Cancer* (2012) 77(3):556–60. doi:10.1016/j.lungcan.2012.05.092
36. Grommes C, Oxnard GR, Kris MG, Miller VA, Pao W, Holodny AI, et al. "Pulsatile" high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. *Neuro Oncol* (2011) 13(12):1364–9. doi:10.1093/neuonc/nor121
37. Yu HA, Sima C, Feldman D, Liu LL, Vaitheesvaran B, Cross J, et al. Phase 1 study of twice weekly pulse dose and daily low-dose erlotinib as initial treatment for patients with EGFR-mutant lung cancers. *Ann Oncol* (2017) 28(2):278–84. doi:10.1093/annonc/mdw556
38. Lee E, Keam B, Kim DW, Kim TM, Lee SH, Chung DH. Erlotinib versus gefitinib for control of leptomenigeal carcinomatosis in non-small-cell lung cancer. *J Thorac Oncol* (2013) 8(8):1069–74. doi:10.1097/JTO.0b013e318294c8e8
39. Katayama T, Shimizu J, Suda K, Onozato R, Fukui T, Ito S, et al. Efficacy of erlotinib for brain and leptomeningeal metastasis in patients with lung adenocarcinoma who showed initial good response to gefitinib. *J Thorac Oncol* (2009) 4(11):1415–9. doi:10.1097/JTO.0b013e3181b62572
40. McGranahan T, Nagpal SA. Neuro-oncologist's perspective on management of brain metastases in patients with EGFR mutant non-small cell lung cancer. *Curr Treat Options Oncol* (2017) 18(4):22. doi:10.1007/s11864-017-0466-0
41. Chen Y, Wang M, Zhong W, Zhao J. Pharmacokinetic and pharmacodynamics study of Gefitinib in a mouse model of non-small-cell lung carcinoma with brain metastasis. *Lung Cancer* (2013) 82(2):313–8. doi:10.1016/j.lungcan.2013.08.013
42. Hotta K, Kiura K, Ueoka H, Tabata M, Fujiwara K, Kozuki T, et al. Effect of gefitinib ('Iressa', ZD1839) on brain metastases in patients with advanced non-small-cell lung cancer. *Lung Cancer* (2004) 46(2):255–61. doi:10.1016/j.lungcan.2004.04.036
43. Namba Y, Kijima T, Yokota S, Ninaka M, Kawamura S, Iwasaki T, et al. Gefitinib in patients with brain metastases from non-small-cell lung cancer:review of 15 clinical cases. *Clin Lung Cancer* (2004) 6(2):123–8. doi:10.3816/CLC.2004.n.026
44. Kim JE, Lee DH, Choi Y, Yoon DH, Kim SW, Suh C, et al. Epidermal growth factor receptor tyrosine kinase inhibitors as a first-line therapy for never-smokers with adenocarcinoma of the lung having asymptomatic synchronous brain metastasis. *Lung Cancer* (2009) 65(3):351–4. doi:10.1016/j.lungcan.2008.12.011
45. Zhang Q, Zhang X, Yan H, Jiang B, Xu C, Yang J, et al. Effects of epidermal growth factor receptor-tyrosine kinase inhibitors alone on EGFR-mutant non-small cell lung cancer with brain metastasis. *Thorac Cancer* (2016) 7(6):648–54. doi:10.1111/1759-7714.12379
46. Ceresoli GL, Cappuzzo F, Gregorc V, Bartolini S, Crinò L, Villa E. Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. *Ann Oncol* (2004) 15(7):1042–7. doi:10.1093/annonc/mdh276
47. Chiu CH, Tsai CM, Chen YM, Chiang SC, Liou JL, Perng RP. Gefitinib is active in patients with brain metastases from non-small cell lung cancer and response is related to skin toxicity. *Lung Cancer* (2005) 47(1):129–38. doi:10.1016/j.lungcan.2004.05.014
48. Wu C, Li YL, Wang ZM, Li Z, Zhang TX, Wei Z. Gefitinib as palliative therapy for lung adenocarcinoma metastatic to the brain. *Lung Cancer* (2007) 57(3):359–64. doi:10.1016/j.lungcan.2007.03.011
49. Ma S, Xu Y, Deng Q, Yu X. Treatment of brain metastasis from non-small cell lung cancer with whole brain radiotherapy and Gefitinib in a Chinese population. *Lung Cancer* (2009) 65(2):198–203. doi:10.1016/j.lungcan.2008.10.028
50. Iuchi T, Shingyoi M, Sakaida T, Hatano K, Nagano O, Itakura M, et al. Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. *Lung Cancer* (2013) 82(2):282–7. doi:10.1016/j.lungcan.2013.08.016
51. Zhou L, He J, Xiong W, Liu Y, Xiang J, Yu Q, et al. Impact of whole brain radiation therapy on CSF penetration ability of Icotinib in EGFR-mutated

non-small cell lung cancer patients with brain metastases: results of phase I dose-escalation study. *Lung Cancer* (2016) 96:93–100. doi:10.1016/j.lungcan.2016.04.003

52. Yang JJ, Zhou C, Huang Y, Feng J, Lu S, Song Y, et al. Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicenter, phase 3, open-label, parallel, randomized controlled trial. *Lancet Respir Med* (2017) 5(9):707–16. doi:10.1016/S2213-2600(17)30262-X
53. Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in pre-clinical lung cancer models. *Oncogene* (2008) 27(34):4702–11. doi:10.1038/onc.2008.109
54. Solca F, Dahl G, Zoephel A, Bader G, Sanderson M, Klein C, et al. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. *J Pharmacol Exp Ther* (2012) 343(2):342–50. doi:10.1124/jpet.112.197756
55. Subramaniam DS, Hwang J. BIBW 2992 in non-small cell lung cancer. *Expert Opin Investig Drugs* (2011) 20(3):415–22. doi:10.1517/13543784.2011.557063
56. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* (2013) 31(27):3327–34. doi:10.1200/JCO.2012.44.2806
57. Schuler M, Wu YL, Hirsh V, O'Byrne K, Yamamoto N, Mok T, et al. First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. *J Thorac Oncol* (2016) 11(3):380–90. doi:10.1016/j.jtho.2015.11.014
58. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung6): an open-label, randomized phase 3 trial. *Lancet Oncol* (2014) 15(2):213–22. doi:10.1016/S1470-2045(13)70604-1
59. Hoffknecht P, Tufman A, Wehler T, Pelzer T, Wiewrodt R, Schutz M, et al. Efficacy of the irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease. *J Thorac Oncol* (2015) 10(1):156–63. doi:10.1097/JTO.0000000000000380
60. Park K, Tan EH, O'Byrne K, Zhange L, Boyer M, Mok T, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomized controlled trial. *Lancet Oncol* (2016) 17(5):577–89. doi:10.1016/S1470-2045(16)30033-X
61. Ellis PM, Shepherd FA, Millward M, Perrone F, Seymour L, Liu G, et al. Dacomitinib compared with placebo in pretreated patients with advanced or metastatic non-small-cell lung cancer (NCIC CTG BR.26): a double-blind, randomized, phase 3 trial. *Lancet Oncol* (2014) 15(12):1379–88. doi:10.1016/S1470-2045(14)70472-3
62. Ramalingam SS, Janne PA, Mok T, O'Byrne K, Boyer MJ, Von Pawel J, et al. Dacomitinib versus erlotinib in patients with advanced-stage, previously treated non-small-cell lung cancer (ARCHER 1009): a randomised double-blind, phase 3 trial. *Lancet Oncol* (2014) 15(12):1369–78. doi:10.1016/S1470-2045(14)70452-8
63. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* (2017) 376(7):629–40. doi:10.1056/NEJMoa1612674
64. Ballard P, Yates JW, Yang Z, Kim DW, Yang JCC, Cantarini M, et al. Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. *Clin Cancer Res* (2016) 22(20):5130–40. doi:10.1158/1078-0432.CCR-16-0399
65. Goss G, Tsai CM, Shepherd F, Ahn MJ, Bazhenova L, Crino L, et al. MA16.11 CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials. *J Thorac Oncol* (2017) Volume 12(Issue 1):S440–1. doi:10.1016/j.jtho.2016.11.514
66. Yang JCH, Cho BC, Kim DW, Kim SW, Lee JS, Su WC. Osimertinib for patients (pts) with leptomeningeal metastases (LM) from EGFR-mutant non-small cell lung cancer (NSCLC): Updated results from the BLOOM study. *J Clin Oncol* (2017) 35(no.15_suppl):2020–2020. doi:10.1200/JCO.2017.35.15_suppl.2020
67. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* (2018) 378(2):113–25. doi:10.1056/NEJMoa1713137
68. Osimertinib Prescribing Information. *AstraZeneca Pharmaceuticals LP*. Wilminton, DE. Available from: https://www.azpicentral.com/tagrisso/tagrisso.pdf#page=1 (Accessed: June 8, 2018).
69. Sequist LV, Soria J-C, Goldman JW, Wakelee HA, Gadgeel SM, Varga A, et al. Rociletinib in EGFRmutated non–small-cell lung cancer. *N Engl J Med* (2015) 372:1700–9. doi:10.1056/NEJMoa1413654
70. Camidge DR, Sequist LV, Soria JC, Wakelee HA, Ou SH, Goldman JW, et al. Activity of rociletinib in EGFR mutant NSCLC patients with a history of CNS involvement. Presented at the 16th World Conference on Lung Cancer. *J Thorac Oncol* (2015) Volume 10(Suppl 2).
71. Gadgeel S, Chen W, Piotrowska Z, Goldman JW, Wakelee H, Camidge DR, et al. P3.02b-115 clinical activity of osimertinib in EGFR mutation positive non-small cell lung cancer (NSCLC) patients (Pts) previously treated with rociletinib. *J Thorac Oncol* (2017) 12(Suppl 1):S1263. doi:10.1016/j.jtho.2016.11.1783
72. Zeng Q, Wang J, Cheng Z, Chen K, Johnstrom P, Varnas K, et al. Discovery and evaluation of clinical candidate AZD3759, a potent, oral active, central nervous system-penetrant, epidermal growth factor receptor tyrosine kinase inhibitor. *J Med Chem* (2015) 58(20):8200–15. doi:10.1021/acs.jmedchem.5b01073
73. Yang Z, Guo Q, Wang Y, Chen K, Zhang L, Cheng Z, et al. AZD3759, a BBB-penetrating EGFR inhibitor for the treatment of EGFR mutant NSCLC with CNS metastases. *Sci Transl Med* (2016) 8(368):368ra172. doi:10.1126/scitranslmed.aag0976
74. Ahn MJ, Kim DW, Cho BC, Kim SW, Lee JS, Ahn JS, et al. Phase I study (BLOOM) of AZD3759, a BBB penetrable EGFR inhibitor, in patients with TKI-naïve, EGFRm NSCLC with CNS metastases. *J Clin Oncol* (2017) 35(no.15_suppl):2006–2006. doi:10.1200/JCO.2017.35.15_suppl.2006
75. Tonra JR, Poyurovsky M, Liu KG, Patel J, Rao N, Tilton R, et al. KD019: blood brain barrier penetrant HER2/neu, Src, and EGFR inhibitor. *Cancer Res* (2015) 75(15 Suppl):2590. doi:10.1158/1538-7445.AM2015-2590
76. Berz D, Subramaniam DS, Tonra JR, Berger M, Camidge DR. Tesevatinib in NSCLC patients with EGFR activating mutations and brain metastases (BM) or leptomeningeal metastases (LM). *J Thorac Oncol* (2017) 12(1):S942–3. doi:10.1016/j.jtho.2016.11.1297
77. Zhang J, Yu J, Sun X, Meng X. Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of central nerve system metastases from non-small cell lung cancer. *Cancer Lett* (2014) 351(1):6–12. doi:10.1016/j.canlet.2014.04.019
78. Huang SM, Li J, Armstrong EA, Harari PM. Modulation of radiation response and tumor-induced angiogenesis after epidermal growth factor receptor inhibition by ZD1839 (Iressa). *Cancer Res* (2002) 62(15):4300–6.
79. Chinnaiyan P, Huang S, Vallabhaneni G, Armstrong E, Varambally S, Tomlins SA, et al. Mechanisms of enhanced radiation response following epidermal growth factor receptor signaling inhibition by erlotinib (Tarceva). *Cancer Res* (2005) 65(8):3328–35. doi:10.1158/0008-5472.CAN-04-3547
80. Bianco C, Tortora G, Bianco R, Caputo R, Veneziani BM, Caputo R, et al. Enhancement of antitumor activity of ionizing radiation by combined treatment with selective epidermal growth factor receptor-tyrosine kinase inhibitor ZD1839 (Iressa). *Clin Cancer Res* (2002) 8(10):3250–8.
81. Wang Y, Li Y, Xia L, Niu K, Chen X, Lu D, et al. Continued EGFR-TKI with concurrent radiotherapy to improved time to progression (TTP) in patients with locally progressive non-small cell lung cancer (NSCLC) after front-line EGFR-TKI treatment. *Clin Transl Oncol* (2018) 20(3):366–73. doi:10.1007/s12094-017-1723-1
82. Zheng H, Liu QX, Hou B, Zhou D, Li JM, Lu X, et al. Clinical outcomes of WBRT plus EGFR-TKIs versus WBRT or TKIs alone for the treatment of cerebral metastatic NSCLC patients: a meta-analysis. *Oncotarget* (2017) 8(34):57356–64. doi:10.18632/oncotarget.19054
83. Jiang T, Min W, Li Y, Yue Z, Wu C, Zhou C. Radiotherapy plus EGFR TKIs in non-small cell lung cancer patients with brain metastases: an update meta-analysis. *Cancer Med* (2016) 5(6):1055–65. doi:10.1002/cam4.673
84. Soon YY, Leong CN, Koh WY, Tham IWK. EGFR tyrosine kinase inhibitors versus cranial radiation therapy for EGFR mutant non-small cell lung cancer with brain metastases: a systematic review and meta-analysis. *Radiother Oncol* (2015) 114(2):167–72. doi:10.1016/j.radonc.2014.12.011

85. Gerber NK, Yamada Y, Rimner A, Shi W, Riely GJ, Beal K, 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):322–9. doi:10.1016/j.ijrobp.2014.02.022
86. Magnuson WJ, Lester-Coll NH, Wu AJ, Yang TJ, Lockney NA, Gerber NK, et al. Management of brain metastaseses in tyrosine Kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. *J Clin Oncol* (2017) 35(10):1070–7. doi:10.1200/JCO.2016.69.7144
87. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Chiang AC, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol* (2016) 17(87):976–83. doi:10.1016/S1470-2045(16)30053-5
88. Chen N, Fang W, Zhan J, Hong S, Tang Y, Kang S, et al. Upregulation of PD-L1 by EGFR activation mediates the immune escape in EGFR-driven NSCLC: implication for optional immune targeted therapy for NSCLC patients with EGFR mutation. *J Thorac Oncol* (2015) 10(6):910–23. doi:10.1097/JTO.0000000000000500
89. Akbay EA, Koyama S, Carretero J, Altabef A, Tchaicha JH, Christensen CL, et al. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. *Cancer Discov* (2013) 3(12):1355–63. doi:10.1158/2159-8290.CD-13-0310
90. Takamori S, Toyokawa G, Okamoto I, Takada K, Kozuma Y, Matsubara T, et al. Discrepancy in programmed cell death-ligand 1 between primary and metastatic non-small cell lung cancer. *Anticancer Res* (2017) 37(8):4223–8. doi:10.21873/anticanres.11813
91. Mansfield AS, Aubry MC, Moser JC, Harrington SM, Dronca RS, Park SS, et al. Temporal and spatial discordance of programmed cell death-ligand 1 expression and lymphocyte tumor infiltration between paired primary lesions and brain metastases in lung cancer. *Ann Oncol* (2016) 27(10):1953–8. doi:10.1093/annonc/mdw289
92. Berghoff AS, Inan C, Ricken G, Widhalm G, Dieckmann K, Birner P, et al. Tumor-Infiltrating Lymphocytes (TILS) and PD-L1 expression in non-small cell lung cancer brain metastases (BM) and matched primary tumors (PT). *Ann Oncol* (2014) 25:465–6. doi:10.1093/annonc/mdu466.1
93. Lee CK, Man J, Lor S, Links M, Gebski V, Mok T, et al. Checkpoint inhibitors in metastatic EGFR-mutated non-small cell lung cancer- a meta-analysis. *J Thorac Oncol* (2017) 12(2):403–7. doi:10.1016/j.jtho.2016.10.007
94. Wang J, Chen J, Guo Y, Wang B, Chu H. Strategies targeting angiogenesis in advanced non-small cell lung cancer. *Oncotarget* (2017) 8(32):53854–72. doi:10.18632/oncotarget.17957
95. Rosell R, Dafni U, Felip E, Curioni-Fontecedro A, Gautschi O, Peters S, et al. Erlotinib and bevacizumab in patients with advanced non-small-cell lung cancer and activating EGFR mutations (BELIEF): an international, multicenter, single-arm, phase 2 trial. *Lancet Respir Med* (2017) 5(5):435–44. doi:10.1016/S2213-2600(17)30129-7
96. Letarte N, Bressler LR, Villano JL. Bevacizumab and central nervous system (CNS) hemorrhage. *Cancer Chemother Pharmacol* (2013) 71(6):1561–5. doi:10.1007/s00280-013-2155-4
97. Lin JJ, Cardarella S, Lydon CA, Dahlberg SE, Jackman DM, Janne PA, et al. Five-year survival in EGF-mutant metastatic lung adenocarcinoma treated with EGFR-TKIs. *J Thorac Oncol* (2016) 111(4):556–65. doi:10.1016/j.jtho.2015.12.103
98. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol* (2013) 15(10):1429–37. doi:10.1093/neuonc/not114

Conflict of Interest Statement: WK and NS do not have personal, professional, or financial relationships that constitute conflict of interest. DS has received honoraria for her role as advisory board member or speaker for Bristol Myers-Squibb, Takeda Oncology, and Astra Zeneca.

frontiers in Oncology

REVIEW
published: 11 April 2018
doi: 10.3389/fonc.2018.00088

Brain Metastases in Oncogene-Addicted Non-Small Cell Lung Cancer Patients: Incidence and Treatment

J. Remon[1]* *and Benjamin Besse*[2,3]*

[1] Medical Oncology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain, [2] Cancer Medicine Department, Institut Gustave Roussy, Villejuif, France, [3] University Paris-Sud, Orsay, France

Brain metastases (BM) are common in non-small cell lung cancer patients including in molecularly selected populations, such as *EGFR*-mutant and *ALK*-rearranged tumors. They are associated with a reduced quality of life, and are commonly the first site of progression for patients receiving tyrosine kinase inhibitors (TKIs). In this review, we summarize incidence of BM and intracranial efficacy with TKI agents according to oncogene driver mutations, focusing on important clinical issues, notably optimal first-line treatment in oncogene-addicted lung tumors with upfront BM (local therapies followed by TKI vs. TKI monotherapy). We also discuss the potential role of newly emerging late-generation TKIs as new standard treatment in oncogene-addicted lung cancer tumors compared with sequential strategies.

Keywords: brain, metastases, non-small cell lung cancer, EGFR, ALK

OPEN ACCESS

Edited by:
Marco Lucchi,
Università degli Studi di Pisa, Italy

Reviewed by:
Minesh P. Mehta,
Baptist Health South Florida, United States
Emilio Bria,
University of Verona, Italy

***Correspondence:**
J. Remon
jremon@vhio.net;
Benjamin Besse
benjamin.besse@gustaveroussy.fr

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *29 December 2017*
Accepted: *14 March 2018*
Published: *11 April 2018*

Citation:
Remon J and Besse B (2018) Brain Metastases in Oncogene-Addicted Non-Small Cell Lung Cancer Patients: Incidence and Treatment. Front. Oncol. 8:88. doi: 10.3389/fonc.2018.00088

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide (1). Because of the lack of screening programs in most countries, more than half of non-small cell lung cancer (NSCLC) patients are diagnosed at an advanced stage[1]. The brain is a common metastatic site in this population, with 30% of patients developing brain metastases (BM) during the course of their disease, with the brain being the only site of metastatic disease in 51% of these cases. Median delay between diagnosis of the primary tumor and development of BM is 11 months. Up to half of cases, patients present with synchronous diagnosis of BM at the time of diagnosis of the primary lung tumor (2). Ironically, the lifetime incidence of BM is increasing due to prolonged survival seen in NSCLC patients thanks to new systemic therapies and improved neuro-imaging techniques (3). Unfortunately, prognosis associated with BM remains poor with reports of median overall survival (OS) between 3 and 14.8 months (4), and compared to other metastatic sites, BM are responsible for a major decrease in quality of life (5).

The discovery of targetable genomic alterations in approximately 30% of advanced NSCLC tumors, mainly adenocarcinomas, has altered the therapeutic landscape and outcome of many of these subgroups of NSCLC patients (6, 7). In the recent era of personalized treatment targeting these alterations, prognosis of NSCLC patients with BM has improved significantly achieving a median OS of nearly 4 years (8). The question whether BM harbor distinct genetic alterations beyond those observed in primary tumors has not been definitively addressed. Recent data with

[1] Available from: www.seer.cancer.gov (Accessed: March 23, 2018).

whole-exome sequencing in 86 patient-matched BM (including 38 NSCLC patients) reported 53% of cases with potentially clinically informative alterations in BM that were not detected in the matched primary-tumor sample (9). However, these findings have a number of technical limitations and are yet to be supported by clinical evidence. On the other hand, response rates (RR) to targeted therapies in molecularly defined NSCLC patients are typically similar in central nervous system (CNS) and extra-CNS disease, arguing for fewer molecular discordances between the primary tumor and CNS metastases, at least for actionable mutations. This is an important issue to resolve for determining the best treatment strategies for managing BM.

One important consideration, when interpreting CNS efficacy with tyrosine kinase inhibitors (TKIs) in molecularly selected NSCLC patients, is the inherent limitation of the standard RECIST criteria for the measurement of baseline CNS disease and response (10). This assessment does not account for potential pseudo-progression correlating with radionecrosis and non-viable tumors in patients who have received brain radiotherapy (11). New imaging tests might offer better characterization of CNS progression vs. pseudo-progression (12). While the systemic efficacy of TKI in oncogene-addicted NSCLC has been well established, their intracranial efficacy is today less well validated for a number of reasons. Brain imaging during follow-up is often optional in clinical trials, MRI is not commonly used compared to the less sensitive CT scan, and patients with BM are often excluded from NSCLC trials, and when they are accepted, BM is not a stratification criteria. The CNS is shielded by the blood–brain barrier (BBB) and is considered a "pharmacological sanctuary." The key molecular properties that influence the BBB are the P-glycoprotein (P-gp) or breast cancer resistance protein substrate nature of the TKIs, their molecular weight, polar surface area and lipophilicity index (LogP) (13). These factors may explain why only 2% of small-molecule drugs are able to effectively cross the BBB (14), likely explaining why the CNS is a frequent site of failure after clinical benefit with some TKIs.

In this review, we summarize the incidence of BM in oncogene-addicted NSCLC patients and CNS efficacy for personalized treatment in these different sub-populations. We also evaluate new challenges such as the value of upfront personalized treatment vs. radiotherapy in oncogene-addicted NSCLC patients with BM at baseline, and administration of more potent drugs upfront vs. sequential treatment.

EGFR-MUTANT NSCLC PATIENTS

Within the lung cancer population, activated epidermal growth factor receptor (*EGFR)* mutations occur in 10% of Caucasians and 50% of Asians (15). There are several classes of activating somatic *EGFR* mutations, with in-frame deletions in exon 19 (ELREA, *Del19*) and single-point mutations in exon 21 (*L858R*) being the most common. These mutations predict sensitivity to first- and second-generation EGFR TKIs, such as erlotinib, gefitinib, or afatinib. RRs and progression-free survival (PFS) with EGFR TKIs have proven superior to standard first-line platinum doublet chemotherapy, making them the current upfront standard of care (16). Recently, osimertinib a third-generation EGFR TKI, showed a significant improvement in PFS compared with standard of care (erlotinib or gefitinib) as first-line treatment, making it a new treatment option in the first-line setting (17).

Incidence of BM in EGFR-Mutant NSCLC

The baseline incidence of BM in *EGFR*-mutant NSCLC is similar to that of other oncogenic driver mutations, ranging from 23 to 32% (18–20). The cumulative incidence increases over time (19, 21), with a 2-year actuarial risk of CNS progression of approximately 15–20% when patients received standard of care EGFR TKIs (21, 22). BM development on EGFR TKI treatment is significantly more common among patients with baseline BM (2-year cumulative incidence of 47% among patients with pre-existing BM compared to 11% among those with no prior BM; $p = 0.003$) and correlates with a worse outcome (21, 23, 24). Literature reporting the risk of cumulative incidence of brain progression according to *EGFR* mutation subtype is contradictory, some studies reporting higher cumulative risk among *Del19*-mutant tumors (21), and others among *L858R*-mutant tumors (22, 24).

Although, it has been suggested that *EGFR* mutations appear early during multistep carcinogenesis and may even be associated with an increased propensity for metastatic cell to spread into the brain (25), the lifetime risk is confounded by this molecular subgroup's longer survival. However, some reports suggest that the incidence of BM is higher in *EGFR*-mutant patients compared to *EGFR*-wild type (31.4 vs. 19.7%, odds ratio 1.86, 95% CI: 1.39–2.49; $p < 0.001$) (18), but it could be explained by inability of first-generation EGFR TKIs to cross BBB, reported in up to 60% of patients (26, 27). The high incidence and significant rate of CNS failure highlights the need for additional strategies to prevent CNS progression.

Treatment With EGFR TKIs

First- and second-generation EGFR TKI brain penetration potential, measured by the unbound brain-to-plasma ratio, termed $K_{p,uu}$, is very low (28), indicating that penetration into the brain is diffusion-limited or low passive BBB permeability (13). However, the importance of the BBB for intracranial tumors is debated. Retrospective observational and phase II studies have reported activity with erlotinib and gefitinib in *EGFR*-mutant patients with BM (29–34). Two studies with erlotinib showed intracranial RRs of 58 and 82% and intracranial PFS of 10.1 and 11.7 months (29, 30). Gefitinib achieved an intracranial RR of 88% and intracranial PFS of 14.5 months, with a time to salvage brain radiation from diagnosis of 17.9 months (32) (**Table 1**).

In vivo studies in NSCLC mice showed that afatinib penetrated the BBB and cerebrospinal fluid (CSF) levels correlated with plasma levels (35). In a compassionate-use program including 31 patients, afatinib demonstrated a 35% CNS response in molecularly non-selected patients who had previously failed TKI therapy, with a median time to treatment failure of 3.6 months (36). In a combined dataset *post hoc* analysis in 81 *EGFR*-mutant NSCLC patients with BM (30% had received brain radiotherapy) in the first-line LUX-Lung 3 and LUX-Lung 6 phase III clinical trials, afatinib significantly improved PFS (8.2 vs. 5.4 months, hazard ratio (HR) 0.50, $p = 0.0297$) and RR (21 vs. 5%, $p = 0.0027$), although without a significant difference in OS (22.4 vs.

TABLE 1 | Efficacy of EGFR tyrosine kinase inhibitors (TKIs) in *EGFR*-mutant non-small cell lung cancer (NSCLC) patients and brain metastases (BM).

Drug	Trial	*N*	icRR (%)	icDOR (months)	icPFS (months)
Erlotinib	Retrospective (29)	17	82	NA	11.7
	Ph II (30)	8	58.4	NA	10.1
Gefitinib	Ph II (32)	41	88	NA	14.5
	Retrospective (34)	14	43	7.7	9.1
Afatinib	Pooled analysis (37)	81	21[a]	NA	8.2[a]
Icotinib[b]	Ph III (38)	85	65	NA	10.0
AZD3759	Ph I (28)	18	83	NA	NA
Osimertinib	AURA + AURA2 (49, 50)	128	54[c]	NR	1 year: 56%
	AURA3 (51)	116	70[d]	8.9[d]	11.7
	FLAURA (17)	128	66	NA	NR

icDOR, intracranial duration of response; icRR, intracranial response rate; icPFS, intracranial progression-free survival; NA, not available; NR, not reached.

[a]*Systemic RR and progression-free survival (PFS).*

[b]*Patients should have at least 3 metastatic brain lesions.*

[c]*In 50 evaluable patients.*

[d]*In 30 evaluable patients with osimertinib.*

25.0 months; HR 1.14, $p = 0.64$) compared with platinum-based chemotherapy (37). The magnitude of the PFS benefit was suggested being increased, for patients who had received prior whole brabin radiotherapy (WBRT, $n = 24$; 13.8 vs. 4.7 months; HR 0.37, $p = 0.07$). Evaluation of intracranial response was not assessed as a separate endpoint in these trials (37), however, these results suggest that asymptomatic BM are not a limitation for upfront treatment with an EGFR TKI (**Table 1**).

Icotinib, another EGFR TKI only available in Asia, gave an intracranial RR of 65% and median PFS of 10 months in treatment-naïve *EGFR*-mutant patients with at least three BM (38). AZD3759 is a novel reversible EGFR TKI, only active against sensitizing *EGFR* mutations, which was designed to effectively cross the BBB and achieves high drug-free exposure in the brain. In a phase I trial, it achieved an intracranial RR of 83% among 18 EGFR TKI treatment-naïve patients with evaluable BM (28) (**Table 1**).

The substitution of threonine to methionine at amino acid position 790 (*T790M*) in exon 20 of the *EGFR* gene reduces first-generation EGFR TKI binding by enhancing the ATP binding affinity of the kinase domain of the *EGFR*-mutant receptor (39). It accounts for acquired resistance in approximately 50–60% of patients (40, 41). Knowledge of acquired resistance mechanisms to EGFR TKIs was one of the triggers behind the development of third-generation EGFR-TKIs, such as osimertinib, which are active against *exon19* and *21* mutations as well as the *T790M* mutations. Osimertinib was the first such agent to receive FDA and EMA approval (in November 2015 and February 2016, respectively) for metastatic *EGFR*-mutant and acquired *EGFR T790M*-mutant NSCLC patients progressing on or after EGFR TKI therapy[2,3].

[2]Available from: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm (Accessed: March 23, 2018).

[3]Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004124/WC500202022.pdf (Accessed: March 23, 2018).

The rate of acquired *T790M* mutations is discordant between intracranial and extracranial metastases. In a study of 78 *EGFR*-mutant patients who had undergone re-biopsy after TKI failure, only 17% of CNS lesions were *T790M* mutated compared to 41% of systemic lesions (42), suggesting that the selection pressure is lower intracranially owing to the lower EGFR TKI concentrations in CSF compared to serum concentrations (42, 43). Preclinical data demonstrated greater penetration and brain exposure with osimertinib than with gefitinib, rociletinib, or afatinib (44).

Central nervous system activity of osimertinib was reported in pretreated *T790M*-positive NSCLC patients in the AURA study phase II extension component (45), the phase II AURA2 trial (46), and was recently confirmed in the phase III AURA3 trial (47) and the first-line FLAURA trial (17). In the pooled analysis of the two phase II trials ($N = 411$), osimertinib demonstrated an overall RR of 66% and median PFS of 11 months (48). In the pre-specified subgroup analysis of CNS response in this pooled analysis among 128 patients with CNS metastases at baseline, 50 were evaluable for CNS response. CNS response and DCR were 54 and 92%, respectively, and CNS response was observed regardless of prior radiotherapy. Median CNS duration of response (DOR) was not reached and at 9 months 75% of patients were estimated to remain in response. Median CNS PFS was not reached (49), with 1-year PFS of 56% (50). In the AURA3 trial, osimertinib demonstrated significantly greater efficacy in RR (71 vs. 31%) and PFS (10.1 vs. 4.4, HR 0.30, 95% CI: 0.23–0.41, $p < 0.001$) than platinum-pemetrexed chemotherapy, in 419 *T790M*-positive NSCLC patients who had progressed on first-line EGFR TKIs (47). Among 116 patients from the AURA3 trial with BM (measurable or not), PFS was longer with osimertinib compared to chemotherapy (11.7 vs. 5.6 months, HR 0.32; 95% CI: 0.15–0.69) and cumulative incidence of CNS progression at 6 months was lower with osimertinib compared to chemotherapy (11.5 vs. 28.2%) (51). Among 46 patients with evaluable BM, the intracranial RR was 70% with osimertinib compared with 31% with chemotherapy, with a median DOR of 8.9 vs. 5.7 months, respectively (51) (**Table 1**). It has been proposed that BM may not develop secondary resistance mutations to EGFR TKIs that develop during extracranial progression, due to reduced drug penetration of the BBB (52). However, CNS efficacy with osimertinib reported in AURA3 trial, appears to contradict this theory. In the CNS full analysis set ($N = 128$) from FLAURA trial, osimertinib reported improved CNS RR (66 vs. 43%) and longer CNS PFS (NR vs. 13.9 months, HR 0.48, 95% CI: 0.26–0.86, $p = 0.04$) and reduced the risk of CNS progression compared with the standard of care. Among evaluable CNS evaluable patients ($N = 41$), osimertinib improved the CNS RR (91 vs. 68%) with similar DOR compared with the standard of care (15.4 vs. 18.7 months) (53).

In light of the reduced CSF concentrations of EGFR TKIs, various studies have examined administration of high doses in an attempt to achieve therapeutic levels (54–57). "Pulsatile" erlotinib at 1,500 mg given weekly resulted in an intracranial RR of 67% with a median time to CNS progression of 2.7 months in nine patients (55). In a phase I trial, pulse and daily low-dose erlotinib prevented progression of untreated or new CNS metastases, without improving extracranial outcome compared with

standard-dose (58). However, the limited number of patients, the short follow-up period and the fact that half of the patients with baseline BM had already been treated are confounding factors that prevent any conclusions being reached regarding efficacy in the CNS with this strategy.

Combined EGFR TKIs and Antiangiogenics

Activity and an acceptable safety profile of bevacizumab, an anti-VEGF monoclonal antibody, have been reported in NSCLC patients with asymptomatic and untreated BM (59). Moreover, in a preclinical model of lung adenocarcinoma, bevacizumab prevented BM formation (60). In a phase II trial in 154 Asian *EGFR*-mutant NSCLC patients, the addition of bevacizumab to erlotinib as first-line treatment significantly improved PFS compared to erlotinib alone (16.0 vs. 9.7 months, HR 0.54; 95% CI: 0.36–0.79, $p = 0.0015$) (61), leading to EMA approval of the combination in this population in April 2016. Two ongoing phase III trials evaluating erlotinib combined with ramucirumab (NCT02411448) or bevacizumab (BEVERLY study, NCT02633189) compared with erlotinib, will hopefully further validate this strategy.

In the single arm phase II BELIEF trial in 109 Caucasian *EGFR*-mutant NSCLC patients, combined erlotinib and bevacizumab gave median PFS and OS of 13.2 and 28.2 months, respectively. However, the primary endpoint was only met in baseline *T790M*-positive tumors with a median PFS of 16 months, whereas in *T790M*-negative tumors, median PFS was 10.5 months (62). In the subgroup of patients with pretreated BM ($N = 21$), median PFS was 8.8 months. The efficacy of this combination in the BM population does not appear to be superior to standard EGFR TKI therapy (37), however only 21 patients with BM were included in the BELIEF trial. Results from the ongoing randomized phase II BRILLANT trial (NCT0265536), testing bevacizumab plus erlotinib vs. erlotinib in BM *EGFR*-mutant patients, should reveal the efficacy of this combination in this population. Also the combination of osimertinib and bevacizumab in *EGFR*-mutant NSCLC patients and BM is currently assessed in a phase II trial (NCT02971501).

ALK-REARRANGED NSCLC PATIENTS

Anaplastic lymphoma kinase (*ALK)* rearrangements result from inversions or translocations on chromosome 2 and are present in ~5% of NSCLC tumors, with no apparent differences in incidence according to race. Crizotinib was the first treatment to be approved in this population achieving a median PFS of 10.9 vs. 7.0 months with platinum-pemetrexed chemotherapy in the front-line setting in the phase III PROFILE 1014 study (63). In the subsequent phase III ASCEND-4 trial in *ALK*-positive (by central immunohistochemistry) NSCLC patients, upfront ceritinib, a second-generation ALK TKI, gave a median PFS of 16.6 vs. 8.8 months with platinum-pemetrexed chemotherapy (64). Based on these results, the FDA approved ceritinib as first-line treatment in *ALK*-positive NSCLC patients in May 2017. More recently, the phase III ALEX trial demonstrated a significant improvement in PFS with alectinib (a second-generation ALK TKI) compared with crizotinib (25.7 vs. 10.4 months, HR: 0.50, 95%CI: 0.36–0.70, $p < 0.001$) by independent review, and with a better toxicity profile, as first-line treatment in *ALK*-positive NSCLC patients (65). The EMA and FDA approved alectinib as first-line treatment in 12 October 2017 and in 6 November 2017, respectively. Treatment strategies in this population are provided below and in **Figure 1**.

Incidence of BM in ALK-Positive NSCLC

In *ALK*-positive NSCLC patients, CNS metastases affect from 24 to 42% of patients (19, 65–68) with risk increasing over time, reaching 58% at 3 years (19). In this population, median OS after development of BM was 49.5 months, with no survival differences detected according the number of BM (single vs. more than one BM) (69), confirming the prolonged survival of *ALK*-positive NSCLC patients with BM. However, the CNS is a common site of progression with crizotinib; in patients with known BM (treated or untreated), the CNS was a site of new lesions or non-target progression in 70% of cases of progression during crizotinib treatment. In patients without BM at the time of crizotinib initiation, 20% subsequently experienced CNS progression (68, 70). It remains controversial whether this increased risk was an expression of the natural *ALK*-rearranged disease course independent of the therapy received, or if, as in *EGFR*-mutant NSCLC patients, it is related to low CSF penetrance of ALK TKIs. Crizotinib is a substrate for the ATP-binding cassette (ABC) drug efflux transporters, P-gp and ABC subfamily G member 2, and has been associated with poor accumulation of the drug in the brain, a CSF-to-plasma ratio of 0.0026 reported in a case study (71). In support of this, ABCB1−/− and ABCG2−/− mice had a 25- to 70-fold higher brain concentration following oral administration of crizotinib compared to wild type (71).

Nonetheless clinical evidence for crizotinib CNS efficacy has been reported. A pooled retrospective analysis of crizotinib efficacy in *ALK*-positive NSCLC patients with BM from the PROFILE 1005 phase II and PROFILE 1007 phase III trials has been reported (68). At baseline, 31% of patients (275 of 888) had asymptomatic BM. Analytic subgroups were stratified according to prior brain radiotherapy (60%) or not. The intracranial disease control rate (DCR) at 12 weeks was similar in these two groups at 62 and 56%, respectively. Of note, previously treated patients demonstrated higher CNS objective RR with crizotinib (33 vs. 18%, respectively), as well as prolongation of the median time to intracranial progression (13.2 vs. 7.0 months, respectively; **Table 2**) (68). Intracranial efficacy of crizotinib in treatment-naïve *ALK*-positive patients was studied in the PROFILE 1014 trial (70). Of 343 patients, 79 (23%) had treated BM at baseline. Compared to chemotherapy, crizotinib demonstrated longer PFS (9.0 vs. 4.0 months; HR 0.40, 95% CI: 0.23–0.69, $p < 0.001$) and a better RR (77% vs. 28%, $p < 0.01$). Crizotinib achieved a 12-week intracranial DCR of 85% and median intracranial time to progression of 15.7 months in patients with treated BM (**Table 2**). CNS progression as the only site of progression on crizotinib was reported in 38% of patients with treated BM at baseline and 19% without (70). In the randomized phase III ALEX trial, crizotinib was used as the standard of care in the control arm and brain MRIs were mandatory at baseline and during follow-up (65). Among the 22 patients with measurable BM

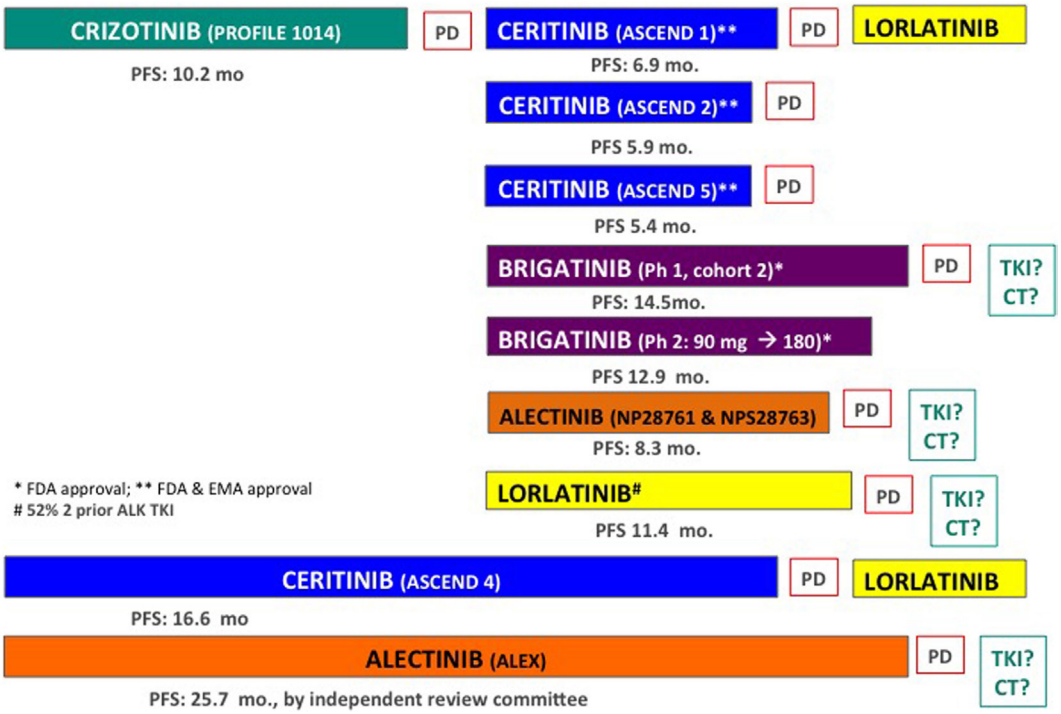


FIGURE 1 | Systematic treatment stratergies in *ALK*-positive non-small cell lung cancer (NSCLC) patients. TKI, other ALK tyrosine kinase inhibitor; CT, chemotherapy.

at baseline, crizotinib achieved an intracranial RR of 50% and a median duration of intracranial response of 5.5 months. For the seven patients previously treated with brain radiotherapy, crizotinib gave an intracranial RR of 71% and median DOR of 17.3 months (72). Despite these data suggesting intracranial efficacy with crizotinib, especially among previously-treated BM patients, recent data showed that the cumulative incidence rate of CNS progression at 12 months was consistently higher with crizotinib compared with alectinib (32 vs. 4.6% respectively in patients without BM at baseline; HR 0.14, 95% CI: 0.06–0.33, $p < 0.0001$) (65, 72), suggesting that the risk of BM progression may correlate more closely with ALK TKI subtype and not the natural *ALK*-rearranged disease course.

Treatment With Novel ALK TKIs

Ceritinib

Ceritinib is a second-generation ALK inhibitor that is 20 times as potent as crizotinib. It is effective in *ALK*-positive patients upfront and patients who progress while on crizotinib, including patients with BM (73). In the phase III ASCEND-4 trial, among 121 *ALK*-positive TKI-naïve NSCLC patients with BM, first-line treatment with ceritinib improved PFS (10.7 vs. 6.7 months, HR 0.70) compared to chemotherapy. Intracranial RR in 22 patients with measurable BM at baseline was 73%, with a median duration of intracranial response of 16.6 months (64). The CNS efficacy of ceritinib in crizotinib-pretreated and ALK-naïve patients was tested in the phase I ASCEND-1 trial (73), as well as the phase II ASCEND-2 (74), and ASCEND-3 (75) trials (**Table 2**). In the phase III, ASCEND-5 trial in previously treated (chemotherapy and crizotinib) *ALK*-positive NSCLC patients, ceritinib compared with chemotherapy significantly improved PFS across all patient subgroups, including in 133 patients with BM at baseline (56% previously treated with brain radiotherapy), from 1.5 months to 4.4 months (HR 0.54, 95% CI: 0.36–0.80). Among the 17 patients with measurable BM, ceritinib gave a 35% intracranial RR and median duration of intracranial response of 6.9 months (76). Nonetheless, despite these second-generation more potent ALK TKIs, BM remained the main site of progression among patients with BM at baseline (76). Based on ceritinib efficacy, an international prospective phase II open-label study is ongoing (ASCEND-7, NCT02336451) specifically evaluating the anti-tumor activity of ceritinib in *ALK*-positive NSCLC patients with BM or leptomeningeal disease (previously treated with radiotherapy or not).

Gastrointestinal toxicity by ceritinib may reduce treatment compliance. The ASCEND-8 (NCT02299505) aimed to evaluate whether administering ceritinib, 450 or 600 mg, with a low-fat meal may enhance gastrointestinal tolerability vs. 750 mg fasted while maintaining similar exposure in 267 treatment-naive ALK-positive NSCLC (neurologically stable BM were stable). The study demonstrated similar efficacy in terms of ORR and DCR with less frequent dose reductions/interruptions and higher relative dose

TABLE 2 | Efficacy of ALK tyrosine kinase inhibitor (TKIs) in patients with baseline brain metastases (BM).

Drug	Trial (reference)	Brain M1	Measurable Brain M1	icRR (%)	icTTP (months)	s/ic PFS (months)	icDOR (monthss)
Crizotinib	PROFILE 1005 + 1007 pooled. ALK-naïve (previous CT) (68)	275	22/18[b]	18/33[b]	7.0/13.2	NA	26.4,/NR[b]
	PROFILE 1014. Ph III ALK-naïve (70)	79	79	85[c]	15.7	sPFS: 9	NA
Ceritinib	ASCEND 5. Ph III Crizotinib + CT resistant (76)	133	17	35 72.7	NA	sPFS: 4.4	6.9 16.6
	ASCEND 4. Ph III ALK-naïve (64)	121	22	62	NA	sPFS: 10.7	NA
	ASCEND 3. Ph II ALK TKI-naïve[a] (75)	49	13	39.4	NA	sPFS: 10.8	9.2
	ASCEND 2. Ph II Crizotinib-resistant (74)	100	33	63	NA	sPFS: 5.4	8.2,
	ASCEND 1. Ph I Naïve and pretreated (73)	94	36	61[d]	NA	NA	11.1[d]
Alectinib	Pooled analysis of ph II. Crizotinib resistant (85)	136	50	64	9.2	NA	10.8
	ALUR ph II. Crizotinib and CT resistant (86, 87)	76	40	54	NA	sPFS: 9.6	17.3
	ALEX. Ph III. ALK TKI-naïve (65, 72)	122	21	81	NA	sPFS: 25.7	
Lorlatinib	Ph I in *ALK*-positive (11% crizotinib-naïve) (90)	41	19	42	NA	sPFS: 9.6	12.4
	Ph I in *ROS1*-positive (90)	12	5	60	NA	sPFS: 7.0	12.0
	Ph II in *ALK/ROS1*-positive (91)						
	ALK TKI treatment-naïve	8	8	75	NA	NR	NA
	Prior crizotinib only and crizotinib ± 1-2 CT	37	37	68	NA	NR	NA
	No-crizotinib TKI ± CT	12	12	42	NA	sPFS: 5.5	NA
	2-3 ALK TKI ± CT	83	83	48	NA	sPFS: 6.9	NA
	ROS1-positive any prior line	25	25	56	NA	sPFS:9.6	NA
Brigatinib	Ph I ALK-naïve and crizotinib resistant (93)	46	15	53	NA	icPFS: 15.6	18.9
	ALTA. Ph II in crizotinib-resistant (94, 95)	153	18	67[e]	NA	icPFS: 18.4[e]	NR[e]

icRR, intracranial response rate; icTTP, intracranial time to progression; s/icPFS, systemic/intracranial progression-free survival (PFS); icDOR, intracranial duration of response; CT, chemotherapy; NA, not available; NR, not reached.

[a]*ALK TKI naïve and chemotherapy-naïve or up to three lines of chemotherapy with progression during or after the last chemotherapy regimen.*

[b]*Data reported for previously untreated BM/previously treated BM.*

[c]*12-week intracranial disease control rate.*

[d]*Results expressed as ALK inhibitor-naïve patients, ALK inhibitor-pretreated patients.*

[e]*Patients receiving 180 mg/day.*

intensity. Ceritinib administered at 450 mg fed dose demonstrated an ORR of 78% and a median PFS of 17.6 months, suggesting this dose as a potential new treatment regimen. However, fed doses of ceritinib in patients with BM were not reported to provide a clear recommendation in this subset (77, 78).

Alectinib

Alectinib is a potent ALK TKI, active against several *ALK* mutations that confer resistance to crizotinib (79). It is able to penetrate the CNS and activity is expected based on animal models showing high brain-to-plasma ratios (0.63–0.94) and activity in intracranial tumor implantation models. Unlike crizotinib and ceritinib, preclinical studies suggest that alectinib is not a substrate of P-gp, a key drug efflux pump typically expressed in the BBB, and that it has greater CNS activity than other ALK TKIs (80). In the clinic, alectinib gave an intracranial RR of 52% in 21 crizotinib-resistant patients with baseline BM treated in a phase I trial (81). Alectinib was approved by the FDA in 2015 for *ALK*-positive crizotinib-resistant NSCLC patients based on two phase II clinical trials demonstrating a systemic objective RR of 50–52% (82, 83). A pooled analysis evaluating systemic efficacy of alectinib in both phase II trials enrolling 225 *ALK*-positive crizotinib-resistant NSCLC patients has been performed. Alectinib gave a systemic RR of 51%, and median PFS and OS of 8.3 and 26 months, respectively (84), with 11% of patients having CNS as the only site of progression (85). Intracranial efficacy of alectinib in this population was assessed in 136 crizotinib-resistant patients with BM (37% with measurable disease and 70% previously treated). Intracranial RR in the whole population was 43% (36% in previously irradiated vs. 59% in patients without prior radiation) with a median DOR of 11.1 months. For patients with measurable disease ($N = 50$), the intracranial RR was 64%, with complete response in 22%, and median intracranial DOR was 10.8 months (85). The phase III ALUR trial comparing alectinib with chemotherapy in 107 previously treated (chemotherapy and crizotinib) *ALK*-positive NSCLC patients, reported improved outcome with alectinib (PFS 9.6 vs. 1.4 months, HR 0.15; 95% CI: 0.08–0.29; $p < 0.001$) (86). Among 76 patients with baseline BM, alectinib achieved an intracranial RR of 36% reaching to 54% among the 40 patients with measurable BM (87). These results endorse preclinical data showing promising CNS efficacy profile with alectinib.

In the phase III ALEX trial, 303 previously untreated *ALK*-positive (by immunohistochemistry) NSCLC patients were randomized to receive either alectinib (600 mg twice daily) or crizotinib (250 mg twice daily). Crossover was not allowed. As mentioned previously, PFS was significantly longer with alectinib than with crizotinib and delayed the onset of BM (65). In the ALEX trial, 122 out of 303 (40%) patients had asymptomatic BM at baseline. Alectinib achieved an intracranial RR of 59% with a systemic PFS similar to that reported in the whole population (HR 0.40, 95% CI: 0.25–0.64, $p < 0.0001$) (65), with a median PFS of 14 months among patients with BM at baseline who had not received previous radiotherapy (72). Among the 21 patients with measurable

BM, alectinib gave an intracranial RR of 81% and median DOR of 17.3 months (65) (**Table 2**). Patients with previously-irradiated BM measurable lesions had higher intracranial RR (86 vs. 79%) and intracranial DOR (not reached vs. 17.3 months), compared with patients without prior radiotherapy (72). Similarly, the phase III J-ALEX trial in 207 Japanese *ALK*-positive NSCLC patients demonstrated the superiority of alectinib in terms of PFS over crizotinib (HR 0.34, 95% CI: 0.17–0.71, $p < 0.0001$), and delayed risk of CNS progression in patients with BM at baseline (HR 0.16, 95% CI: 0.02–1.28) and those without (HR 0.41, 95% CI: 0.17–1.01). Among 43 patients with BM at baseline, alectinib significantly improved systemic PFS over crizotinib as first-line treatment (HR 0.08; 95% CI: 0.01–0.61) (88).

Lorlatinib

Lorlatinib (PF06463922) is a selective, potent, brain-penetrant next-generation ALK and ROS1 TKI, active against most known resistance mutations (79, 89). Lorlatinib was tested in a phase I trial in 54 pretreated or treatment-naïve *ALK*- ($N = 41$) or *ROS-1* ($N = 12$) positive NSCLC patients (11% treatment-naïve, 52% two or more previous TKIs, and 72% with BM). Patients reached a RR of 46% in the *ALK*-positive population irrespective of the number of prior ALK TKI therapies, and median PFS and DOR of 9.6 and 12.4 months, respectively. Lorlatinib was highly active in the CNS, including intracranial responses in 8 of 19 (42%) *ALK*-positive patients with baseline measurable BM, in over a half of whom two or more previous ALK TKIs had failed (90) (**Table 2**). The recommended dose for the phase II trial was 100 mg/day.

In the phase II trial (91), lorlatinib conferred a clinically meaningful benefit, including substantial intracranial efficacy ranging from 42 to 75% in patients with advanced *ALK*-positive disease who were treatment-naïve or who had received a range of prior ALK inhibitors and/or chemotherapies (**Table 2**). In the treatment-naïve cohort ($N = 30$), lorlatinib achieved an RR of 90%, neither PFS nor DOR were reached, while the intracranial RR was 75% among eight patients with BM at baseline. Among the 111 heavily pretreated (two or three previous TKI with or without chemotherapy) patients, lorlatinib reached an overall RR of 39% with median PFS of 6.9 months, and 48% intracranial response among 48 patients with BM at baseline (91). Lorlatinib received breakthrough therapy designation in April 2017 for *ALK*-positive patients previously treated with at least one ALK TKI. Based on these results, the ongoing randomized phase III CROWN trial (NCT03052608) is assessing the efficacy of lorlatinib compared to crizotinib as first-line treatment in *ALK*-positive NSCLC patients. Asymptomatic and pretreated BM are not exclusion criteria.

Brigatinib

Brigatinib is another new ALK TKI (also active against *ROS1*, *EGFR-T790M*, *IGFR*, and *FLT3* mutations) with a broader spectrum of preclinical activity than ceritinib and alectinib against known crizotinib-resistant *ALK*-mutants (79, 92). Brigatinib was granted break-through therapy designation by the FDA in October 2014 on the basis of its early phase I/II trial data (93). In the phase I trial, among 71 crizotinib-resistant *ALK*-positive NSCLC patients treated with brigatinib the confirmed RR was 62% with a median PFS of 13.2 months. Among 46 patients with BM at baseline, the RR was 53% and 35% for those with measurable ($n = 15$) and non-measurable ($n = 31$) intracranial metastases, respectively. The median intracranial PFS and DOR in this population was 15.6 and 18.9 months, respectively. The recommended dose for the phase II study was determined to be 180 mg/day with a 7-day lead-in at 90 mg to reduce the risk of pulmonary toxicity (93).

In the phase II trial, 222 crizotinib-refractory *ALK*-positive NSCLC patients were randomized to brigatinib 90 mg/day (arm A) or 180 mg/day with a 7-day lead-in at 90 mg (arm B) (94), and updated results were recently presented (95). By independent review, the RR was 51 and 55%, in arms A and B, respectively, and PFS was 9.2 and 16.7 months, respectively, while OS was not reached in arm A and was 27.6 months in arm B. This is the longest PFS in crizotinib-resistant tumors reported with new ALK TKIs. Based on these results, the FDA approved brigatinib in crizotinib-pretreated patients in 28 April 2017. Among the 154 patients with BM at baseline (69%), intracranial RR (by independent-review) in patients with measurable disease ($N = 44$) was 50 and 67% in arm A and B, respectively. For patients with active BM ($N = 34$) RRs were similar to those with baseline BM, 47 and 73% in arms A and B, respectively. Median intracranial PFS was 12.8 and 18.4 months in arms A and B, respectively (95). The intracranial efficacy of brigatinib compares favorably with other second-generation ALK TKIs (74, 85) (**Table 2**). Brigatinib is currently being investigated in a randomized phase III ALTA-1L (NCT02737501) trial comparing brigatinib vs. crizotinib in *ALK*-positive TKI-naïve patients. Asymptomatic and pretreated BM are not exclusion criteria. This trial allows crossover from crizotinib to brigatinib and may help to elucidate whether a sequential strategy is better than upfront brigatinib.

Ensartinib

Efficacy of ensartinib (X-396) 225 mg/day in an expansion study has been reported. Forty of the 80 enrolled patients were evaluable for response, achieving 58% partial responses (88% in eight crizotinib-naïve patients, and 64% in 22 crizotinib-resistant) (96). Updated results among 15 TKI-naïve patients showed an 80% RR and median PFS of 23.8 months (97). CNS responses [(60% partial responses) were observed in both crizotinib-naïve and crizotinib-resistant populations, with a median DOR of 5.8 months (98)]. The ongoing phase III XALT3 (NCT02767804) will compare ensartinib with crizotinib as first-line treatment (previous chemotherapy allowed).

OTHER MOLECULAR ALTERATIONS: ROS1, RET, BRAF, AND NTRK

ROS1 Rearrangements

ROS1 rearrangement occurs in approximately 1 to 2% of NSCLC patients. Compared with ALK rearrangements, ROS1 rearrangements are associated with lower rates of extrathoracic metastases, including fewer BM at initial metastatic diagnosis (19 vs. 39%, $p = 0.033$) (99), however *ROS1* does increase the likelihood of BM (100).

In 50 *ROS1*-positive NSCLC patients, crizotinib achieved an RR of 72% and median PFS of 19.2 months (101). Based on these

results, the FDA and EMA approved crizotinib for treatment of *ROS1*-positive NSCLC patients in March and August 2016, respectively. Recently, a phase II trial in 32 Asian *ROS1*-positive NSCLC patients, ceritinib gave an RR of 62%, median PFS of 9.3 months (19.3 months among 30 crizotinib-naïve patients), and median OS of 24 months. Among eight patients with BM, intracranial RR with ceritinib was 63% (102). In a phase I trial with lorlatinib, 12 *ROS1*-positive NSCLC patients achieved an intracranial RR of 50% (80% among five patients with target lesions) and median systemic PFS and DOR of 7 and 12 months, respectively (90) (**Table 2**).

In a phase II study in 47 *ROS*-positive NSCLC patients (28% TKI-naïve, 64% one previous TKI and 8% two or more previous TKIs) treated with lorlatinib, the RR was 36%, with a 45% DCR at 24 weeks, and median PFS and DOR of 9.6 and 13.8 months, respectively (91). Among the 25 patients with BM at baseline, intracranial RR was 56%.

Entrectinib is another ROS1 TKI (also active against *ALK* and *NTRK*) specifically designed to cross the BBB. In a phase I/II trial, entrectinib (600 mg QD) achieved a RR of 78% and median PFS of 29.6 months among 32 treatment-naïve *ROS1*-positive NSCLC patients. The intracranial RR was 83% among 11 patients with BM at baseline (103, 104). Pending questions are the best treatment sequential strategy and whether *ROS1*-positive NSCLC patients with BM should be treated upfront with entrectinib. Given the low *ROS*-1 incidence, it is difficult to perform a randomized trial comparing different treatment strategies.

RET Rearrangements

In NSCLC, *RET* rearrangements occur in 1 to 2% of unselected cases and 16% of NSCLC tumors that lack other oncogenic drivers. They are more common in adenocarcinomas and in never or lighter-smokers (105, 106). *RET*-rearranged NSCLC patients benefit from pemetrexed-based chemotherapy to a comparable extent as *ALK*- and *ROS1*-rearranged patients (107). Multikinase inhibitors, such as cabozantinib (108) and vandetanib (109, 110) in phase II or retrospective studies (105), have limited efficacy, with RR between 18 and 53%, median PFS between 2.3 and 4.5 months (105, 108–110), and median OS of 6.8 months (105). It has been speculated that the type of fusion partner may play a role in determining treatment response (109); however, this was not validated in the retrospective study (105).

Baseline BM incidence in *RET*-rearranged NSCLC is 27%, without differences in age, smoking status or fusion-partner type. Lifetime incidence of BM in *RET*-rearranged NSCLC patients is 49%. In 37 patients treated with multikinase inhibitors with activity against RET, there were no significant differences in median PFS (2.1 vs. 2.1, $p = 041$) or median OS (3.9 vs. 7.0 months, $p = 0.10$) in patients with BM ($N = 10$) vs. without ($N = 27$) (111). In the phase II trial with cabozantinib, baseline untreated BM were present in five patients. Cabozantinib achieved intracranial disease control in two patients with measurable disease (−34 and −1%). Brain progression during TKI treatment may be less common than in other oncogenic alterations. Of 22 patients who discontinued cabozantinib, BM was the cause in only 10% of cases (111). Similarly, intracranial responses have been reported with alectinib, one patient responding after escalating alectinib to 900 mg twice daily (112). The efficacy of alectinib (900–1200 mg/day) as first-line treatment in *RET*-positive NSCLC patients will be assessed in a multi-cohort phase II/III B-FAST trial (NCT03178552). Treated and asymptomatic BM will be allowed. LOXO-292, another RET TKI has reported tolerability and efficacy in *RET*-dependent cancers even in progressive BM after alectinib (113).

In a phase I trial, vandetanib and everolimus showed antitumor activity in *RET*-positive NSCLC patients with BM (114, 115). The short-term outcomes with multikinase inhibitors with activity against RET compared to EGFR/ALK TKIs in *EGFR*-mutant/*ALK*-rearranged NSCLC, strongly suggest that there is a need for more selective and potent RET targeted agents as monotherapy or in combination in order to enhance activity (116).

BRAF-Mutants

The combination of the BRAF inhibitor dabrafenib with the MEK inhibitor trametinib was approved by the FDA and EMA based on clinical activity in 57 pretreated *BRAF-V600E*-mutated NSCLC patients (1–2% of lung adenocarcinoma patients) following a phase II trial giving an RR of 67% and median PFS and OS of 8.6 and 18.2 months, respectively, however no data regarding CNS efficacy are available (117). Similar outcomes were recently replicated among 36 TKI-naïve BRAF (*V600E*)-mutant NSCLC patients (118). In melanoma BM patients, this combination has reported intracranial responses (119), making it highly probable that activity will be observed in NSCLC patients, although this needs to be validated.

NTRK Rearrangements

Fusions involving the genes *NTRK1, NTRK2,* and *NTRK3* are oncogenic drivers. They encode the proteins TRKA, TRKB, and TRKC, respectively, and play roles in neuronal development, cell survival, and cellular proliferation (104). These fusion genes have been detected in a variety of tumors including lung in up to 3% of cases, using different assay (NGS or FISH-based) (120). Entrectinib has reported efficacy in *NTRK*-positive tumors, including NSCLC patients, with a median PFS of 15.6 months (104) and also intracranial activity (104, 120), confirming that entrectinib crosses the BBB. Larotrectinib (LOXO 101) is a pan-TRK TKI. In a phase I clinical trial with 55 *NTRK*-positive solid tumors (five NSCLC patients), larotrectinib achieved an RR of 78% across a wide range of ages and tumor types (121). CNS efficacy of this agent remains unknown.

UPFRONT TKIs vs. UPFRONT RADIOTHERAPY IN ONCOGENE-ADDICTED NSCLC

In oncogene-addicted NSCLC, TKIs have clearly demonstrated increased CNS efficacy, including with next-generation TKIs, which are more potent than first-generation TKIs. Most data have been generated in *EGFR*- or *ALK*-positive patients, although similar outcomes are expected with other druggable alterations. Nonetheless, alternative treatment options exist in this group such

as surgery, WBRT or stereotactic radiosurgery (SRS) (122), and the optimal treatment combination or sequence remains unclear.

Sequential Strategies

A systematic review and meta-analysis of 12 non-comparative studies in 363 *EGFR*-mutant NSCLC patients with BM, showed evidence that upfront radiotherapy (SRS or WBRT) improved survival outcomes (123). However, this study is based on published data and not on individual patient data limiting its validation. This study also reported that radiotherapy caused more neurological adverse events relative to EGFR TKIs alone. In a retrospective multi-institutional analysis in 351 *EGFR*-mutant TKI-naïve NSCLC patients with BM, median OS for three alternative strategies, SRS followed by an EGFR TKI ($n = 100$), WBRT followed by an EGFR TKI ($n = 120$), or an upfront EGFR TKI ($n = 131$), was 46, 30, and 25 months, respectively ($p < 0.001$) (124). In a multivariate analysis, SRS and WBRT vs. EGFR TKI were associated with improved OS, but not with median time to intracranial progression, suggesting that an upfront EGFR TKI and deferred radiotherapy is associated with inferior OS. SRS followed by EGFR-TKI resulted in the longest OS and allowed patients to avoid the potential neurocognitive sequelae of WBRT. However, the retrospective setting meant that data for quality of life and chronic neurocognitive assessments, extracranial disease burden were unavailable, and randomized study design was not used, all of which can be considered as limitations of this analysis. In addition, it is likely that there were a higher number of oligo-metastatic patients in the SRS arm, in whom there is not an urgent need for a TKI to control the extracranial disease, which would generate a major bias.

In a retrospective study ($n = 97$), intracranial PFS was improved in patients who received upfront radiotherapy followed by icotinib compared to those receiving icotinib alone, although without OS improvement (125). However, the absence of randomization makes it difficult to draw a conclusion. On the other hand, in a phase III trial, upfront icotinib ($N = 85$) compared with WBRT (30 Gy) plus chemotherapy ($N = 91$) in *EGFR*-mutant patients with at least three BM significantly improved intracranial PFS (10.0 vs. 4.8 months; HR 0.56, 95% CI: 0.36–0.90; $p = 0.014$), intracranial RR (67.1 vs. 40.9%, $p < 0.001$), and systemic RR (55.0 vs. 11.1%, $p < 0.001$), with a better toxicity profile. Median OS had no significant difference between the arms (18.0 vs. 20.5 months; HR 0.93, 95% CI: 0.60–1.44, $p = 0.734$) (38).

Any of these studies evaluated radiotherapy strategies compared to third-generation EGFR TKIs, so, a prospective randomized trial evaluating intracranial progression after SRS (to avoid the potential neurocognitive sequelae of WBRT) followed by third-generation EGFR TKI vs. third-generation EGFR TKI followed by SRS is needed. The clinical question has also been raised as to whether SRS as consolidative treatment in brain residual disease after EGFR TKI response could improve intracranial PFS in this population or whether this radiotherapy should be only administered in cases of progression on an EGFR TKI.

Concomitant Strategies

In a recent meta-analysis, radiotherapy plus EGFR TKIs resulted in a superior RR and DCR, and markedly prolonged the CNS-time to progression and OS of NSCLC patients with BM (126), although patients were not selected according to EGFR status. The role of combining an EGFR TKI with WBRT was investigated in a single arm phase II trial of 40 patients (17 *EGFR*-mutant) (127). Patients received erlotinib 150 mg/day for 1 week, followed by erlotinib with concurrent WBRT (2.5 Gy/day, 5 days per week, to 35 Gy) and underwent formal cognitive testing before enrollment and at each follow-up visit. In the *EGFR*-mutant subset, patients had longer OS compared to wild-type *EGFR* (19.1 vs. 9.3 months, respectively). Erlotinib was well tolerated in combination with WBRT with no unexpected cases of neurotoxicity.

In a retrospective study in 133 *EGFR*-mutant patients with BM, radiotherapy (WBRT, SRS) and EGFR TKIs (erlotinib, gefitinib) improved median cranial PFS (16.0 vs. 11.5 moths, $p = 0.017$) and median OS (22 vs. 15 months, $p = 0.015$) compared with EGFR TKIs alone (128). On the contrary, in another retrospective cohort of 230 *EGFR*-mutant BM NSCLC patients, the addition of WBRT to EGFR TKIs compared to EGFR TKIs alone did not result in significant differences in intracranial PFS (7.4 vs. 6.9, $p = 0.23$) or systemic PFS (7.9 vs. 7.5, $p = 0.55$), and combined treatment was associated with worse survival (26.4 vs. 21.6 months, $p = 0.049$) (129). These results should be interpreted with caution given the sample sizes, absence of evaluation of side effects and non-randomized study design. While it can be argued that EGFR TKIs can be safely administered with concurrent WBRT (although for *ALK*-positive patients no data are available), high level evidence to support this is lacking, and concomitant strategies are not overtly recommended in either clinical guidelines (122) or in a recent systematic review (130). In cases of asymptomatic BM patients, given the unclear potential synergistic cognitive toxicities caused by combined therapies, WBRT or SRS should be delayed when other effective systemic therapies are available. A recent systematic literature review about results of combined irradiation and targeted therapies has been also recently published (131).

Continuing TKIs With and Without Local Therapy

Many strategies to treat CNS disease in *ALK*-positive NSCLC patients have been reported as case reports, such as high-dose crizotinib with a limited intracranial PFS of 1 month (132) and high-dose pemetrexed in combination with high-dose crizotinib with overall stable cerebral disease for 7 months. However, it remains unknown whether the response is attributable to one or both drugs given at high dose (133). In preclinical models, for enhancing CNS drug penetration, P-gp inhibitors such as elacridar, increased the intracranial concentration of crizotinib ~70-fold (134).

In 120 *ALK*-positive NSCLC patients continuing crizotinib beyond initial progression (51% with brain progression), longer median survival was reported compared with patients who received other chemotherapy (16.4 vs. 5.4 months) (135), although this benefit could also be related to local therapies and more indolent disease in the crizotinib arm. Treating isolated CNS progression with local therapies (surgery and/or radiotherapy) while continuing crizotinib could be viewed as an acceptable option (136). In the PROFILE 1014 study, among 25

patients with intracranial progression on crizotinib, 19 received radiotherapy, while continued crizotinib achieved a median treatment time beyond progression of 5.1 months, which was longer than the 2.9 months achieved with crizotinib beyond progression among patients with extracranial progression (70). In a retrospective single-institution study, local therapy (either surgery or radiotherapy) for BM in *EGFR*-mutant (17 treated with erlotinib) or *ALK*-rearranged (38 treated with crizotinib) NSCLC patients and CNS progression allowed continuation of therapy for an additional 7.1 months (137).

Recent studies have reported that *ALK*-positive NSCLC patients with BM treated with SRS and/or WBRT and TKIs have prolonged survival (68, 69, 138). Given the extended OS for *ALK*-positive patients and frequent need for repeated courses of CNS radiotherapy, SRS is the preferred strategy for minimizing cerebral toxicity. Synergistic efficacy of crizotinib and radiotherapy could be explained by increased BBB permeability and decreased P-gp expression following irradiation (139). These results suggest intracranial interventions and TKIs beyond progression are of value in patients with asymptomatic and limited CNS progression on a TKI. This SRS strategy is being validated in an ongoing phase II clinical trial (NCT02314364) among oncogene-addicted *(EGFR-, ALK-, ROS1*-positive*)* NSCLC patients with up to four BM.

The promising CNS activity of the next-generation TKIs suggests that switching targeted agents may be a reasonable alternative to local therapies. However, prospective data are needed to determine which strategy offers the best OS, intracranial control rate, quality of life and therapeutic ratio, taking into account the number of BM and whether patients are symptomatic at the time of progression.

Second- or Third-Generation TKIs Upfront or Sequentially

In *EGFR*-mutant NSCLC patients, osimertinib has reported higher intracranial activity compared with chemotherapy (51) and first-generation EGFR TKIs (17), and longer delay of onset of BM (51). However, lack of stratification according the presence of BM, no reported survival benefit with osimertinib and no prospective validation of this efficacy, limit interpretation. Nonetheless, preclinical data strongly support the increased intracranial efficacy of osimertinib compared with other EGFR TKIs (44). The ongoing phase II APPLE trial (NCT02856893) assesses the optimal strategy for delivering osimertinib in *EGFR*-mutant NSCLC patients and will prospectively validate the efficacy of osimertinib among those patients with BM at baseline (stratification criteria and brain MRI will be performed at baseline) and also the time to radiological brain progression respect to with first-generation EGFR TKI (gefitinib) (140).

In *ALK*-positive NSCLC patients, based on this significant PFS improvement with alectinib and the delay of CNS progression compared with the current standard first-line crizotinib in *ALK*-positive NSCLC patients, alectinib has became a new standard treatment, and is approved by the EMA and FDA. However, it has not yet been demonstrated whether upfront treatment with second-generation ALK TKIs impact OS compared with sequential treatment strategies (**Figure 1**). In *ALK*-positive NSCLC patients, 4-year OS was 57% with upfront crizotinib in the randomized phase III PROFILE 1014 trial ($N = 172$), and was 70% with alectinib (300 mg twice daily) among 43 Japanese patients included in a phase II trial (141). Although data are immature, no survival benefit has been reported with upfront alectinib compared with crizotinib in the ALEX trial (65). Also, in PROFILE 1014, patients who received crizotinib followed by another ALK-TKI had longer OS compared with those randomized to chemotherapy followed by no ALK-TKI or other treatment (who had the poorest OS), suggesting a potential benefit of sequential strategies (142).

In a multicentre retrospective study, OS in patients treated with crizotinib followed by alectinib tended to be longer than in patients treated with alectinib alone (143) and median OS up to 50 months has been reported in patients who receive sequential strategies with upfront crizotinib (144, 145). A French nationwide retrospective cohort (CLINALK study) with 318 *ALK*-positive NSCLC patients reported that patients who received next-generation ALK TKIs after crizotinib progression (ceritinib, alectinib, lorlatinib; $N = 84$) had improved OS, reaching a median of 89.6 months (146). Large-scale prospective studies are needed to confirm these preliminary observations.

Finally, each ALK TKI is associated with a distinct spectrum of *ALK*-resistant mutations, and the frequency of mutations increases significantly after treatment with second-generation ALK TKIs (20% with crizotinib vs. 53% with alectinib) (79). It is important to note that there are few new ALK TKIs that may overcome alectinib resistance, and efficacy is dependent on the acquired *ALK* mutation subtype upon progression on alectinib (79). Lack of a tissue biopsy for molecular profiling at progression and limited access to new ALK TKIs worldwide might limit access to subsequent therapies in alectinib-resistant diseases. Validation of liquid biopsies for dynamic markers of TKI efficacy (147) as well as predictive markers for personalized treatment at progression on ALK TKIs is also a challenge. On the other hand, the high CNS response and the delay in the onset of BM with alectinib, which could have a positive impact on patients' quality of life, might justify first-line treatment with alectinib in this population.

CONCLUSION

Brain metastases are common in NSCLC including in molecularly selected populations, and are associated with a reduced quality of life. A multidisciplinary approach is the optimal strategy in oncogene-addicted NSCLC patients with BM. Based on the available clinical data and long OS in patients with asymptomatic synchronous BM at diagnosis, upfront treatment with TKIs alone should be considered with close CNS surveillance for early intervention in patients with an inadequate CNS response. This strategy may defer CNS radiotherapy and avoid long-term neurologic sequelae associated with local therapies. For patients with symptomatic BM, initial TKI therapy is an option, especially in *EGFR*-mutant and *ALK*-positive NSCLC patients treated with new *EGFR* and ALK TKIs based on their higher CNS efficacy. In other cases, sequential treatment initiated with local therapy followed by a TKI is appropriate. For patients who experience CNS progression with controlled extracranial disease while on TKI treatment, local therapy

(preferably SRS) followed by the same TKI is an option in patients with a limited number of lesions or who are asymptomatic. In cases of multiple CNS progression, a switch to another TKI with higher CNS-penetration activity with or without WBRT is appropriate.

AUTHOR CONTRIBUTIONS

Review concept, design, acquisition, analysis, and interpretation of data performed equally by BB and JR.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* (2015) 136:E359–86. doi:10.1002/ijc.29210
2. Berghoff AS, Schur S, Füreder LM, Gatterbauer B, Dieckmann K, Widhalm G, et al. Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers. *ESMO Open* (2016) 1:e000024. doi:10.1136/esmoopen-2015-000024
3. Eichler AF, Chung E, Kodack DP, Loeffler JS, Fukumura D, Jain RK. The biology of brain metastases-translation to new therapies. *Nat Rev Clin Oncol* (2011) 8:344–56. doi:10.1038/nrclinonc.2011.58
4. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* (2012) 30:419–25. doi:10.1200/JCO.2011.38.0527
5. Peters S, Bexelius C, Munk V, Leighl N. The impact of brain metastasis on quality of life, resource utilization and survival in patients with non-small-cell lung cancer. *Cancer Treat Rev* (2016) 45:139–62. doi:10.1016/j.ctrv.2016.03.009
6. Barlesi F, Mazieres J, Merlio J-P, Debieuvre D, Mosser J, Lena H, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French cooperative thoracic intergroup (IFCT). *Lancet* (2016) 387:1415–26. doi:10.1016/S0140-6736(16)00004-0
7. Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA* (2014) 311:1998–2006. doi:10.1001/jama.2014.3741
8. Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, et al. Estimating survival in patients with lung cancer and brain metastases: an update of the graded prognostic assessment for lung cancer using molecular markers (lung-molGPA). *JAMA Oncol* (2017) 3(6):827–31. doi:10.1001/jamaoncol.2016.3834
9. Brastianos PK, Carter SL, Santagata S, Cahill DP, Taylor-Weiner A, Jones RT, et al. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. *Cancer Discov* (2015) 5:1164–77. doi:10.1158/2159-8290.CD-15-0369
10. Gandhi L, Ignatius Ou S-H, Shaw AT, Barlesi F, Dingemans A-MC, Kim D-W, et al. Efficacy of alectinib in central nervous system metastases in crizotinib-resistant ALK-positive non-small-cell lung cancer: comparison of RECIST 1.1 and RANO-HGG criteria. *Eur J Cancer* (1990) 2017(82):27–33. doi:10.1016/j.ejca.2017.05.019
11. Ou S-HI, Klempner SJ, Azada MC, Rausei-Mills V, Duma C. Radiation necrosis presenting as pseudoprogression (PsP) during alectinib treatment of previously radiated brain metastases in ALK-positive NSCLC: implications for disease assessment and management. *Lung Cancer* (2015) 88:355–9. doi:10.1016/j.lungcan.2015.03.022
12. Chuang M-T, Liu Y-S, Tsai Y-S, Chen Y-C, Wang C-K. Differentiating radiation-induced necrosis from recurrent brain tumor using MR perfusion and spectroscopy: a meta-analysis. *PLoS One* (2016) 11:e0141438. doi:10.1371/journal.pone.0141438
13. Di L, Rong H, Feng B. Demystifying brain penetration in central nervous system drug discovery. Miniperspective. *J Med Chem* (2013) 56:2–12. doi:10.1021/jm301297f
14. Pardridge WM. The blood-brain barrier: bottleneck in brain drug development. *NeuroRx* (2005) 2:3–14. doi:10.1602/neurorx.2.1.3
15. Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). *Am J Cancer Res* (2015) 5(9):2892–911.
16. Reguart N, Remon J. Common EGFR-mutated subgroups (Del19/L858R) in advanced non-small-cell lung cancer: chasing better outcomes with tyrosine-kinase inhibitors. *Future Oncol* (2015) 11(8):1245–57. doi:10.2217/fon.15.15
17. Soria J-C, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* (2018) 378(2):113–25. doi:10.1056/NEJMoa1713137
18. Iuchi T, Shingyoji M, Itakura M, Yokoi S, Moriya Y, Tamura H, et al. Frequency of brain metastases in non-small-cell lung cancer, and their association with epidermal growth factor receptor mutations. *Int J Clin Oncol* (2015) 20:674–9. doi:10.1007/s10147-014-0760-9
19. Rangachari D, Yamaguchi N, VanderLaan PA, Folch E, Mahadevan A, Floyd SR, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer* (2015) 88:108–11. doi:10.1016/j.lungcan.2015.01.020
20. Hendriks LEL, Smit EF, Vosse BA, Mellema WW, Heideman DA, Bootsma GP, et al. EGFR mutated non-small cell lung cancer patients: more prone to development of bone and brain metastases? *Lung Cancer* (2014) 84:86–91. doi:10.1016/j.lungcan.2014.01.006
21. Heon S, Yeap BY, Britt GJ, Costa DB, Rabin MS, Jackman DM, et al. Development of central nervous system metastases in patients with advanced non-small cell lung cancer and somatic EGFR mutations treated with gefitinib or erlotinib. *Clin Cancer Res* (2010) 16:5873–82. doi:10.1158/1078-0432.CCR-10-1588
22. Patel SH, Rimner A, Foster A, Zhang Z, Woo KM, Yu HA, et al. Patterns of initial and intracranial failure in metastatic EGFR-mutant non-small cell lung cancer treated with erlotinib. *Lung Cancer* (2017) 108:109–14. doi:10.1016/j.lungcan.2017.03.010
23. Heon S, Yeap BY, Lindeman NI, Joshi VA, Butaney M, Britt GJ, et al. The impact of initial gefitinib or erlotinib versus chemotherapy on central nervous system progression in advanced non-small cell lung cancer with EGFR mutations. *Clin Cancer Res* (2012) 18:4406–14. doi:10.1158/1078-0432.CCR-12-0357
24. Ma X, Zhu H, Guo H, Han A, Wang H, Jing W, et al. Risk factors of brain metastasis during the course of EGFR-TKIs therapy for patients with EGFR-mutated advanced lung adenocarcinoma. *Oncotarget* (2016) 7:81906–17. doi:10.18632/oncotarget.11918
25. Matsumoto S, Takahashi K, Iwakawa R, Matsuno Y, Nakanishi Y, Kohno T, et al. Frequent EGFR mutations in brain metastases of lung adenocarcinoma. *Int J Cancer* (2006) 119:1491–4. doi:10.1002/ijc.21940
26. Omuro AMP, Kris MG, Miller VA, Franceschi E, Shah N, Milton DT, et al. High incidence of disease recurrence in the brain and leptomeninges in patients with nonsmall cell lung carcinoma after response to gefitinib. *Cancer* (2005) 103:2344–8. doi:10.1002/cncr.21033
27. Lee YJ, Choi HJ, Kim SK, Chang J, Moon JW, Park IK, et al. Frequent central nervous system failure after clinical benefit with epidermal growth factor receptor tyrosine kinase inhibitors in Korean patients with nonsmall-cell lung cancer. *Cancer* (2010) 116:1336–43. doi:10.1002/cncr.24877
28. Ahn M-J, Kim D-W, Cho BC, Kim S-W, Lee JS, Ahn J-S, et al. Activity and safety of AZD3759 in EGFR-mutant non-small-cell lung cancer with CNS metastases (BLOOM): a phase 1, open-label, dose-escalation and dose-expansion study. *Lancet Respir Med* (2017) 5(11):891–902. doi:10.1016/S2213-2600(17)30378-8
29. Porta R, Sánchez-Torres JM, Paz-Ares L, Massutí B, Reguart N, Mayo C, et al. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. *Eur Respir J* (2011) 37:624–31. doi:10.1183/09031936.00195609
30. Wu Y-L, Zhou C, Cheng Y, Lu S, Chen G-Y, Huang C, et al. Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer

and asymptomatic brain metastases: a phase II study (CTONG-0803). *Ann Oncol* (2013) 24:993–9. doi:10.1093/annonc/mds529
31. Park SJ, Kim HT, Lee DH, Kim KP, Kim S-W, Suh C, et al. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. *Lung Cancer* (2012) 77:556–60. doi:10.1016/j.lungcan.2012.05.092
32. Iuchi T, Shingyoji M, Sakaida T, Hatano K, Nagano O, Itakura M, et al. Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. *Lung Cancer* (2013) 82:282–7. doi:10.1016/j.lungcan.2013.08.016
33. Zhang Q, Zhang X, Yan H, Jiang B, Xu C, Yang J, et al. Effects of epidermal growth factor receptor-tyrosine kinase inhibitors alone on EGFR-mutant non-small cell lung cancer with brain metastasis. *Thorac Cancer* (2016) 7:648–54. doi:10.1111/1759-7714.12379
34. Hotta K, Kiura K, Ueoka H, Tabata M, Fujiwara K, Kozuki T, et al. Effect of gefitinib ('Iressa', ZD1839) on brain metastases in patients with advanced non-small-cell lung cancer. *Lung Cancer* (2004) 46:255–61. doi:10.1016/j.lungcan.2004.04.036
35. Zhang S-R, Zhu L-C, Jiang Y-P, Zhang J, Xu R-J, Xu Y-S, et al. Efficacy of afatinib, an irreversible ErbB family blocker, in the treatment of intracerebral metastases of non-small cell lung cancer in mice. *Acta Pharmacol Sin* (2017) 38:233–40. doi:10.1038/aps.2016.107
36. Hoffknecht P, Tufman A, Wehler T, Pelzer T, Wiewrodt R, Schütz M, et al. Efficacy of the irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease. *J Thorac Oncol* (2015) 10:156–63. doi:10.1097/JTO.0000000000000380
37. Schuler M, Wu Y-L, Hirsh V, O'Byrne K, Yamamoto N, Mok T, et al. First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. *J Thorac Oncol* (2016) 11:380–90. doi:10.1016/j.jtho.2015.11.014
38. Yang J-J, Zhou C, Huang Y, Feng J, Lu S, Song Y, et al. Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial. *Lancet Respir Med* (2017) 5(9):707–16. doi:10.1016/S2213-2600(17)30262-X
39. Yun C-H, Mengwasser KE, Toms AV, Woo MS, Greulich H, Wong K-K, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci U S A* (2008) 105:2070–5. doi:10.1073/pnas.0709662105
40. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* (2011) 3:75ra26. doi:10.1126/scitranslmed.3002003
41. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* (2013) 19:2240–7. doi:10.1158/1078-0432.CCR-12-2246
42. Hata A, Katakami N, Yoshioka H, Takeshita J, Tanaka K, Nanjo S, et al. Rebiopsy of non-small cell lung cancer patients with acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitor: comparison between T790M mutation-positive and mutation-negative populations. *Cancer* (2013) 119:4325–32. doi:10.1002/cncr.28364
43. Hata A, Katakami N, Yoshioka H, Kaji R, Masago K, Fujita S, et al. Spatiotemporal T790M heterogeneity in individual patients with EGFR-mutant non-small-cell lung cancer after acquired resistance to EGFR-TKI. *J Thorac Oncol* (2015) 10:1553–9. doi:10.1097/JTO.0000000000000647
44. Ballard P, Yates JWT, Yang Z, Kim D-W, Yang JC-H, Cantarini M, et al. Preclinical Comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. *Clin Cancer Res* (2016) 22:5130–40. doi:10.1158/1078-0432.CCR-16-0399
45. Yang JC-H, Ahn M-J, Kim D-W, Ramalingam SS, Sequist LV, Su W-C, et al. Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study phase II extension component. *J Clin Oncol* (2017) 35(12):1288–96. doi:10.1200/JCO.2016.70.3223
46. Goss G, Tsai C-M, Shepherd FA, Bazhenova L, Lee JS, Chang G-C, et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol* (2016) 17:1643–52. doi:10.1016/S1470-2045(16)30508-3
47. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* (2017) 376(7):629–40. doi:10.1056/NEJMoa1612674
48. Yang J, Ramalingam SS, Jänne PA, Cantarini M, Mitsudomi T. LBA2_PR: osimertinib (AZD9291) in pre-treated pts with T790M-positive advanced NSCLC: updated phase 1 (P1) and pooled phase 2 (P2) results. *J Thorac Oncol* (2016) 11:S152–3. doi:10.1016/S1556-0864(16)30325-2
49. Goss G, Tsai C-M, Shepherd FA, Ahn M-J, Bazhenova L, Crinò L, et al. CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials. *Ann Oncol* (2017). doi:10.1093/annonc/mdx820
50. Goss G, Tsai C-M, Shepherd F, Ahn M-J, Bazhenova L, Crinò L, et al. MA16.11 CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials. *J Thorac Oncol* (2017) 12:S440–1. doi:10.1016/j.jtho.2016.11.514
51. Mok T, Ahn M-J, Han J-Y, Kang JH, Katakami N, Kim H, et al. CNS response to osimertinib in patients (pts) with T790M-positive advanced NSCLC: data from a randomized phase III trial (AURA3). *J Clin Oncol* (2017) 35:9005–9005. doi:10.1200/JCO.2017.35.15_suppl.9005
52. Zhang J, Yu J, Sun X, Meng X. Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of central nerve system metastases from non-small cell lung cancer. *Cancer Lett* (2014) 351:6–12. doi:10.1016/j.canlet.2014.04.019
53. Vansteenkiste J, Reungwetwattana T, Nakagawa K, Cho BC, Dols MAC, Cho EK, et al. LBA5CNS response to osimertinib vs standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with EGFR-TKI sensitising mutation (EGFRm)-positive advanced non-small cell lung cancer (NSCLC): data from the FLAURA study. *Ann Oncol* (2017) 28:.007–.729. doi:10.1093/annonc/mdx729.007
54. Jackman DM, Holmes AJ, Lindeman N, Wen PY, Kesari S, Borras AM, et al. Response and resistance in a non-small-cell lung cancer patient with an epidermal growth factor receptor mutation and leptomeningeal metastases treated with high-dose gefitinib. *J Clin Oncol* (2006) 24:4517–20. doi:10.1200/JCO.2006.06.6126
55. Grommes C, Oxnard GR, Kris MG, Miller VA, Pao W, Holodny AI, et al. "Pulsatile" high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. *Neuro Oncol* (2011) 13:1364–9. doi:10.1093/neuonc/nor121
56. Kuiper JL, Smit EF. High-dose, pulsatile erlotinib in two NSCLC patients with leptomeningeal metastases – one with a remarkable thoracic response as well. *Lung Cancer* (2013) 80:102–5. doi:10.1016/j.lungcan.2012.12.024
57. Kuiper JL, Heideman DAM, Thunnissen E, van Wijk AW, Postmus PE, Smit EF. High-dose, weekly erlotinib is not an effective treatment in EGFR-mutated non-small cell lung cancer-patients with acquired extracranial progressive disease on standard dose erlotinib. *Eur J Cancer* (1990) 2014(50):1399–401. doi:10.1016/j.ejca.2014.02.005
58. Yu HA, Sima C, Feldman D, Liu LL, Vaitheesvaran B, Cross J, et al. Phase 1 study of twice weekly pulse dose and daily low-dose erlotinib as initial treatment for patients with EGFR-mutant lung cancers†. *Ann Oncol* (2017) 28:278–84. doi:10.1093/annonc/mdw556
59. Besse B, Le Moulec S, Mazieres J, Senellart H, Barlesi F, Chouaid C, et al. Bevacizumab in patients with nonsquamous non-small cell lung cancer and asymptomatic, untreated brain metastases (BRAIN): a nonrandomized, phase II study. *Clin Cancer Res* (2015) 21(8):1896–903. doi:10.1158/1078-0432.CCR-14-2082
60. Ilhan-Mutlu A, Osswald M, Liao Y, Gömmel M, Reck M, Miles D, et al. Bevacizumab prevents brain metastases formation in lung adenocarcinoma. *Mol Cancer Ther* (2016) 15:702–10. doi:10.1158/1535-7163.MCT-15-0582
61. Seto T, Kato T, Nishio M, Goto K, Atagi S, Hosomi Y, et al. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. *Lancet Oncol* (2014) 15:1236–44. doi:10.1016/S1470-2045(14)70381-X
62. Rosell R, Dafni U, Felip E, Curioni-Fontecedro A, Gautschi O, Peters S, et al. Erlotinib and bevacizumab in patients with advanced non-small-cell

lung cancer and activating EGFR mutations (BELIEF): an international, multicentre, single-arm, phase 2 trial. *Lancet Respir Med* (2017) 5:435–44. doi:10.1016/S2213-2600(17)30129-7
63. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2016) 27:v1–27. doi:10.1093/annonc/mdw326
64. Soria J-C, Tan DSW, Chiari R, Wu Y-L, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet* (2017) 389:917–29. doi:10.1016/S0140-6736(17)30123-X
65. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim D-W, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med* (2017) 377(9):829–38. doi:10.1056/NEJMoa1704795
66. Shaw AT, Kim D-W, Nakagawa K, Seto T, Crino L, Ahn M-J, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* (2013) 368:2385–94. doi:10.1056/NEJMoa1214886
67. Shaw AT, Kim D-W, Mehra R, Tan DSW, Felip E, Chow LQM, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med* (2014) 370:1189–97. doi:10.1056/NEJMoa1311107
68. Costa DB, Shaw AT, Ou S-HI, Solomon BJ, Riely GJ, Ahn M-J, et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. *J Clin Oncol* (2015) 33:1881–8. doi:10.1200/JCO.2014.59.0539
69. Johung KL, Yeh N, Desai NB, Williams TM, Lautenschlaeger T, Arvold ND, et al. Extended survival and prognostic factors for patients with ALK-rearranged non-small-cell lung cancer and brain metastasis. *J Clin Oncol* (2016) 34:123–9. doi:10.1200/JCO.2015.62.0138
70. Solomon BJ, Cappuzzo F, Felip E, Blackhall FH, Costa DB, Kim D-W, et al. Intracranial efficacy of crizotinib versus chemotherapy in patients with advanced ALK-positive non-small-cell lung cancer: results from PROFILE 1014. *J Clin Oncol* (2016) 34:2858–65. doi:10.1200/JCO.2015.63.5888
71. Costa DB, Kobayashi S, Pandya SS, Yeo W-L, Shen Z, Tan W, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol* (2011) 29:e443–5. doi:10.1200/JCO.2010.34.1313
72. Gadgeel S, Peters S, Mok TSK, Shaw AT, Kim D-W, Ou S-HI, et al. 1298O_PRAlectinib vs crizotinib in treatment-naïve ALK+ NSCLC: CNS efficacy results from the ALEX study. *Ann Oncol* (2017) 28:.057–.440. doi:10.1093/annonc/mdx440.057
73. Kim D-W, Mehra R, Tan DSW, Felip E, Chow LQM, Camidge DR, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. *Lancet Oncol* (2016) 17:452–63. doi:10.1016/S1470-2045(15)00614-2
74. Crinò L, Ahn M-J, De Marinis F, Groen HJ, Wakelee H, Hida T, et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: results from ASCEND-2. *J Clin Oncol* (2016) 34(24):2866–73. doi:10.1200/JCO.2015.65.5936
75. Felip E, Orlov S, Park K, Yu C-J, Tsai C-M, Nishio M, et al. Phase 2 study of ceritinib in ALKi-naïve patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC): whole body responses in the overall pt group and in pts with baseline brain metastases (BM). *Ann Oncol* (2016) 27:1208O. doi:10.1093/annonc/mdw383.03
76. Shaw AT, Kim TM, Crinò L, Gridelli C, Kiura K, Liu G, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* (2017) 18:874–86. doi:10.1016/S1470-2045(17)30339-X
77. Cho BC, Kim D-W, Bearz A, Laurie SA, McKeage M, Borra G, et al. ASCEND-8: a randomized phase 1 study of ceritinib, 450 mg or 600 mg, taken with a low-fat meal versus 750 mg in fasted state in patients with anaplastic lymphoma kinase (ALK)-rearranged metastatic non–small cell lung cancer (NSCLC). *J Thorac Oncol* 12:1357–67. doi:10.1016/j.jtho.2017.07.005
78. Cho BC, Obermannová R, Bearz A, Kim D, Orlov S, Borra G, et al. OA 05.07 efficacy and updated safety of ceritinib (450 Mg or 600 Mg) with low-fat meal vs 750 Mg fasted in ALK+ metastatic NSCLC. *J Thorac Oncol* 12:S1757. doi:10.1016/j.jtho.2017.09.352
79. Gainor JF, Dardaei L, Yoda S, Friboulet L, Leshchiner I, Katayama R, et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discov* (2016) 6:1118–33. doi:10.1158/2159-8290.CD-16-0596
80. Gainor JF, Sherman CA, Willoughby K, Logan J, Kennedy E, Brastianos PK, et al. Alectinib salvages CNS relapses in ALK-positive lung cancer patients previously treated with crizotinib and ceritinib. *J Thorac Oncol* (2015) 10:232–6. doi:10.1097/JTO.0000000000000455
81. Gadgeel SM, Gandhi L, Riely GJ, Chiappori AA, West HL, Azada MC, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. *Lancet Oncol* (2014) 15:1119–28. doi:10.1016/S1470-2045(14)70362-6
82. Shaw AT, Gandhi L, Gadgeel S, Riely GJ, Cetnar J, West H, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. *Lancet Oncol* (2016) 17:234–42. doi:10.1016/S1470-2045(15)00488-X
83. Ou S-HI, Ahn JS, De Petris L, Govindan R, Yang JC-H, Hughes B, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase II global study. *J Clin Oncol* (2016) 34:661–8. doi:10.1200/JCO.2015.63.9443
84. Yang JC-H, Ou S-I, De Petris L, Gadgeel S, Gandhi L, Kim D-W, et al. Pooled systemic efficacy and safety data from the pivotal phase II studies (NP28673 and NP28761) of alectinib in ALK-positive non-small-cell lung cancer. *J Thorac Oncol* (2017) 12(10):1552–60. doi:10.1016/j.jtho.2017.06.070
85. Gadgeel SM, Shaw AT, Govindan R, Gandhi L, Socinski MA, Camidge DR, et al. Pooled analysis of CNS response to alectinib in two studies of pretreated patients with ALK-positive non-small-cell lung cancer. *J Clin Oncol* (2016) 34:4079–85. doi:10.1200/JCO.2016.68.4639
86. Novello S, Mazieres J, Oh I-J, de Castro J, Migliorino MR, Helland A, et al. 1299O_PRPrimary results from the phase III ALUR study of alectinib versus chemotherapy in previously treated ALK+ non-small-cell lung cancer (NSCLC). *Ann Oncol* (2017) 28:.058–.440. doi:10.1093/annonc/mdx440.058
87. de Castro J, Novello S, Mazieres J, Oh I-J, Migliorino MR, Helland A, et al. 1346PCNS efficacy results from the phase III ALUR study of alectinib vs chemotherapy in previously treated ALK+ NSCLC. *Ann Oncol* (2017) 28:.048–.380. doi:10.1093/annonc/mdx380.048
88. Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, Seto T, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet* (2017) 390:29–39. doi:10.1016/S0140-6736(17)30565-2
89. Zou HY, Friboulet L, Kodack DP, Engstrom LD, Li Q, West M, et al. PF-06463922, an ALK/ROS1 inhibitor, overcomes resistance to first and second generation ALK inhibitors in preclinical models. *Cancer Cell* (2015) 28:70–81. doi:10.1016/j.ccell.2015.05.010
90. Shaw AT, Felip E, Bauer TM, Besse B, Navarro A, Postel-Vinay S, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol* (2017) 18(12):1590–9. doi:10.1016/S1470-2045(17)30680-0
91. Solomon B, Shaw A, Ou S, Besse B, Felip E, Bauer T, et al. OA 05.06 phase 2 study of lorlatinib in patients with advanced ALK+/ROS1+ non-small-cell lung cancer. *J Thorac Oncol* 12:S1756. doi:10.1016/j.jtho.2017.09.351
92. Zhang S, Anjum R, Squillace R, Nadworny S, Zhou T, Keats J, et al. The potent ALK inhibitor brigatinib (AP26113) overcomes mechanisms of resistance to first- and second-generation ALK inhibitors in preclinical models. *Clin Cancer Res* (2016) 22:5527–38. doi:10.1158/1078-0432.CCR-16-0569
93. Gettinger SN, Bazhenova LA, Langer CJ, Salgia R, Gold KA, Rosell R, et al. Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. *Lancet Oncol* (2016) 17:1683–96. doi:10.1016/S1470-2045(16)30392-8
94. Kim D-W, Tiseo M, Ahn M-J, Reckamp KL, Hansen KH, Kim S-W, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. *J Clin Oncol* (2017) 35(22):2490–8. doi:10.1200/JCO.2016.71.5904
95. Ahn M, Camidge DR, Tiseo M, Reckamp K, Hansen K, Kim S, et al. OA 05.05 brigatinib in crizotinib-refractory ALK+ NSCLC: updated efficacy and safety results from ALTA, a randomized phase 2 trial. *J Thorac Oncol* (2017) 12:S1755–6. doi:10.1016/j.jtho.2017.09.350

96. Horn L, Wakelee H, Reckamp K, Blumenschein G, Infante J, Carter C, et al. P3.02a-001 response and plasma genotyping from phase I/II trial of ensartinib (X-396) in patients (Pts) with ALK+ NSCLC. *J Thorac Oncol* (2017) 12:S1159. doi:10.1016/j.jtho.2016.11.1631
97. Wakelee H, Sanborn R, Nieva J, Waqar S, Brzezniak C, Bauman J, et al. MA 07.02 response to ensartinib in TKI naïve ALK+ NSCLC patients. *J Thorac Oncol* 12:S1826. doi:10.1016/j.jtho.2017.09.504
98. Reckamp KL, Wakelee HA, Patel S, Blumenschein G, Neal JW, Gitlitz B, et al. 88OCNS activity of ensartinib in ALK+ non-small cell lung cancer (NSCLC) patients (pts). *Ann Oncol* (2017) 28:mdx091.008. doi:10.1093/annonc/mdx091.008
99. Gainor JF, Tseng D, Yoda S, Dagogo-Jack I, Friboulet L, Lin JJ, et al. Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non–small-cell lung cancer. *JCO Precis Oncol* (2017) 1:1–13. doi:10.1200/PO.17.00063
100. Preusser M, Streubel B, Birner P. ROS1 translocations and amplifications in lung cancer brain metastases. *J Neurooncol* (2014) 118:425–6. doi:10.1007/s11060-014-1446-x
101. Shaw AT, Ou S-HI, Bang Y-J, Camidge DR, Solomon BJ, Salgia R, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med* (2014) 371:1963–71. doi:10.1056/NEJMoa1406766
102. Lim SM, Kim HR, Lee J-S, Lee KH, Lee Y-G, Min YJ, et al. Open-label, multicenter, phase II study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement. *J Clin Oncol* (2017) 35(23):2613–8. doi:10.1200/JCO.2016.71.3701
103. Ahn M, Cho BC, Siena S, Drilon A, De Braud F, Krebs M, et al. OA 14.06 entrectinib in patients with locally advanced or metastatic ROS1 fusion-positive non-small cell lung cancer (NSCLC). *J Thorac Oncol* 12:S1783. doi:10.1016/j.jtho.2017.09.411
104. Drilon A, Siena S, Ou S-HI, Patel M, Ahn MJ, Lee J, et al. Safety and antitumor activity of the multitargeted pan-TRK, ROS1, and ALK inhibitor entrectinib: combined results from two phase I trials (ALKA-372-001 and STARTRK-1). *Cancer Discov* (2017) 7:400–9. doi:10.1158/2159-8290.CD-16-1237
105. Gautschi O, Milia J, Filleron T, Wolf J, Carbone DP, Owen D, et al. Targeting RET in patients with RET-rearranged lung cancers: results from the global, multicenter ret registry. *J Clin Oncol* (2017) 35:1403–10. doi:10.1200/JCO.2016.70.9352
106. Ferrara R, Auger N, Auclin E, Besse B. Clinical and translational implications of RET rearrangements in non-small cell lung cancer. *J Thorac Oncol* (2018) 13(1):27–45. doi:10.1016/j.jtho.2017.10.021
107. Drilon A, Bergagnini I, Delasos L, Sabari J, Woo KM, Plodkowski A, et al. Clinical outcomes with pemetrexed-based systemic therapies in RET-rearranged lung cancers. *Ann Oncol* (2016) 27:1286–91. doi:10.1093/annonc/mdw163
108. Drilon A, Rekhtman N, Arcila M, Wang L, Ni A, Albano M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol* (2016) 17:1653–60. doi:10.1016/S1470-2045(16)30562-9
109. Yoh K, Seto T, Satouchi M, Nishio M, Yamamoto N, Murakami H, et al. Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial. *Lancet Respir Med* (2017) 5:42–50. doi:10.1016/S2213-2600(16)30322-8
110. Lee S-H, Lee J-K, Ahn M-J, Kim D-W, Sun J-M, Keam B, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial. *Ann Oncol* (2017) 28:292–7. doi:10.1093/annonc/mdw559
111. Drilon AE, Filleron T, Bergagnini I, Milia J, Hatzoglou V, Velcheti V, et al. Baseline frequency of brain metastases and outcomes with multikinase inhibitor therapy in patients with RET-rearranged lung cancers. *J Clin Oncol* (2017) 35:9069–9069. doi:10.1200/JCO.2017.35.15_suppl.9069
112. Lin JJ, Kennedy E, Sequist LV, Brastianos PK, Goodwin KE, Stevens S, et al. Clinical activity of alectinib in advanced RET-rearranged non-small cell lung cancer. *J Thorac Oncol* (2016) 11:2027–32. doi:10.1016/j.jtho.2016.08.126
113. Velcheti V, Bauer T, Subbiah V, Cabanillas M, Lakhani N, Wirth L, et al. OA 12.07 LOXO-292, a potent, highly selective RET inhibitor, in MKI-resistant RET fusion-positive lung cancer patients with and without brain metastases. *J Thorac Oncol* (2017) 12:S1778. doi:10.1016/j.jtho.2017.09.399
114. Subbiah V, Berry J, Roxas M, Guha-Thakurta N, Subbiah IM, Ali SM, et al. Systemic and CNS activity of the RET inhibitor vandetanib combined with the mTOR inhibitor everolimus in KIF5B-RET re-arranged non-small cell lung cancer with brain metastases. *Lung Cancer* (2015) 89:76–9. doi:10.1016/j.lungcan.2015.04.004
115. Cascone T, Hess KR, Piha-Paul SA, Hong DS, Subbiah IM, Bhatt T, et al. Safety, toxicity and activity of multi-kinase inhibitor vandetanib in combination with everolimus in advanced solid tumors. *J Clin Oncol* (2016) 34:9073–9073. doi:10.1200/JCO.2016.34.15_suppl.9073
116. Plenker D, Riedel M, Brägelmann J, Dammert MA, Chauhan R, Knowles PP, et al. Drugging the catalytically inactive state of RET kinase in RET-rearranged tumors. *Sci Transl Med* (2017) 9:eaah6144. doi:10.1126/scitranslmed.aah6144
117. Planchard D, Besse B, Kim TM, Quoix EA, Souquet PJ, Mazieres J, et al. Updated survival of patients (pts) with previously treated BRAF V600E–mutant advanced non-small cell lung cancer (NSCLC) who received dabrafenib (D) or D + trametinib (T) in the phase II BRF113928 study. *J Clin Oncol* (2017) 35:9075–9075. doi:10.1200/JCO.2017.35.15_suppl.9075
118. Planchard D, Smit EF, Groen HJM, Mazieres J, Besse B, Helland Å, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol* (2017) 18:1307–16. doi:10.1016/S1470-2045(17)30679-4
119. Davies MA, Saiag P, Robert C, Grob J-J, Flaherty KT, Arance A, et al. Dabrafenib plus trametinib in patients with BRAF(V600)-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol* (2017) 18:863–73. doi:10.1016/S1470-2045(17)30429-1
120. Farago AF, Le LP, Zheng Z, Muzikansky A, Drilon A, Patel M, et al. Durable clinical response to entrectinib in NTRK1-rearranged non-small cell lung cancer. *J Thorac Oncol* (2015) 10:1670–4. doi:10.1097/01.JTO.0000473485.38553.f0
121. Hyman DM, Laetsch TW, Kummar S, DuBois SG, Farago AF, Pappo AS, et al. The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers. *J Clin Oncol* (2017) 35:LBA2501–2501. doi:10.1200/JCO.2017.35.18_suppl.LBA2501
122. Soffietti R, Abacioglu U, Baumert B, Combs SE, Kinhult S, Kros JM, et al. Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European association of neuro-oncology (EANO). *Neuro Oncol* (2017) 19:162–74. doi:10.1093/neuonc/now241
123. Soon YY, Leong CN, Koh WY, Tham IWK. EGFR tyrosine kinase inhibitors versus cranial radiation therapy for EGFR mutant non-small cell lung cancer with brain metastases: a systematic review and meta-analysis. *Radiother Oncol* (2015) 114:167–72. doi:10.1016/j.radonc.2014.12.011
124. Magnuson WJ, Lester-Coll NH, Wu AJ, Yang TJ, Lockney NA, Gerber NK, et al. Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. *J Clin Oncol* (2017) 35:1070–7. doi:10.1200/JCO.2016.69.7144
125. Fan Y, Xu Y, Gong L, Fang L, Lu H, Qin J, et al. Effects of icotinib with and without radiation therapy on patients with EGFR mutant non-small cell lung cancer and brain metastases. *Sci Rep* (2017) 7:45193. doi:10.1038/srep45193
126. Jiang T, Min W, Li Y, Yue Z, Wu C, Zhou C. Radiotherapy plus EGFR TKIs in non-small cell lung cancer patients with brain metastases: an update meta-analysis. *Cancer Med* (2016) 5:1055–65. doi:10.1002/cam4.673
127. Welsh JW, Komaki R, Amini A, Munsell MF, Unger W, Allen PK, et al. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. *J Clin Oncol* (2013) 31:895–902. doi:10.1200/JCO.2011.40.1174
128. Zhu Q, Sun Y, Cui Y, Ye K, Yang C, Yang D, et al. Clinical outcome of tyrosine kinase inhibitors alone or combined with radiotherapy for brain metastases from epidermal growth factor receptor (EGFR) mutant non small cell lung cancer (NSCLC). *Oncotarget* (2017) 8:13304–11. doi:10.18632/oncotarget.14515
129. Jiang T, Su C, Li X, Zhao C, Zhou F, Ren S, et al. EGFR TKIs plus WBRT demonstrated no survival benefit other than that of TKIs alone in patients with NSCLC and EGFR mutation and brain metastases. *J Thorac Oncol* (2016) 11:1718–28. doi:10.1016/j.jtho.2016.05.013

130. Hendriks LEL, Schoenmaekers J, Zindler JD, Eekers DBP, Hoeben A, De Ruysscher DKM, et al. Safety of cranial radiotherapy concurrent with tyrosine kinase inhibitors in non-small cell lung cancer patients: a systematic review. *Cancer Treat Rev* (2015) 41:634–45. doi:10.1016/j.ctrv.2015.05.005
131. Tallet AV, Dhermain F, Le Rhun E, Noël G, Kirova YM. Combined irradiation and targeted therapy or immune checkpoint blockade in brain metastases: toxicities and efficacy. *Ann Oncol* (2017) 28:2962–76. doi:10.1093/annonc/mdx408
132. Kim YH, Ozasa H, Nagai H, Sakamori Y, Yoshida H, Yagi Y, et al. High-dose crizotinib for brain metastases refractory to standard-dose crizotinib. *J Thorac Oncol* (2013) 8:e85–6. doi:10.1097/JTO.0b013e31829cebbb
133. Gandhi L, Drappatz J, Ramaiya NH, Otterson GA. High-dose pemetrexed in combination with high-dose crizotinib for the treatment of refractory CNS metastases in ALK-rearranged non-small-cell lung cancer. *J Thorac Oncol* (2013) 8:e3–5. doi:10.1097/JTO.0b013e3182762d20
134. Tang SC, Nguyen LN, Sparidans RW, Wagenaar E, Beijnen JH, Schinkel AH. Increased oral availability and brain accumulation of the ALK inhibitor crizotinib by coadministration of the P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) inhibitor elacridar. *Int J Cancer* (2014) 134:1484–94. doi:10.1002/ijc.28475
135. Ou S-HI, Jänne PA, Bartlett CH, Tang Y, Kim D-W, Otterson GA, et al. Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. *Ann Oncol* (2014) 25:415–22. doi:10.1093/annonc/mdt572
136. Takeda M, Okamoto I, Nakagawa K. Clinical impact of continued crizotinib administration after isolated central nervous system progression in patients with lung cancer positive for ALK rearrangement. *J Thorac Oncol* (2013) 8:654–7. doi:10.1097/JTO.0b013e31828c28e7
137. Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol* (2012) 7:1807–14. doi:10.1097/JTO.0b013e3182745948
138. Mak KS, Gainor JF, Niemierko A, Oh KS, Willers H, Choi NC, et al. Significance of targeted therapy and genetic alterations in EGFR, ALK, or KRAS on survival in patients with non-small cell lung cancer treated with radiotherapy for brain metastases. *Neuro Oncol* (2015) 17:296–302. doi:10.1093/neuonc/nou146
139. Sullivan I, Planchard D. Treatment modalities for advanced ALK-rearranged non-small-cell lung cancer. *Future Oncol* (2016) 12:945–61. doi:10.2217/fon.16.15
140. Remon J, Menis J, Hasan B, Peric A, De Maio E, Novello S, et al. The APPLE trial: feasibility and activity of AZD9291 (osimertinib) treatment on positive plasma T790M in EGFR-mutant NSCLC patients. EORTC 1613. *Clin Lung Cancer* (2017) 18:583–8. doi:10.1016/j.cllc.2017.02.005
141. Nishio M, Kiura K, Seto T, Nakagawa K, Maemondo M, Inoue A, et al. OA 05.08 final result of phase I/II study (AF-001JP) of alectinib, a selective CNS-active ALK inhibitor, in ALK+ NSCLC patients (Pts). *J Thorac Oncol* 12:S1757. doi:10.1016/j.jtho.2017.09.353
142. Mok TSK, Kim D-W, Wu Y-L, Nakagawa K, Mekhail T, Felip E, et al. LBA50Overall survival (OS) for first-line crizotinib versus chemotherapy in ALK+ lung cancer: updated results from PROFILE 1014. *Ann Oncol* (2017) 28:.053–.440. doi:10.1093/annonc/mdx440.053
143. Ito K, Hataji O, Kobayashi H, Fujiwara A, Yoshida M, D'Alessandro-Gabazza CN, et al. Sequential therapy with crizotinib and alectinib in ALK-rearranged non-small cell lung cancer-a multicenter retrospective study. *J Thorac Oncol* (2017) 12:390–6. doi:10.1016/j.jtho.2016.07.022
144. Gainor JF, Tan DSW, De Pas T, Solomon BJ, Ahmad A, Lazzari C, et al. Progression-free and overall survival in ALK-positive NSCLC patients treated with sequential crizotinib and ceritinib. *Clin Cancer Res* (2015) 21:2745–52. doi:10.1158/1078-0432.CCR-14-3009
145. Watanabe S, Hayashi H, Okamoto K, Fujiwara K, Hasegawa Y, Kaneda H, et al. Progression-free and overall survival of patients with ALK rearrangement-positive non-small cell lung cancer treated sequentially with crizotinib and alectinib. *Clin Lung Cancer* (2016) 17:528–34. doi:10.1016/j.cllc.2016.05.001
146. Duruisseaux M, Besse B, Cadranel J, Pérol M, Mennecier B, Bigay-Game L, et al. Overall survival with crizotinib and next-generation ALK inhibitors in ALK-positive non-small-cell lung cancer (IFCT-1302 CLINALK): a French nationwide cohort retrospective study. *Oncotarget* (2017) 8:21903–17. doi:10.18632/oncotarget.15746
147. Pailler E, Oulhen M, Borget I, Remon J, Ross K, Auger N, et al. Circulating tumor cells with aberrant ALK copy number predict progression-free survival during crizotinib treatment in ALK-rearranged non-small cell lung cancer patients. *Cancer Res* (2017) 77:2222–30. doi:10.1158/0008-5472.CAN-16-3072

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

CASE REPORT
published: 22 May 2018
doi: 10.3389/fonc.2018.00176

Response to HER2 Inhibition in a Patient With Brain Metastasis With EGFR TKI Acquired Resistance and an HER2 Amplification

*Arenda D. Meedendorp, Arja ter Elst, Nils A. 't Hart, Harry J. M. Groen, Ed Schuuring and Anthonie J. van der Wekken**

University of Groningen and University Medical Center Groningen, Groningen, Netherlands

A 62-year-old man was referred to our university hospital for treatment of advanced adenocarcinoma of the lung after disease progression on two lines of EGFR TKI and one line of chemotherapy. Fluorescent *in situ* hybridization analysis upon progression showed an *HER2* amplification. At our weekly Molecular Tumor Board (MTB), a decision was made to treat this patient with afatinib, which resulted in a partial response. However, progression was observed with a facial nerve paresis due to a metastasis in the skull. A biopsy of a location in the thorax revealed the presence of an EGFR-T790M mutation associated with acquired resistance, after which treatment with osimertinib was started. After 6 months, disease progression was observed, and a new biopsy was taken from the pelvic bone, which revealed the original amplification of *HER2* together with the EGFR-L858R mutation, the EGFR-T790M mutation was not detected. The MTB decided to treat the patient with trastuzumab/paclitaxel. A partial response was observed in different bone lesions, while the skull metastasis with ingrowth in the brain remained stable for 6 months. Because of progression of the bone metastases after 6 months, a biopsy of a lesion in the thorax wall was taken. In this lesion, the EGFR-T790M mutation could be detected again. The MTB advised to start treatment with a combination of osimertinib and afatinib. This resulted in an impressive clinical improvement and a partial response of the bone metastases on the most recent 18-fluorodeoxyglucose positron emission tomography and computer tomography-scan. In conclusion, adjusting treatment to the mutational make-up of the tumor is a great challenge. For optimal treatment response multiple biopsies and re-biopsy upon progression are imperative. As more genes are investigated, treatment decision becomes increasingly difficult, therefore, expert opinions from an MTB is essential.

Keywords: EGFR, HER2, non-small-cell lung carcinoma, TKI, brain metastasis, Molecular Tumor Board

OPEN ACCESS

Edited by:
Lizza E. L. Hendriks, Maastricht University Medical Center, Netherlands

Reviewed by:
Timothy F. Burns, University of Pittsburgh Cancer Institute, United States
Luigi Formisano, Vanderbilt University Medical Center, United States

***Correspondence:**
Anthonie J. van der Wekken
a.j.van.der.wekken@umcg.nl

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *10 January 2018*
Accepted: *04 May 2018*
Published: *22 May 2018*

Citation:
Meedendorp AD, ter Elst A, 't Hart NA, Groen HJM, Schuuring E and van der Wekken AJ (2018) Response to HER2 Inhibition in a Patient With Brain Metastasis With EGFR TKI Acquired Resistance and an HER2 Amplification. Front. Oncol. 8:176. doi: 10.3389/fonc.2018.00176

INTRODUCTION

Treatment of driver mutations cannot be based on large clinical trials or high levels of evidence at all times. However, a Molecular Tumor Board (MTB) can help in making treatment decisions based on databases, case reports, xenograft models, and cell lines. Here, we present such a case.

A 62-year-old man was referred to our university hospital for treatment of advanced adenocarcinoma of the lung after disease progression on two lines of EGFR TKI and one line of chemotherapy in September 2015 (**Figure 1**).

Four months prior, in April 2015, he was diagnosed with an adenocarcinoma of the left lung with multiple bone metastases in sternum, ribs, and vertebrae. A biopsy from a metastasis in the left femur showed a mutation in the *EGFR* gene: c.2573T>G; p.(L858R). He was initially treated with gefitinib. After 2 months, the patient showed progression of bone metastases; the same EGFR mutation was found in a biopsy of a rib metastasis, without additional mutations in other mutational hotspots (e.g., *BRAF*, *KRAS*, *HER2*, *KIT*, *ALK*, *NRAS*, *PDGFRA*, *PIK3CA*, and *MET*). Therefore, at that time, carboplatin and pemetrexed were provided and because of pain, local irradiation of a sternal metastasis was applied. After two cycles of chemotherapy, the patient showed disease progression and was referred to our hospital. Because of lack of new treatment options, this patient was discussed in the Groningen MTB consisting of pulmonary oncologists, pathologists, clinical molecular biologists in pathology, general oncologists, and a structural biologist (www.moloncopath.nl). The MTB advised to determine the HER2-copy number status as a possible resistant mechanism for EGFR TKI. Fluorescent *in situ* hybridization (FISH) on a biopsy of a subcutaneous thoracic metastasis revealed *HER2* amplification and treatment with afatinib (dual EGFR and HER2 inhibitor) 30 mg QD was started in October 2015. Evaluation by 18-fluorodeoxyglucose positron emission tomography and computer tomography (18-FDG-PET-CT) showed after 6 weeks a significant partial response with disappearance of the FDG activity of the bone metastases and after 4 months in the left upper lobe a single FDG-positive lesion was left. This lesion was irradiated by means of stereotactic ablative radiotherapy (1× 20 Gy), and afatinib was continued. Treatment with afatinib was well tolerated with minor skin rash; patient showed clinical improvement: he had less pain and more energy. Nine months after start of afatinib, progressive disease was again noticed. Growth of the primary tumor in the left upper lobe, a new ipsilateral pulmonary lesion and multiple new bone metastases including the skull, with ingrowth into the brain, causing paralysis of the right facial nerve (**Figure 1**). Sequence analysis of a new right-sided rib lesion showed the known L858R *EGFR* mutation and an additional T790M mutation.

Because of the novel T790M, afatinib was discontinued and replaced by osimertinib 80 mg QD (1). Eight weeks after start of osimertinib a PET-CT showed a response of most lesions except for a growing lesion in the pelvic region and the skull with ingrowth in the brain. Clinically there was, however, temporary improvement of the patient's ability to move his right eyelid and right corner of the mouth, which had been paralyzed due to ingrowth of a skull metastasis into the brain and right facial nerve. A biopsy was performed of a growing FDG-positive lesion in the left pelvic bone that showed adenocarcinoma with the known L858R *EGFR* mutation, but the previously found T790M mutation was not present in this location (no biopsy of the skull metastasis available). The MTB advised to perform immunohistochemistry on Her2Neu (positive in agreement with HER2 amplification) and to determine *MET* amplification (negative by FISH). Based on these findings, it was decided to discontinue osimertinib because of the loss of the T790M mutation and to start a combination of paclitaxel 90 mg/m^2 on days 1, 8, and 15, and trastuzumab 4 mg/kg on days 1 and 15, in cycles of 4 weeks, because trastuzumab is an HER2 antibody. Radiotherapy 1× 8 Gy was given on the pelvic lesion because of localized pain. 18-FDG-PET-scan after four cycles, paclitaxel and trastuzumab showed again a partial tumor response. No major side effects were observed although symptoms of the

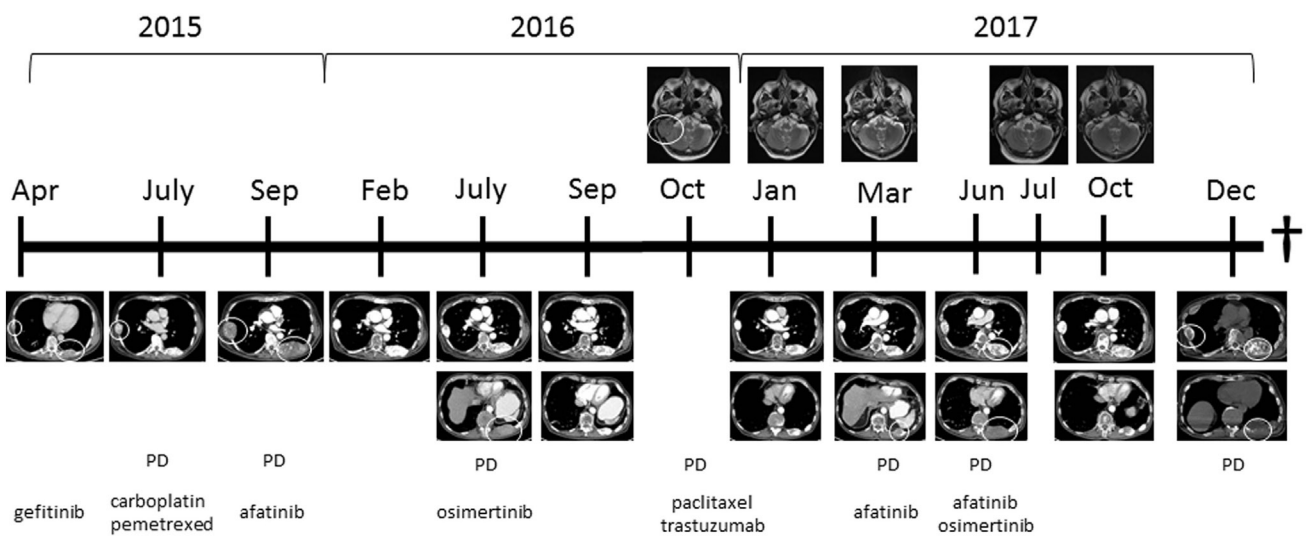


FIGURE 1 | Computed tomography images showing the thoracic wall lesions of the adenocarcinoma of the lung and MRI images showing the metastasis in the skull with ingrowth in the brain at different time points in combination with treatment started at those time points. Abbreviation: PD, progressive disease. White circles indicate lesion, which showed progression.

paralysis of the right facial nerve did not improve further; it remained stable during the course of therapy. The patient underwent plastic surgery on his right eyelid, which improved the closure of his right eye.

Two months after the fourth and last cycle, the patient presented with a subcutaneous metastasis on his forehead. Afatinib 30 mg QD was started, because this treatment worked before, pending results of a new biopsy. The biopsy, however, yielded insufficient material for mutation analysis, and re-biopsy was scheduled. In the meantime, 18-FDG-PET-scan showed multiple FDG-positive bone lesions (partly new lesions), some close to the myelum, and the patient was admitted to the hospital for radiotherapy on cervical and thoracic vertebrae. Afatinib was discontinued. Biopsy of a new lesion in the thoracic wall showed an *EGFR*-L858R, T790M mutation, and *HER2* amplification. There were no other hotspot mutations in *EGFR*, *BRAF*, *KRAS*, *ERBB2 (HER2)*, *ALK*, *PIK3CA*, or *MET* detected. The case was again reviewed by MTB. It was decided to treat the patient with afatinib 30 mg QD as well as osimertinib 80 mg QD at alternating days, to address the T790M mutation as well as the *HER2* amplification resistance mechanism. Since the start of this latest treatment regimen, the subcutaneous skull metastasis disappeared, and the patient experienced less pain, regained his energy, and was able to walk outdoors again. The most recent 18-FDG-PET-CT-scan, 4 months after the start of this latest treatment regimen, showed again a partial response of the bone metastases again. Two months later (December 2017) progression of disease was observed, and the performance status deteriorated. Patient insisted to take a new biopsy from a new thoracic wall metastasis. Mutations analysis showed the known *EGFR* L858R and T790M mutations together with a new mutation in *HER2*: L755S. However, his condition got worse in short time, and he died in January 2018. An overview of the clinical findings, the mutational status at different time points and the given treatment regimens is provided in **Table 1**.

BACKGROUND

EGFR

The incidence of *EGFR* mutations in advanced stage adenocarcinoma of the lung in Caucasian patients is 10–15 and 40–60% in Asian patients (2). In the north of the Netherlands, the incidence is 9% (3). L858R mutation in exon 21 of the EGFR kinase domain is the main hotspot mutation in the *EGFR* gene and accounts for 35–45% of *EGFR* mutations (4, 5). L858R mutation increases the kinase activity of EGFR, leading to hyperactivation of downstream signaling pathways improving cell survival and proliferation (6). An EGFR TKI is the preferred first-line treatment in patients with activating *EGFR* mutation in non-small-cell lung carcinoma (NSCLC) (4). Gefitinib and erlotinib are first-generation TKI and registered as first-line treatment in patients with metastatic NSCLC with a tumor harboring an activating *EGFR* mutation within the European Union and according to the Dutch guideline for treatment of NSCLC (7). These small molecules bind competitively and reversibly to the adenosine triphosphate (ATP) binding site of the tyrosine kinase domain of

TABLE 1 | Overview of clinical and pathological findings and subsequent therapeutic decisions.

Clinical evaluation	Mutational status	CT/MRI evaluation	Therapy
Adenocarcinoma of the left lung with multiple bone metastases in sternum, ribs, and vertebrae	Femur: *EGFR*-L858R	April 2015	Gefitinib
Progression of bone metastases (time to progression: 2 months)	Rib: *EGFR*-L858R	July 2015	Carboplatinum and pemetrexed Irradiation on sternum
Progression of bone and subcutaneous metastases (time to progression: 2 months)	Thoracic subcutis: *HER2* amplification 3+	September 2015	Afatinib
Partial response with disappearance of the FDG activity of the bone metastases. Only 1 FDG-positive lesion in the left upper lobe	N.a.	March 2016	Stereotactic ablative radiotherapy of lesion left upper lobe Continuation of afatinib
Growth of primary tumor left upper lobe, ipsilateral pulmonary lesion, and multiple new bone metastases including the skull, with ingrowth into the brain (time to progression: 9 months)	Rib: *EGFR*-L858R and T790M	July 2016	Osimertinib
Mixed response: growing lesion left pelvic bone	Pelvic bone: *EGFR*-L858R, HER2 amplification 3+, no T790M	October2016	Paclitaxel and trastuzumab Irradiation on pelvic lesion
Subcutaneous metastasis on forehead and progression of bone metastases (time to progression: 6 months)	HER2 expression	April 2017	Afatinib Irradiation on cervical and thoracic vertebrae
N.a.	Thorax wall: *EGFR*-L858R and T790M mutation and *HER2* amplification 3+	June 2017	Afatinib and osimertinib
Partial response	N.a.	November 2017	Continuation of afatinib and osimertinib
Progressive disease	Thorax wall: *EGFR*-L858R, T790M, and HER2 L755S	December 2017	
Death		January 2018	

EGFR. This prevents the autophosphorylation of the TK, blocks the activation of the EGFR signal transduction, inhibits tumor cell proliferation, and induces cell cycle arrest and apoptosis (8). The majority of patients will progress after 9–12 months of treatment due to various mechanisms of intrinsic or acquired resistance to first-generation EGFR TKIs (9).

EGFR T790M

The most common mechanism of acquired TKI resistance is the acquisition of a single recurrent missense mutation within exon 20, the T790M mutation (10). This mutation leads to the substitution of threonine by methionine at position 790, which encodes part of the kinase domain of the receptor and results in increased affinity for ATP (11). The T790M mutation can be detected in about 60% of tissue biopsy samples taken after acquired resistance (12, 13). As residue threonine at position 790 (T790) is located at the entrance in the back of the ATP binding cleft, substitution of residue threonine at position 790 with a bulky methionine (resulting in T790M) may cause steric interference with binding of TKIs (14). Irreversible inhibitors overcome this resistance simply through covalent binding (15). Osimertinib is registered for the treatment of NSCLC with an *EGFR* T790M mutation. It is a selective third-generation TKI which targets the ATP binding site of EGFR *via* irreversible covalent bond formation. In contrast to many other TKI, osimertinib penetrates the blood–brain barrier (16, 17). Osimertinib improves overall survival and progression-free survival in T790M-positive NSCLC patients with and without brain metastases (18, 19). Acquired resistance to osimertinib may be caused by primary coexistence of tumor cell populations with and without T790M mutation due to EGFR C797S mutation. Tumor progression can be explained by growth of the T790M negative population, while the tumor cells expressing T790M mutation are effectively suppressed by osimertinib (20).

HER2

Overexpression of *HER2* induces cell transformation and tumorigenic growth and is clinically associated with resistance to erlotinib (21). *HER2* amplification is detected in a subset of EGFR TKI resistant lung tumors. *HER2* amplification and T790M mutation are thought to be mutually exclusive (22). However, in our patient *HER*2 amplification as well as T790M mutation appeared in the same biopsy of a new lesion in the thorax wall. Afatinib is an ATP-competitive aniline-quinazoline derivate which covalently binds to EGFR, HER2, and HER4 and irreversibly inhibits HER-family phosphorylation and signal transduction (23). As second generation TKI it is highly potent, irreversible dual EGFR/HER2 tyrosine kinase inhibitor, including the oncogenic *EGFR*-L858R mutation (23, 24). Afatinib is registered for advanced NSCLC with *EGFR* mutations. Clinical benefit of afatinib seems less in patients with *de novo* T790M mutations (25). Although afatinib is equally potent against wild-type EGFR and EGFR harboring the T790M mutation, in patients the dose is lower due to toxicity constraints (26).

Trastuzumab, a humanized monoclonal antibody against HER2, has been reported to be effective in *HER2*-positive NSCLC *in vitro* and in case reports (4, 27, 28).

DISCUSSION

Here, we describe a patient with EGFR mutant advanced NSCLC with recurrent episodes of disease progression due to subsequent mutant clones. Yu et al. selected 155 patients with lung adenocarcinomas and acquired resistance to erlotinib or gefitinib. These patients underwent a re-biopsy. The most common finding was a T790M mutation. They also found transformation to small cell lung carcinoma, *MET* amplification and *HER2* amplification (10). Sequist et al. described a wide variety of gained and lost *EGFR* mutations in a patient population with acquired drug resistance. They recommended reassessing cancers by taking new biopsies of growing lesions in patients with progressive disease after an initial response to TKI treatment (29). Following this strategy, we observed HER2 amplification and T790M mutation at different time points under the selective pressure of different EGFR TKI treatment. Of note, the occurrence of both aberrations at the same time has not been described earlier.

After discussion in the MTB about the most suitable therapy, as mentioned in the background, treatment was adjusted accordingly. Case evaluation by a multidisciplinary MTB is important to benefit from individualized genetic data and maximize clinical impact (30–32). MTB interprets results of routine molecular NGS-testing with those of other techniques, for example, immunohistochemistry, FISH, DNA methylation testing, and multiplex ligation-dependent probe amplification. NGS testing is not only performed on biopsies but currently also from tumor DNA in peripheral blood. The spectrum of molecular markers is constantly growing. Patients who progress after an EGFR TKI should undergo a re-biopsy to perform molecular analysis specifically looking for acquired mechanisms of resistance, such as *EGFR* T790M mutation. This approach can influence the next therapeutic step or reveal alternative EGFR TKI resistance mechanisms such as transformation to small cell lung cancer or bypass tracks that could potentially be addressed in clinical trials (11). Our patient responded well to subsequent treatment based on aberrations found in NGS, IHC, and FISH after discussion in the MTB. We observed that a change in treatment gave a short-lasting clinical improvement of several months and tumor response of fast growing new metastases. Osimertinib alternating with afatinib for T790M in EGFR and HER2 amplification was very effective in decreasing tumor sites. However, we expected that our patient would have immense toxicity of skin rash and diarrhea, but toxicity was not more than CTC grade 1. Long-lasting tiredness grade 1 was the most prominent side effect.

CONCLUDING REMARKS

This case report shows the importance of re-biopsy of growing lesions in lung cancer patients with metastatic progressive disease under targeted therapies. Mutation status can vary under selection pressure of these drugs, and knowledge of these changes makes it possible to adapt treatments. This patient also exemplifies the importance of having a multidisciplinary expert team (MTB) to give rational treatment advice in cancer patients with uncommon mutations or combinations of mutations causing complex resistance mechanisms.

ETHICS STATEMENT

This case report was written and offered for publication with written informed consent from the patient. The patient gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

AM: organized the relevant information about the patient; wrote all paragraphs of the article, did the literature research, and applied changes brought in by the other authors. AE, HG, and ES: supervised and corrected the manuscript. NH: supervised and gave advice. AW: main supervisor; supervised and corrected the manuscript.

ACKNOWLEDGMENTS

Written informed consent to write and publish this case report was obtained from the patient. We thank the patient for his permission to publish this case report.

REFERENCES

1. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* (2017) 376:629–40. doi:10.1056/NEJMoa1612674
2. Tan DS, Mok TS, Rebbeck TR. Cancer genomics: diversity and disparity across ethnicity and geography. *J Clin Oncol* (2016) 34:91–101. doi:10.1200/JCO.2015.62.0096
3. Kerner GS, Schuuring E, Sietsma J, Hiltermann TJ, Pieterman RM, de Leede GP, et al. Common and rare EGFR and KRAS mutations in a Dutch non-small-cell lung cancer population and their clinical outcome. *PLoS One* (2013) 8: e70346. doi:10.1371/journal.pone.0070346
4. Besse B, Adjei A, Baas P, Meldgaard P, Nicolson M, Paz-Ares L, et al. 2nd ESMO consensus conference on lung cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. *Ann Oncol* (2014) 25:1475–84. doi:10.1093/annonc/mdu123
5. Marchetti A, Martella C, Felicioni L, Barassi F, Salvatore S, Chella A, et al. EGFR mutations in non-small-cell lung cancer: analysis of a large series of cases and development of a rapid and sensitive method for diagnostic screening with potential implications on pharmacologic treatment. *J Clin Oncol* (2005) 23:857–65. doi:10.1200/JCO.2005.08.043
6. Sordella R, Bell DW, Haber DA, Settleman J. Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. *Science* (2004) 305:1163–7. doi:10.1126/science.1101637
7. Felip E, Gridelli C, Baas P, Rosell R, Stahel R, Panel Members. Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy: 1st ESMO Consensus Conference in Lung Cancer; Lugano 2010. *Ann Oncol* (2011) 22:1507–19. doi:10.1093/annonc/mdr150
8. Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. *J Pharmacol Exp Ther* (2005) 315:971–9. doi:10.1124/jpet.105.084145
9. Cortot AB, Janne PA. Molecular mechanisms of resistance in epidermal growth factor receptor-mutant lung adenocarcinomas. *Eur Respir Rev* (2014) 23:356–66. doi:10.1183/09059180.00004614
10. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* (2013) 19:2240–7. doi:10.1158/1078-0432.CCR-12-2246
11. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2016) 27:v1–27. doi:10.1093/annonc/mdw326
12. Arcila ME, Oxnard GR, Nafa K, Riely GJ, Solomon SB, Zakowski MF, et al. Rebiopsy of lung cancer patients with acquired resistance to EGFR inhibitors and enhanced detection of the T790M mutation using a locked nucleic acid-based assay. *Clin Cancer Res* (2011) 17:1169–80. doi:10.1158/1078-0432.CCR-10-2277
13. Kobayashi S, Ji H, Yuza Y, Meyerson M, Wong KK, Tenen DG, et al. An alternative inhibitor overcomes resistance caused by a mutation of the epidermal growth factor receptor. *Cancer Res* (2005) 65:7096–101. doi:10.1158/0008-5472.CAN-05-1346
14. Zou B, Lee VHF, Chen L, Ma L, Wang DD, Yan H. Deciphering mechanisms of acquired T790M mutation after EGFR inhibitors for NSCLC by computational simulations. *Sci Rep* (2017) 7:6595. doi:10.1038/s41598-017-06632-y
15. Yun CH, Mengwasser KE, Toms AV, Woo MS, Greulich H, Wong KK, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci U S A* (2008) 105:2070–5. doi:10.1073/pnas.0709662105
16. Sullivan I, Planchard D. Next-generation EGFR tyrosine kinase inhibitors for treating EGFR-mutant lung cancer beyond first line. *Front Med* (2017) 3:76. doi:10.3389/fmed.2016.00076
17. Ward RA, Anderton MJ, Ashton S, Bethel PA, Box M, Butterworth S, et al. Structure- and reactivity-based development of covalent inhibitors of the activating and gatekeeper mutant forms of the epidermal growth factor receptor (EGFR). *J Med Chem* (2013) 56:7025–48. doi:10.1021/jm400822z
18. Santarpia M, Liguori A, Karachaliou N, Gonzalez-Cao M, Daffina MG, D'Aveni A, et al. Osimertinib in the treatment of non-small-cell lung cancer: design, development and place in therapy. *Lung Cancer* (2017) 8:109–25. doi:10.2147/LCTT.S119644
19. Yang JC, Ahn MJ, Kim DW, Ramalingam SS, Sequist LV, Su WC, et al. Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study phase II extension component. *J Clin Oncol* (2017) 35:1288–96. doi:10.1200/JCO.2016.70.3223
20. Planchard D, Loriot Y, Andre F, Gobert A, Auger N, Lacroix L, et al. EGFR-independent mechanisms of acquired resistance to AZD9291 in EGFR T790M-positive NSCLC patients. *Ann Oncol* (2015) 26:2073–8. doi:10.1093/annonc/mdv319
21. Moasser MM. The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. *Oncogene* (2007) 26:6469–87. doi:10.1038/sj.onc.1210477
22. Takezawa K, Pirazzoli V, Arcila ME, Nebhan CA, Song X, de Stanchina E, et al. HER2 amplification: a potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFRT790M mutation. *Cancer Discov* (2012) 2:922–33. doi:10.1158/2159-8290.CD-12-0108
23. Solca F, Dahl G, Zoephel A, Bader G, Sanderson M, Klein C, et al. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. *J Pharmacol Exp Ther* (2012) 343:342–50. doi:10.1124/jpet.112.197756
24. Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene* (2008) 27:4702–11. doi:10.1038/onc.2008.109
25. Yang JC, Sequist LV, Geater SL, Tsai CM, Mok TS, Schuler M, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol* (2015) 16:830–8. doi:10.1016/S1470-2045(15)00026-1
26. van der Wekken AJ, Saber A, Hiltermann TJ, Kok K, van den Berg A, Groen HJ. Resistance mechanisms after tyrosine kinase inhibitors afatinib and crizotinib in non-small cell lung cancer, a review of the literature. *Crit Rev Oncol Hematol* (2016) 100:107–16. doi:10.1016/j.critrevonc.2016.01.024
27. Mazieres J, Peters S, Lepage B, Cortot AB, Barlesi F, Beau-Faller M, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. *J Clin Oncol* (2013) 31:1997–2003. doi:10.1200/JCO.2012.45.6095
28. Cappuzzo F, Bemis L, Varella-Garcia M. HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer. *N Engl J Med* (2006) 354:2619–21. doi:10.1056/NEJMc060020

29. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* (2011) 3:75ra26. doi:10.1126/scitranslmed.3002003
30. Tafe LJ, Gorlov IP, de Abreu FB, Lefferts JA, Liu X, Pettus JR, et al. Implementation of a molecular tumor board: the impact on treatment decisions for 35 patients evaluated at Dartmouth-Hitchcock Medical Center. *Oncologist* (2015) 20:1011–8. doi:10.1634/theoncologist.2015-0097
31. Petty JK, Vetto JT. Beyond doughnuts: tumor board recommendations influence patient care. *J Cancer Educ* (2002) 17:97–100. doi:10.1080/08858190209528807
32. van der Velden DL, van Herpen CML, van Laarhoven HWM, Smit EF, Groen HJM, Willems SM, et al. Molecular Tumor Boards: current practice and future needs. *Ann Oncol* (2017) 28:3070–5. doi:10.1093/annonc/mdx528

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling Editor declared a past co-authorship with one of the authors AW.

frontiers in Oncology

MINI REVIEW
published: 27 July 2018
doi: 10.3389/fonc.2018.00278

Management of Leptomeningeal Metastases in Non-oncogene Addicted Non-small Cell Lung Cancer

Ana Turkaj[1], *Anna M. Morelli*[1]*, *Tiziana Vavalà*[2] *and Silvia Novello*[1]

[1] *Department of Oncology, University of Torino, Ospedale San Luigi Gonzaga, Orbassano, Italy,* [2] *SC of Oncology, ASL CN1, Ospedale Civile di Saluzzo, Saluzzo, Italy*

Brain metastases in non-small cell lung cancer (NSCLC) patients are more often detected due to imaging modalities improvements but also emerge because of improved treatments of the primary tumor which lead to a longer survival. In this context, development of leptomeningeal metastases (LM) is a devastating complication and its prognosis remains poor despite advances in systemic and local approaches. Histology characterization of NSCLC and molecular expression influence LM management. For those with "oncogene addiction," new generation epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) were developed to strongly penetrate the blood-brain barrier (BBB) with the aim to prevent central nervous system cancer dissemination, eventually impacting on LM appearance and its subsequent management. Systemic chemotherapy, often combined with intrathecal chemotherapy (when possible), was one of common indications for lung cancer patients affected by LM, without driver mutations and a good performance status but currently, with the advent of innovative systemic approaches treatment solutions in this subgroup of patients are rapidly evolving. Whole brain radiation therapy (WBRT) is the conventional treatment for patients with brain metastases. Furthermore, modern radiation techniques, as stereotactic radiotherapy (SRT), improve outcomes in those cases with a limited number of lesions. However, LM represent a minority of CNS metastases and few literature data are available to drive the radiotherapy approach. Considering all relevant progress made in this setting, after a literature review, the aim of this paper is to discuss about recent developments and therapeutic options in LM management of non-oncogene addicted NSCLC.

Keywords: non-small cell lung cancer (NSCLC), brain metastases, leptomeningeal metastases, chemotherapy, intra-thecal chemotherapy, immunotherapy, radiotherapy

OPEN ACCESS

Edited by:
Deepa S. Subramaniam, MedStar Georgetown University Hospital, United States

Reviewed by:
K. Shilo, The Ohio State University, United States
Timothy F. Burns, University of Pittsburgh Cancer Institute, United States

***Correspondence:**
Anna M. Morelli
a.mariamorelli@gmail.com

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *29 March 2018*
Accepted: *04 July 2018*
Published: *27 July 2018*

Citation:
Turkaj A, Morelli AM, Vavalà T and Novello S (2018) Management of Leptomeningeal Metastases in Non-oncogene Addicted Non-small Cell Lung Cancer. Front. Oncol. 8:278. doi: 10.3389/fonc.2018.00278

INTRODUCTION

Non-small cell lung cancer (NSCLC) is characterized by a high incidence of central nervous system (CNS) dissemination, with approximately 40% of patients developing brain metastases (BM) in the course of their disease (1, 2) and leptomeningeal metastases (LM) appearance in a smaller percentage (3–5%) (3). Particularly, LM incidence among NSCLC patients is 3.8% more frequent in adenocarcinoma subtype, with about a third of those patients having concomitant BM (4). LM usually manifest as a late complication, which have been reported to emerge as late as up to 112

months after initial diagnosis (5). LM cases are increasing in incidence as a result of improved survival in subgroups of patients with targetable mutations treated with molecular therapies, but also because of modern neuro-imaging tools, able to clearly identify even small foci of meningeal dissemination (6–8). Median survival of NSCLC patients affected by LM is particularly poor even with signs of improvement, from a historical median survival of 1–3 to 3–11 months with novel therapies and integration of local and systemic treatments (9). Specific treatments of LM depends on histology characterization of NSCLC, molecular expression, time of appearance and patient's performance status. Molecularly targeted therapies and immunotherapy showed antitumor activity for brain metastases although effectiveness in cytologically confirmed and symptomatic LM is still limited or unknown (3). Systemic and intrathecal (IT) chemotherapy with site-specific radiotherapy are usually applied, particularly in non-oncogene addicted NSCLC, while up to one-third of the patients are treated with best supportive care alone. Despite the lack of the standard treatments, active treatments have been associated independently with longer overall survival (OS) (10). Recent advances in the understanding of LM biology in NSCLC patients along with the development of highly active targeted drugs for tumors with specific genetic alterations, helped to redefine the prognosis in this subgroup of patients and the same evolution is largely awaited in those NSCLC patients without oncogene addiction (5, 11–14). Based on literature review, this paper aims to discuss about recent developments and therapeutic options of LM in NSCLC patients without driver mutations.

BIOLOGY OF BLOOD BRAIN BARRIER AND DRUG DELIVERY

The blood–brain barrier (BBB) is constituted by a continuous stratum of endothelial cells connected by tight junctions surrounded by pericytes and perivascular end feet of astrocytes, thus being a highly selective barrier which separates systemic circulation from cerebrospinal fluid (CSF) (15).

BBB maintains CNS homeostasis by enabling the transport of selected substances only, through a combined result of influx and efflux mechanisms. Therapeutic efficacy in this area is determined by whether drug concentrations can be achieved in the CSF and these differ as a result of multiple conditions. The ability of a drug to cross the BBB is substantially improved by particular physic-chemical properties, including low potential for active efflux, few rotatable bonds, small polar surface area, few hydrogen bond donors (9). For instance, anticancer therapeutics (tyrosine kinase inhibitors or chemotherapeutic agents), are substrates of efflux transport proteins, such as P-glycoprotein, which is responsible for the transport of most drugs outside the intracranial region. Most chemotherapy agents have low CSF concentrations, with relevant liquor permeability reported only for temozolomide, methotrexate and topotecan (16–19), however predicted CNS penetration does not necessary correlate with known response rates to chemotherapeutic agents. Moreover, free diffusion of molecules across the BBB requires both lipophilicity and low molecular weight (less than 0.5 kDa): chemotherapy drugs are usually larger than 150 kDa, hydrophilic and frequently protein-bound molecules, therefore unable to penetrate an intact BBB (20–23). In this context, growing scientific evidence highlights that CNS metastases cause BBB interruption; this process, probably due to tumor neo-angiogenesis, lead to generate new vessels lacking of structural and physiological features of normal BBB, thus favoring the passage of drugs into the brain (24, 25). The same hypothesis emerges after whole brain radiation (WBRT) approach, thus providing a biologic rationale for using concomitant or sequential systemic and local treatments in these cases (26, 27).

DIAGNOSIS OF LEPTOMENINGEAL METASTASES

LM involve penetration of inner layers of meninges and subarachnoid space in which CSF circulates. Its diagnosis is specifically based on three different assessments: clinical signs and symptoms, CSF cytological examinations and neuro-radiological imaging.

Early clinical presentation can be subtle and may include headaches and back pain, cranial nerve deficits, cauda equine symptoms or signs, visual disturbances, diplopia, hearing loss and neurocognitive syndromes. In later stages, symptoms related to elevated intracranial pressure could occur (28, 29). Cytological identification of malignant cells in CSF is the gold standard for diagnosis of LM. The sensitivity of the initial lumbar puncture was reported to be as low as 50%, with a potential increase to 75–85% with a second CSF analysis (30). A meningeal biopsy is rarely needed to confirm a clinical suspect. A recent study performed by Jiang et al. demonstrated that the use of next-generation sequencing (NGS) performed on cerebrospinal fluid circulating tumor cells (CSF-CTC) may be a more sensitive and an effective way to diagnose LM, serving also as a liquid biopsy for gene profiles in NSCLC patients with LM (31). Besides clinical and cytological diagnosis, brain and spine imaging are able to identify involved sites, even in cytology-negative cases (32).

Magnetic resonance imaging (MRI), ideally with a 3 Tesla scanner is the most useful imaging modality for the detection of LM. Both T1 with and without contrast enhancement and high resolution T2 fluid attenuated inversion recovery sequences post-contrast are important in establishing a radiological diagnosis of LM.

Particularly the disruption of BBB in presence of CNS metastases is often evidenced by peritumoral edema and accumulation of contrast during the imaging scans and, as more recently observed, penetration of CNS metastases is identified by nuclear medicine tracers, such as 18-Sodium Fluoride (33).

The EANO-ESMO clinical practice guidelines propose to classify LM by using two major criteria, being "type I" those LM when the diagnosis has been verified citologically or histologically and "type II" in the absence of verification. While on the basis of the neuroimaging findings: linear leptomeningeal disease (type A), nodular leptomeningeal disease (type B), both (type C) or

neither nor, e.g., no neuroimaging evidence of LM except possibly hydrocephalus (type D) (34).

TREATMENT OPTIONS OF LEPTOMENINGEAL METASTASES

Treatment of LM is preferentially multidisciplinary and mostly indicated when diagnosis is unequivocal or symptoms are strongly suggestive, in case of negative cytology.

The goals of treatment in patients with LM are to improve or stabilize the neurologic status of the patient, maintain or regain quality of life and optimally to prolong survival together with marginal toxicity. Limited data are available to establish treatment recommendations in the management of LM: no randomized trials proved a survival benefit of a specific treatment modality and, accordingly, the optimal strategy is still poorly defined, particularly in non-oncogene addicted NSCLC. In this last setting of patients, palliative radiotherapy to symptomatic sites of disease, cytotoxic chemotherapies, intrathecal therapy (or a combination of these modalities) are traditionally considered, with the new innovative immunotherapy chance (35–39).

Radiation Therapy

In the era of improved radiation modalities, local treatment of BM is rapidly improving: a growing amount of data support an integrate use of WBRT or stereotactic radiosurgery (SRS) with systemic treatment in a variety of clinical scenarios, together with alternative radiation approaches, such as intensity modulated radiation therapy (IMRT) or even proton beam therapy, when applicable (40–42).

LM represent a minority of CNS metastases (11–20%) (43, 44) and less data are available to inform decisions about therapy. RT is mainly administered for symptoms alleviations, CSF flow correction or for debulking to facilitate chemotherapy.

WBRT is typically used in cases of concurrent brain metastases or major meningeal cerebral involvement (45). For BM dose and fractionation scheme is at the discretion of the treating radiation oncologist, though most commonly used dose and fractionation schemes are 20 Gy in 5 fractions of 4 Gy (standard schedule in Europe) and 30 Gy in 10 fractions of 3 Gy (46). For LM focal radiation therapy is recommended on symptomatic, bulky or obstructive sites and the dose depends on performance status (20–40 Gy in 5–20 fractions), volume to treat and available techniques (47). Different studies reported a survival difference in favor of patients with better performance status after various treatments, including WBRT (48, 49). Gani et al. evidenced that WBRT alone in patients with LM from breast and lung cancer is an effective palliative treatment for patients unfit for chemotherapy and poor performance status (49). As tumor dissemination affects the whole CSF compartment, according to some studies, the complete craniospinal axis should be encountered as target volume. Favorable results have been reported in small series. To determine the effects of craniospinal irradiation (CSI) a retrospective study of 16 patients with LM (mostly from breast and lung cancer) was conducted by Hermann et al. In this study, ten patients were additionally treated with intrathecal methotrexate. The authors conclude that craniospinal radiotherapy is feasible and effective for palliative treatment of LM (36).

However, craniospinal irradiation (CSI) is generally not recommended, as it is assumed to cause substantial myelotoxicity. In fact, in his review, Chamberlain stated that "whole neuroaxis radiation of the craniospinal axis is rarely indicated in the treatment of LM in solid tumors" (50).

Conformal radiotherapy may help to limit bone marrow and neurotoxicity making focal radiotherapy better tolerated. Proton therapy is only available in a few centers, but this approach promises further reduction of toxicity and effectiveness from CSI (51, 52).

Focal RT administration in fractionated regimens, such as involved-field or stereotactic RT or administered in single fractions (radiosurgery), can be used to treat nodular disease and symptomatic cerebral or spinal sites (34). By contrast, stereotactic radiosurgery (SRS), which is a radiation therapy technique in which multiple focused radiation beams intersect over a target, results in delivery of a highly conformal, high-dose of radiation to the target and minimal radiation to the surrounding normal tissues. In patients with BM a Gamma Knife Radiosurgery (GKRS) is typically used, depending upon the volume and location prescription doses typically range from 15 to 24 Gy for single fraction session (53). GKRS allow to achieve high rates of local control, and is able to delay the need for WBRT thus avoid potential neurocognitive toxicities, although a phase 2 RTOG study suggested that concomitant administration of memantine together with WBRT may reduce and delay subsequent cognitive consequences (54). Few studies have reported on the role of SRS in the setting of LM (55, 56). In the small and heterogeneous study by Wolf et al. the prescription tumor margin dose was a median of 16 Gy (11–20 Gy) to the 50–80% isodose volumes. The authors suggested SRS capable to provide high rates of local control for restricted LM with a median survival of 10 months and with 60% of the population alive at 6 months. SRS for focal LM is preferable in those patients who are eligible for systemic therapy, including immuno-therapies and targeted therapies, which can potentially further prolong overall survival.

Involved field radiotherapy (IFRT) is considered to be the standard of care for palliative treatment of LM. Relevant to this, the US National Comprehensive Cancer Network (NCCN) 2017 guidelines for management of LM recommend Intrathecal Chemotherapy (IT) in combination with IFRT in patients with good prognosis disease (as defined by high performance status, non-fixed neurologic deficits, minimal systemic disease, and reasonable options for systemic disease treatment). Patients not meeting criteria for good prognosis are recommended to undergo IFRT to symptomatic sites or best supportive care (45). Up to now, no randomized clinical trial to assess the efficacy and tolerance of RT in LM have been conducted, however use of radiation therapy in NSCLC patients with LM, particularly in those not presenting driver mutations, needs to be better defined in clinical trials. Concomitant strategies with ITC are currently not considered as standard care due to the toxicity profile. Phase II clinical trial of combination therapy with involved field RT combined with concurrent intrathecal-MTX or intrathecal-ARA-C is currently underway (57).

Table 1 summarize the published studies from 2000: different types of radiation modality on different histologies in patients with LM are included (36, 49, 56, 58–61).

In the last few years, understanding of immune system's role in the response to ionizing radiation is progressively raising, novel opportunities to study how to combine immunotherapy with radiation-induced cell killing are revolutionizing cancer treatment. Accumulating preclinical and clinical data showed that combination of radiation techniques with immunotherapy stimulates immune response, improves locoregional and distant control finally resulting in better OS. Radiation appears to stimulate the immune system through multiple mechanisms, including the increase of the tumor-associated antigens (TAAs) availability, improving antigen presentation and subsequent stimulation of effector T cells, and enhancing infiltration of dentritic cells and T cells into the tumor microenvironment. The limited evidence for immunotherapy to date in the treatment of BM and LM stems from the deliberate exclusion of patients with active brain metastases from many large randomized trial assessing drug efficacy (61–63). However, comparable efficacy of immunotherapy agents in the brain and at extracerebral sites with radiation therapy has been recently reported by an ongoing study from Goldberg et al. In this initial analyses 36 cases were considered, 18 with melanoma and 18 with NSCLC. Patients were treated with pembrolizumab 10 mg/kg every 2 weeks until progression, no target lesions were previously resected, 20 patients received some form of local CNS therapy prior to enrollment (9 and 7 lesions had been treated respectively with WBRT and SRS, 75 lesions were untreated). The primary endpoint was BM response rate and the initial results presented demonstrated a systemic benefit from immunotherapy in patients with metastatic melanoma and NSCLC (61). Combining immunotherapeutic agents with stereotactic radiosurgery appears to enhance both local and distant control, and result in better survival (42).

Finally, other types of RT in patients without obstruction to CSF flow, as radioimmunotherapy (RIT) consisting of intra CSF administration of radioisotopes like iodine-131 (^{131}I) and yttrium-90 (^{90}Y) with radiolabeled antibodies as HMFG1, 3F8 and 8H9 have been utilized, but further improvement in the pharmacokinetic modeling of CNS RIT modality should refine this emerging therapy to fit the clinical context (63, 64).

Systemic Therapy

In the last decade, the advent of EGFR- tyrosine kinase inhibitors (TKIs) has improved the prognosis of NSCLC patients harboring EGFR mutations on both CNS metastases and extracranial disease, by contrast non-oncogene addicted NSCLC prognosis remains extremely poor.

The role of chemotherapy for patients with CNS metastases from NSCLC has been neglected for years, because of prevailing belief that chemotherapeutic drugs cannot cross at all the BBB. A Platinum based-combination (preceded or not by a local radiation treatment) is the mainstay of treatment in

TABLE 1 | Selected trials published of radiation modality treatment with or without chemotherapy/immunotherapy association in patients with LM/BM [BM, brain metastasis; LM, leptomeningeal metastasis, Involved-field radiotherapy (IF-RT), Intrathecal chemotherapy (IC), Craniospinal Irradiation (CSI) Methotrexate (MTX), Non available (NA), Not reached (NR), Patients (pt)].

Author and year	Number of patients	Histology	CNS metastasis	Status of EGFR/ALK NSCLC	Treatment	Median overall survival (mOS) (weeks)
Wolf et al. (56) (retrospective)	16	8 NSCLC 5 breast cancer 3 other	LM	4 EGFR mutant 1 ALK-rearranged 3 no mutation	SRS (5 pt had prior WBRT)	40
Pan et al. (58) (prospective phase 2 study)	59	32 NSCLC 10 SCLC 11 breast cancer 6 Other	LM	NA	Concomitant IF-RT + IC MTX	26
Ozdemir et al. (59) (retrospective)	51	30 SCC 21 Adenocarcinoma	LM	NA	WBRT	15, 6
Brower et al. (60) (retrospective)	124	32 NSCLC 22 breast cancer 21 SCLC 49 other	LM	NA	Chemotherapy + WBRT	9, 2
Gani et al. (49) (retrospective)	27	20 breast cancer 7 lung cancer	LM	NA	WBRT	8, 1
Hermann et al. (36) (retrospective)	16	9 breast cancer 5 lung cancer 2 other	LM	NA	CSI (10 pt CSI + ITC MTX)	12 8 RT alone 16 RT-ITC
Goldberg et al. (61) (two-cohort phase II trial)	36	18 melanoma 18 NSCLC	BM	KRAS mutant 4 EGFR mutant 1 ALK-rearranged 1 PD-L1 positive 18	Pembrolizumab 20 pt prior CNS therapy (9 lesions WBRT 7 lesions SRS)	Melanoma (NR) NSCLC 30, 8

TABLE 2 | Platinum-based chemotherapy trials for CNS from NSCLC (BM, brain metastasis; LM, leptomeningeal metastasis).

Author and year	Number of patients	CNS metastasis	Histology	Treatment	Intracranial RR (IRR, %)	Median overall survival (mOS) (weeks)
Robinet et al. (71)	171	BM	NSCLC	Cisplatin-Vinorelbine	33	24
Franciosi et al. (68)	43	BM + LM	NSCLC	Cisplatin-Etoposide	37	32
Barlesi et al. (72)	43	BM	NSCLC	Cisplatin-Pemetrexed	41.9	29.6
Cotto et al. (69)	31	BM	NSCLC	Cisplatin-Fotemustine	23	16
Fujita et al. (67)	30	BM	NSCLC	Cisplatin-Ifosfamide-Irinotecan	50	56
Bailon et al. (73)	26	BM	NSCLC	Carboplatin-Pemetrexed	40	39
Cortes et al. (65)	26	BM	NSCLC	Paclitaxel Cisplatin/Vinorelbine-Gemcitabine	38	21.4
Minotti et al. (66)	23	BM	NSCLC	Cisplatin-Teniposide	35	21
Bernardo et al. (70)	22	BM	NSCLC	Carboplatin-Vinorelbine-Gemcitabine	45	33

advanced non-small cell lung cancer (aNSCLC) with BM and or LM NSCLC at diagnosis without oncogenic driver mutations or *programmed death-ligand 1 (PD-L1)* tumor proportion score (TPS) values $\geq$ 50% (65–73). **Table 2** summarize platinum-based chemotherapy for NSCLC patients with CNS (65–73).

Pemetrexed is a compound currently approved both in combination with platinum in first-line setting and as a single agent in maintenance or second line setting for the treatment of non-squamous cell carcinoma (74–77). Although a penetration of CNS of less 5%, pemetrexed demonstrated a consistent activity against BM from NSCLC with an intracranial RR of 30.8−41.9% and an overall clinical benefit of 63% without specific data for LM (72, 73, 78, 79) Bevacizumab is an anti-VEGF monoclonal antibody approved in patients affected by locally advanced or metastatic non-squamous cell carcinoma (80). Recent reports showed that bevacizumab improve intra-tumor penetration of other chemotherapeutic agents, such as carboplatin or paclitaxel by normalizing angiogenesis at the tumor site with a low incidence of CNS hemorrhage (81, 82). Additionally, bevacizumab appeared to alter neuroimaging characteristics of LM, confounded diagnosis and possibly also influenced the pattern of tumor spread of LM (83). Bevacizumab is also known as a "steroid-sparing" drug, that allows reduction in steroid dosage and achieves reductions in mass effect and peritumoral edema getting better control of neurological symptoms (84). In those patients with squamous histology and low PD-L1 expression, gemcitabine and taxanes are largely prescribed, also in patient with BM, but no specific data about LM are available (70, 85, 86).

For both squamous and non-squamous cell carcinoma without oncogene-addiction and TPS $\geq$ 50%, pembrolizumab represents the standard of care in the first-line setting. Data on the efficacy of immunotherapy for BM or LM are currently limited, because of the exclusion of these patients from clinical trials (38, 87–89). In the trial by Goldberg et al., already mentioned above, 36 patients with BM were treated with pembrolizumab. Among patients with NSCLC, BM response rate was 33% and treatment-related serious adverse events were rare. Several aspects of study population need to be considered looking at the results: patients eligible for this trial were those with BM $<$ 20 mm, asymptomatic and not requiring corticosteroids to control neurologic symptoms, without autoimmune disease and with no prior treatment with agents targeting PD-1/PD-L1 (61). Only preliminary data are available on efficacy of anti-programmed cell death 1 (PD-1) agents (nivolumab, pembrolizumab) or anti-PD ligand 1 (atezolizumab) in NSCLC patients with BM. A review on efficacy and safety of nivolumab conducted by Dudnik in five patients with aNSCLC with new/progressing asymptomatic CNS metastasis (including patient with LM) suggested that immune-check inhibitors might have an intracranial activity. Two intracranial responses were observed, while stabilization of LM was achieved in 10 weeks (90). In the Italian Nivolumab Squamous NSCLC Expanded Access Program, 38 patients with treated and asymptomatic BM were included, none of them with LM. In this subgroup of patients immunotherapic agent obtained a disease control rate equal to 47.3% (91). On the other hand, Otsubo et al., reported a case report of the development of LM during a pronounced response of the primary tumor to pembrolizumab therapy in a NSCLC patient (92). Relevant to this, in the era of molecular oncology it will be important to consider genomic differences in systemic malignancies that can implicate a distinct immune response.

Looking at other type of compounds, a phase II trial with abemaciclib (orally bioavailable inhibitor of cyclin-dependent kinases 4 and 6) (93) is ongoing in patients with LM from NSCLC and solid tumors (94).

Intra-Thecal Chemotherapy

Intrathecal administration is the most common method to deliver chemotherapeutic agents in non-nodular and non-bulky LM in solid tumors, although efficacy compared to systemic administration and choice of regimen are poorly understood due to limited randomized controlled trials (95). Systemic chemotherapy, which may be combined with intrathecal chemotherapy, remains standard treatment for lung cancer patients with LM and a good-risk profile (45).

Several retrospective studies demonstrated a survival benefit from IT-therapy. Because of the paucity of available patients, LM studies often accrue multiple primary histologies. Most reports of intrathecal LM treatments include patients who simultaneously receive systemic agents (29, 95–98). Although the compounds routinely used for intra-CSF treatment do not have a key role as single agents for systemic treatment of most common cancers causing LM, three agents are commonly prescribed for the intrathecal treatment of LM: methotrexate (98), cytarabine (including liposomal cytarabine) (99, 100) or thioTEPA (8). Several schedules have been proposed, without agreement on optimal dose, frequency of administration or optimal duration of treatment. No intra-CSF agent has shown a significant survival advantage over another (8, 99, 100). Up to now most of the patients are treated until progression or for 1 year, if tolerated. In the absence of evidence from appropriate clinical trials, clinical symptoms, MRI and CSF findings, as well as tolerance of treatment, guide individual decisions on the duration of treatment (34). Pemetrexed is a newer generation multi-targeted anti-folate agent and, compared with methotrexate, has better tolerability, exhibits a more favorable side effect profile, and possesses fewer-drug interactions (78). A phase I trial (NCT03101579) is ongoing to define safety profile and clinical response rate associated with this specific intrathecal therapy (101).

CONCLUSION

LM is undoubtfully a serious complication in NSCLC patients. Prognosis remains poor, even with the use of personalized treatments, principally due to low penetration into the CSF of currently used agents. To our knowledge no randomized trial has demonstrated a clear survival benefit of any single modality in the treatment of LM. The optimal treatment strategy involves a multi- disciplinary approach. The increasing prevalence of LM warrants further investigation into therapies and prognostic variables to serve as a guide for treatment recommendations and patients counseling. An improved understanding of the biologic mechanisms underlying tumor CNS metastases and novel available diagnostic tools will allow for patient-tailored treatment strategies. Future well-designed randomized controlled studies are needed to evaluate the efficacy of chemotherapeutics, immunotherapies and radiation treatment in this specific subgroup of patients and, more specifically, in those without an "oncogene addiction."

AUTHOR CONTRIBUTIONS

AT and AM wrote the manuscript with support from TV. SN supervised the manuscript.

REFERENCES

1. Levy A, Faivre-Finn C, Hasan B, De Maio E, Berghoff AS, Girard N, et al. Diversity of brain metastases screening and management in non-small cell lung cancer in Europe: Results of the European Organisation for Research and Treatment of Cancer Lung Cancer Group survey. *Eur J Cancer* (2018) 93:37–46. doi: 10.1016/j.ejca.2018.01.067
2. Soffietti R, Abacioglu U, Baumert B, Combs SE, Kinhult S, Kros JM, et al. Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). *Neuro-Oncology* (2017) 19:162–74. doi: 10.1093/neuonc/now241
3. Remon J, Le Rhun E, Besse B. Leptomeningeal carcinomatoses in non-small cell lung cancer patients; a continuing challenge in the personalized treatment era. *Cancer Treat Rev.* (2017) 53:158–37. doi: 10.1016/j.crtv.2016.12.006
4. Liao B-C, Lee J-H, Lin C-C, Chen Y-F, Chang C-H, Ho C-C, et al. Epidermal growth factor receptor tyrosine kinase inhibitors for non-small-cell lung cancer patients with leptomeningeal carcinomatosis. *J Thorac Oncol.* (2015) 10:1754–61. doi: 10.1097/JTO.0000000000000669
5. Lee SJ, Lee JI, Nam DH, Ahn YC, Han JH, Sun JM, et al. Leptomeningeal carcinomatosis in non-small-cell lung cancer patients: impact on survival and correlated prognostic factors. *J Thorac Oncol.* (2013) 8:185–91. doi: 10.1097/JTO.0b013e3182773f21
6. Omuro AMP, Kris MG, Miller VA, Franceschi E, Shah N, Milton DT, et al. High incidence of disease recurrence in the brain and leptomeninges in patients with non small cell lung carcinoma after response to gefitinib. *Cancer* (2005) 103:2344–8. doi: 10.1002/cncr.21033
7. Nugent JL, Bunn PA Jr, Matthews MJ, Ihde DC, Cohen MH, Gazdar A, et al. CNS metastases in small cell bronchogenic carcinoma: increasing frequency and changing pattern with lengthening survival. *Cancer* (1979) 44:1885–93.
8. Grossman SA, Finkelstein DM, Ruckdeschel JC, Trump DL, Moynihan T, Ettinger DS. Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. Eastern Cooperative Oncology Group. *J Clin Oncol.* (1993) 11:561–9. doi: 10.1200/JCO.1993.11.3.561
9. Cheng H, Perez-Soler R. Leptomeningeal metastases in non-small-cell lung cancer. *Lancet Oncol.* (2018) 19:e43–55. doi: 10.1016/S1470-2045 (17) 30689-7
10. Hyun J-W, Jeong IH, Joung A, Cho HJ, Kim S-H, Kim HJ. Leptomeningeal metastasis: clinical experience of 519 cases. *Eur J Cancer* (2016) 56:107–14. doi: 10.1016/j.ejca.2015.12.021
11. Mak KS, Gainor JF, Niemierko A, Oh KS, Willers H, Choi NC, et al. Significance of targeted therapy and genetic alterations in EGFR, ALK or KRAS on survival in patients with non-small cell lung cancer treated with radiotherapy for brain metastases. *Neuro Oncol.* (2015) 17:296–302. doi: 10.1093/neuonc/nou146
12. Riess JW, Nagpal S, Iv M, Zeineh M, Gubens MA, Ramchandran K, et al. Prolonged survival of patients with non-small-cell lung cancer with leptomeningeal carcinomatosis in the modern treatment era. *Clin. Lung Cancer* (2014) 15:202–6. doi: 10.1016/j.cllc.2013.12.009
13. Du C, Hong R, Shi Y, Yu X, Wang J. Leptomeningeal metastasis from solid tumors: A single center experience in Chinese patients. *J. Neuro Oncol.* (2013) 115:285–91. doi: 10.1007/s11060-013-1228-x
14. Park JH, Kim YJ, Lee JO, Lee KW, Kim JH, Bang SM, et al. Clinical outcomes of leptomeningeal metastasis in patients with non-small cell lung cancer in the modern chemotherapy era. *Lung Cancer* (2012) 76:387–92. doi: 10.1016/j.lungcan.2011.11.022
15. Chamberlain MC, Baik CS, Gadi VK, Bhatia S, Chow LQ. Systemic therapy of brain metastases: non-small cell lung cancer, breast cancer, and melanoma. *Neuro Oncol.* (2017) 19:i1–24:doi: 10.1090/neuonc/now197
16. Ostermann G, Csajka C, Buclin T, Leyvraz S, Lejeune F, Decosterd LA, et al. Plasma and cerebrospinal fluid population pharmacokinetics of temozolomide in malignant gliomas patients. *Clin Cancer Res.* (2004) 10:3728–36. doi: 10.1158/1078-0432.CCR-03-0807

17. Shapiro WR, Young DF, Mehta BM. Methotrexate: distribution in the cerebrospinal fluid after intravenous, ventricular and lumbar injections. *N Eng J Med*. (1975) 293:161–6. doi: 10.1056/NEJM197507242930402
18. Balis FM, Blaney SM, McCully Cl, Bacher JD, Murphy RF, Poplack DG. Methotrexate distribution within the subaracnoid space after inthaventricular and intravenous administration. *Cancer Chemothet Pharmacol.* (2000) 45:259–64. doi: 10.1007/s002800050038
19. Sung CA, Blaney SM, Cole DE, Balis FM, Dedrick RL. Pharmacokinetic model of topotecan clerance from plasma and cerebrospinal fluid. *Cancer Res Cancer Res*. (1994) 54:5118–22.
20. Serlin Y, Shelef I, Knyazer B, Friedman A. Anatomy and physiology of the blood-brain barrier. *Semin Cell Dev Biol.* (2015) 8:2–6. doi: 10.1016/j.semcdb.2015.01.002
21. Weidle UH, Niewöhner J, Tiefenthaler G. The Blood-Brain Barrier challenge for the treat of brain cancer, secondary brain metastasis, and neurological diseases. *Cancer Genomics Proteomics* (2015) 12:167–77.
22. Walbert T, Gilbert MR. The role of chemotherapy in the treatment of patients with brain metastases from solid tumors. *Int J Clin Oncol.* (2009) 14:299–306. doi: 10.1007/s10147-009-0916-1
23. Inno A, Di Noia V, D'Argento E, Modena A, Gori S. State of the art of chemotherapy for the treatment of central nervous system metastases from non-small cell lung cancer. *Transl Lung Cancer Res*. (2016) 5:599–609. doi: 10.21037/tlcr.2016.11.01
24. Holash J, Maisonpierre PC, Compton D, Boland P, Alexander CR, Zagzag D, et al. Vessel cooption, regression, and growth in tumors mediated by angiopoietins and VEGF. *Science* (1999) 284:1994–8. doi: 10.1126/science.284.5422.1994
25. Ahluwalia MS, Vogelbaum MV, Chao ST, Mehta MM. Brain metastasis and treatment. *FI000Prime Rep.* (2014) 6:114. doi: 10.12703/P6-114
26. Eichler AF, Chung E, Kodack DP, Loeffler JS, Fukumura D, Jain RK. The biology of brain metastases-translation to new therapies. *Nat Rev Clin Oncol.* (2011) 8:344–56. doi: 10.1038/nrclinonc.2011.58.
27. Zeng YD, Liao H, Qin T, Zhang L, Wei WD, Liang JZ, et al. Blood-brain barrier permeability of gefitinib in patients with brain metastases from non-small-cell lung cancer before and during whole brain radiation therapy. *Oncotarget* (2015) 6:8366–76. doi: 10.18632/oncotarget.3187
28. Mack F, Baumert BG, Schäfer N, Hattingen E, Scheffler B, Herrlinger U, et al. Therapy of leptomeningeal metastasis in solid tumors. *Cancer Treat Rev*. (2016) 43:83–91. doi: 10.1016/j.ctrv.2015.12.004
29. Chamberlain M, Soffietti R, Raizer J, Rud R, Brandsma D, Boogerd W, et al. Leptomeningeal metastasis: a response assessment in neuro-oncology critical review of endpoints and response criteria of published randomized clinical trials. Neuro-Oncology (2014) 16:1176–85. doi: 10.1093/neuonc/nou089
30. Grossman SA, Krabak MJ. Leptomeningeal carcinomatosis. *Cancer Treat Rev*. (1999) 25:103–19. doi: 10.1053/ctrv.1999.0119
31. Jiang BY, Li YS, Guo WB, Zhang XC, Chen ZH, Su J, et al. Detection of driver and resistance mutations in leptomeningeal metastases of NSCLC by next-generation sequencing of cerebrospinal fluid circulation tumour cells. *Clin Cancer Res.* (2017) 23:5480–8. doi: 10.1158/1078-0432.CCR-17-0047
32. Rodesch G, Van Bogaert P, Mavroudakis N, Parizel PM, Martin JJ, Segebarth C, et al. Neuroradiologic findings in leptomeningeal carcinomatosis: the value interest of gadolinium-enhanced MRI. *Neuroradiology* (1990) 32:26–32.
33. Salgarello M, Lunardi G, Inno A, Pasetto S, Severi F, Gorgoni G, et al. 18F-NaF PET/CT imaging of brain metastases. *Clin Nucl Med.* (2016) 41:564–5. doi: 10.1097/RLU.0000000000001186
34. Le Rhun E, Weller M, Brandsma D, Van den Bent M, De Azambuja E, Henriksson R, et al. EANO-ESMO clinical practice guidelines for diagnoses, treatment and follow-up of patients with leptomeningeal metastases from solid tumours. *Ann Oncol.* (2017) 28 (Suppl. 4):iv84–99. doi: 10.1093/annonc/mdx221
35. Chamberlain MC. Leptomeningeal metastasis. *Semin Neurol* (2010) 30:236–44. doi: 10.1055/s-0030-1255220
36. Hermann B, Hültenschmidt B, Sautter-Bihl ML. Radiotherapy of the neuroaxis for palliative treatment of leptomeningeal carcinomatosis. *Strahlenther Onkol.* (2001) 177:195–9. doi: 10.1007/s00066-001-0803-9
37. Boogerd W, van den Bent MJ, Koehler PJ, Heimans JJ, van der Sande JJ, Aaronson NK, et al. The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomized study. *Eur J Cancer* (2004) 40:2726–33. doi: 10.1016/j.ejca.2004.08.012
38. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomized controlled trial. *Lancet* (2016) 387:1540–50. doi: 10.1016/S0140-6736(15)01281-7
39. Barlesi F, Keunchil P, Ciardiello F, von Pawel J, Gadgeel S, Hida T, et al. Primary analysis from OAK, a randomized phase III study comparing atezolizumab with docetaxel in advanced NSCLC, ESMO 2016. *Ann Oncol.* (2016) 27: ix139–ix156. doi: 10.1093/annonc/mdw594
40. Badiyan SN, Regine W, Mehta M. Stereotactic radiosurgery for treatment of brain metastases. *Am Soc Clin Oncol.* (2016) 12:703–12. doi: 10.1200/JOP.2016.012922
41. Lou E, Sperduto PW. Integrating bevacizumab and radiation treatment of brain metastases: is there sense and sensibility in this approach? *Ann Transl Med.* (2016) 4:36. doi: 10.3978/j.issn.2305-5839.2015.12.42
42. Zhang I, Formenti SC, Knisely IPS. Immunotherapy plus stereotactic radiosurgery: building on the promise of precision medicine for the CNC malignancies, part 1: principles of combined treatment. *Oncology* (2018) 35:e28–32.
43. Hee-Jun K, Seock-Ah L, Bhumsuk K, Yu-Jung K, Sae-Won H, Tae K, et al. Clinical outcome of central system metastases from breast cancer: differences in survival depending on systemic treatment. *J Neuro-Oncol.* (2012) 106:303–13. doi: 10.1007/s11060-011-0664-8
44. Altundag K, Bondy ML, Mirza NQ, Kau SW, Broglio K, Hortobagyi GN, et al. Clinicopathologic characteristics and prognostic factors in 420 metastatic breast cancer patients with central nervous system metastases. *Cancer* (2017) 110:2640–7. doi: 10.1002/cncr.23088
45. *Central Nervous System Cancers: Leptomeningeal Metastases* (2017). v.1.2017: Available online at: http://www.nccn.org
46. Schimmel WCM, Verhaak E, Hanssens PEJ, Gehring K, Sitskoorn MM. A randomized trial to compare cognitive out come after gamma knife radiosurgery versus whole brain radiation therapy in patients with multiple brain metastases: research protocol CAR-study B. *BMC Cancer* (2018) 18:218. doi: 10.1186/s12885-018-4106-2
47. Espenel S, Vallard A, Langrand-Escure J, Ben Mrad M, Mery B, Rivoirard R, et al. Méningite carcinomateuse: le point de vue de l'oncologue radiothérapeute. *Cancer/Radiothérapie* (2016) 20:54–9. doi: 10.1016/j.canrad.2016.01.008
48. Waki F, Ando M, Takashima A, Yonemori K, Nokihara H, Miyake M, et al. Prognostic factors and clinical outcomes in patients with leptomeningeal metastasis from solid tumors. *J Neurooncol.* (2009) 93:205–12. doi: 10.1007/s1106-008-9758-3
49. Gani C, Muller AC, Eckert F, Schroeder C, Bender B, Pantazis G, et al. Outcome after whole brain radiotherapy alone in intracranial leptomeningeal carcinomatosis from solid tumors. *Strahlenther Onkol.* 188:148–53. doi: 10.1007/s00066-011-0025-8
50. Chamberlain MC. Neoplastic meningitis. *Oncologist* (2008) 13:967–77. doi: 10.1634/theoncologist.2008-0138
51. Ray GL, Buchsbaum JC, McMullen KP, Simoneaux RV, Hines M, Douglas JG, et al. Definitive treatment of leptomeningeal spinal metastases in children. *Pediatr Blood Cancer* (2013) 60:1839–41. doi: 10.1002/pbc.24659
52. Chang EL, Maor MH. Standard and novel radiotherapeutic approaches to neoplastic meningitis. *Curr Oncol Rep.* (2003) 5:24–8.
53. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys.* (2000) 47:291–8. doi: 10.1016/S0360-3016(99)00507-6
54. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Radiation Therapy Oncology Group (RTOG). *Neuro-Oncology* (2013) 15:1429–37. doi: 10.1093/neuron/not114

55. Bertke MH, Burton EC, Shaughnessy JN. Stereotactic radiosurgery as part as multimodal treatment in a bulky leptomeningeal recurrence of breast cancer. *Cureus* (2016) 8:e523. doi: 10.7759/cureus.523
56. Wolf A, Donahue B, Silverman JS, Chachoua A, Lee JK, Kondziolka D. Stereotactic radiosurgery for focal leptomeningeal disease in patients with brain metastases. *J Neurooncol.* (2017) 134:139–43. doi: 10.1007/s11060-017-2497-6
57. ClinicalTrials.gov Identifer: NCT03082144.
58. Pan Z, Yang G, He H, Zhao G, Yuan T, Li Y, et al. Concurrent radiotherapy and intrathecal methotrexate for treating leptomeningeal metastasis from solid tumors with adverse prognostic factors: a prospective and single-arm study. *Int J Cancer* (2016) 139:1864–72. doi: 10.1002/ijc.30214
59. Ozdemir Y, Yildirim BA, Topkan E. Whole brain radiotherapy in management of non-small-cell lung carcinoma associated leptomeningeal carcinomatosis: evaluation of prognostic factors. *J Neurooncol.* (2016) 129:329–35. doi: 10.1007/s11060-016-2179-9
60. Brower JV, Saha S, Rosenberg SA, Hullett CR, Ian Robins H. Management of leptomeningeal metastases: prognostic factors and associated outcomes. *J Clin Neurosci.* (2016) 27:130–7. doi: 10.1016/j.jocn.2015.11.012
61. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non small-cell lung cancer and untreated brain metastases: early analysis of a non-randomized, open label phase 2 trial. *Lancet Oncol.* (2016) 17:976–83. doi: 10.1016/S1470-2045(16)30053-5
62. Long GV, Atkinson V, Menzies AM, Lo S, Guminski AD, Brown MP, et al. A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients with melanoma brain metastases: the Anti-PD1 Brain Collaboration (ABC). *J Clin Oncol.* (2017) 35:9508. doi: 10.1200/JCO.2017.35.15
63. Moseley RP, Benjamin JC, Ashpole RD, Sullivan NM, Bullimore JA, Coackham HB. Carcinomatous meningitis: antibody-guided therapy with I-131 HMFG1, *J Neurol Neurosurg Psychiatry* (1991) 54:260–5.
64. He P, Kramer K, Smith-Jones P, Zanzonico P, Humm J, Larson SM, et al. Two- compartment model of radioimmunotherapy delivered through cerebrospinal fluid. *Eur J Nucl Med Mol Imaging* (2011) 38:334–42. doi: 10.1007/s00259-010-1633-8
65. Cortes J, Rodriguez J, Aramendia JM, Salgado E, Gurpide A, Garcia-Foncillas J, et al. Front-line paclitaxel/cisplatin-based chemotherapy in brain metastases from non-small-cell lung cancer. *Oncology* (2003) 64:28–35. doi: 10.1159/000066520
66. Minotti V, Crinò L, Meacci ML, Corgna E, Darwish S, Palladino MA, et al. Chemotherapy with cisplatin and teniposide for cerebral metastases in non-small cell lung cancer. *Lung Cancer* (1998) 20:93–8.
67. Fujita A, Fukuoka S, Takabatake H, Tagaki S, Sekine K. Combination chemotherapy of cisplatin, ifosfamide, and irinotecan with rhG-CSF support in patients with brain metastases from non-small cell lung cancer. *Oncology* (2000) 59:291–5. doi: 10.1159/000012185
68. Franciosi V, Cocconi G, Michiara M, Di Costanzo F, Fosser V, Tonato M, et al. Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, non-small-cell lung carcinoma, or malignant melanoma: a prospective study. *Cancer* (1999) 85:1599–605.
69. Cotto C, Berille J, Souquet PJ, Riou R, Croisile B, Turjman F, et al. A phase II trial of fotemustine and cisplatin in central nervous system metastases from non-small cell lung cancer. *Eur J Cancer* (1996) 32A:69–71.
70. Bernardo G, Cuzzoni Q, Strada MR, Bernardo A, Brunetti G, Jedrychowska I, et al. First-line chemotherapy with vinorelbine, gemcitabine, and carboplatin in the treatment of brain metastases from non-small-cell lung cancer: a phase II study. *Cancer Invest.* (2002) 20:293–302.
71. Robinet G, Thomas P, Breton JL, Léna H, Gouva S, Dabouis G, et al. Results of a phase III study of early versus delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination in inoperable brain metastasis of non-small-cell lung cancer: Groupe Francais de Pneumo-Cancerologie (GFPC) Protocol 95-1. *Ann Oncol.* (2001) 12:59–67.
72. Barlesi F, Gervais R, Lena H, Hureaux J, Berard H, Paillotin D, et al. Pemetrexed and cisplatin as first-line chemotherapy for advanced nonsmall-cell lung cancer (NSCLC) with asymptomatic inoperable brain metastases: a multicenter phase II trial (GFPC 07-01). *Ann Oncol.* (2011) 22:2466–70. doi: 10.1093/annonc/mdr003
73. Bailon O, Chouahnia K, Augier A, Bouillet T, Billot S, Coman I, et al. Upfront association of carboplatin plus pemetrexed in patients with brain metastases of lung adenocarcinoma. *Neuro Oncol.* (2012) 14:491–5. doi: 10.1093/neuonc/nos004
74. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* (2008) 26:3543–51. doi: 10.1200/JCO.2007.15.0375
75. Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study *Lancet* (2009) 374:1432–40. doi: 10.1016/S0140-6736(09)61497-5
76. Paz-Ares LG, De Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol.* (2013) 31:2895–902. doi: 10.1200/JCO.2012.47.1102
77. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed vs. docetaxel in patients with non-small-cell-lung cancer previously trated with chemotherapy. *J Clin Oncol.* (2004) 22:1589–97. doi: 10.1200/JCO.2004.08.163
78. Kumthekar P, Grimm SA, Avram MJ, Kaklamani V, Helenowski I. Pharmacokinetics and efficacy of pemetrexed in patients with brain or leptomeningeal metastases. *J Neurooncol.* (2013) 112:247–55. doi: 10.1007/s11060-013-1055-0
79. Bearz A, Garassino I, Tiseo M, Caffo, Soto-Parra H, Boccalon M, et al. Activity of Pemetrexed on brain metastases from Non-Small Cell Lung Cancer. *Lung Cancer* (2010) 68:264–8. doi: 10.1016/j.lungcan.2009.06.018
80. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* (2006) 355:2542–50. doi: 10.1056/NEJMoa061884.82
81. Socinski MA, Langer CJ, Huang JE, Kolb MM, Compton P, Wang L, et al. Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases. *J Clin Oncol.* (2009) 27:5255–61. doi: 10.1200/JCO.2009.22.0616
82. Kleinschmidt-DeMasters BK, Damek DM. The imaging and neuropathological effects of Bevacizumab (Avastin) in patients with leptomeningeal carcinomatosis. *J Neurooncol.* (2010) 96:375–84. doi: 10.1007/s11060-0099969-2
83. Mathews MS, Linskey ME, Hasso AN, Fruehauf JP. The effect of bevacizumab (Avastin) on neuroimaging of brain metastases. *Surg Neurol.* (2008) 70:649–52, discussion 53. doi: 10.1016/j.surneu.2007.06.029
84. Nghiemphu PL, Liu W, Lee Y, Than T, Graham C, Lai A, et al. Bevacizumab and chemotherapy for recurrent glioblastoma: a single-institution experience. *Neurology* (2009) 72:1217–22. doi: 10.1212/01.wnl.0000345668.03039.90
85. Edelman MJ, Belani CP, Socinski MA, Ansari RH, Obasaju CK, Chen R, et al. Outcomes associated with brain metastases in a three-arm phase III trial of gemcitabine-containing regimens versus paclitaxel plus carboplatin for advanced non-small cell lung cancer. *J Thorac Oncol.* (2010) 5:110–6. doi: 10.1097/JTO.0b013e3181c59a3a
86. Volk V, Cathomas R, Mark M, von Moos R, Klingbiel D, Brossart P, et al. Weekly carboplatin in combination with weekly paclitaxel in the treatment of metastatic non-small cell lung cancer: a single center 10-year experience. *Support Care Cancer* (2016) 24:2119–28. doi: 10.1007/s00520-015-3015-z
87. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med.* (2015) 373:123–35. doi: 10.1056/NEJMoa1504627
88. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med.* (2015) 373:1627–39. doi: 10.1056/NEJMoa1507643
89. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label,

multicentre randomised controlled trial. *Lancet* (2017) 389:255–65. doi: 10.1016/S0140-6736(16)32517-X
90. Dudnik E, Yust-Katz S, Nechushtan H, Goldstein DA, Zer A, Flex D, et al. Intracranial response to nivolumab in NSCLC patients with untreated or progressing CNS metastases. *Lung Cancer* (2016) 98:114–7. doi: 10.1016/j.lungcan.2016.05.031
91. Crinò L, Bidoli P, Delmonte A, Grossi F, De Marinis F, Sperandi F, et al. Italian cohort of nivolumab Expanded Access Programme (EAP): efficacy and safety data from a real-world population *Ann Oncol.* (2016) 27(suppl. 4):iv3. doi: 10.1093/annonc/mdw332.01
92. Otsubo K, Seki N, Nakanishi Y, Okamoto I. Development of leptomeningeal carcinomatosis during a marked response of brain metastases to pembrolizumab in a patient with non-small-cell lung cancer. *Ann Oncol.* (2017) 29: 780–1. doi: 10.1093/annonc/mdx700
93. Hall M, Peters G. Genetic alterations of cyclins, cyclin-dependent kinases, and CDK inhibitors in human cancer. *Adv Cancer Res.* (1996) 68:67–108.
94. Patnaik A, Rosen LS, Tolaney SM, Tolcher AW, Goldman JW, Gandhi L, et al. Efficacy and Safety of Abemaciclib, an Inhibitor of CDK4 and CDK6, for Patients with Breast Cancer, Non-Small Cell Lung Cancer, and Other Solid Tumors. *Cancer Discov*. (2016) 6:740–53. doi: 10.1158/2159-8290.CD-16-0095
95. Chamberlain MC, Kormanik PR. Carcinoma meningitis secondary to non-small cell lung cancer: combined modality therapy. *Arch Neurol.* (1998) 55:506–12.
96. Chamberlain MC, Kormanic PR. Carcinomatous meningitis secondary to breast cancer: predictors of response to combined modality therapy. *J Neurooncol*. (1997) 35:55–64.
97. Grant R, Naylor B, Greenberg HS. Clinical outcome in aggressively treated meningeal carcinomatosis. *Arch Neurol*. (1994) 51:457–61. doi: 10.1001/archneur.1994.00540170033013
98. Ahn HK, Han B, Lee SJ, Lim T, Sun JM, Ahn JS, et al. ALK inihibitor crizotinib combined with intrathecal methotrexate treatment for non-small cell lung cancer with leptomeningeal carcinomatosis. *Lung Cancer* (2012) 76:253–4. doi: 10.1016/j.lungcan.2012.02.003
99. Glantz MJ, Jaeckle KA, Chamberlain MC, Phuphanich S, Recht L, Swinnen LJ, et al. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. *Clin Cancer Res*. (1999) 5:3394–402.
100. Hoffmann AL, Buhk JH, Strik H. Neoplastic meningitis from breast cancer: feasibility and activity of long-term intrathecal liposomal Ara-C combined with dose-dense temozolomide. *Anticancer Res*. (2009) 29:5191–5.
101. ClinicalTrials.gov Identifer: NCT03101579.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership