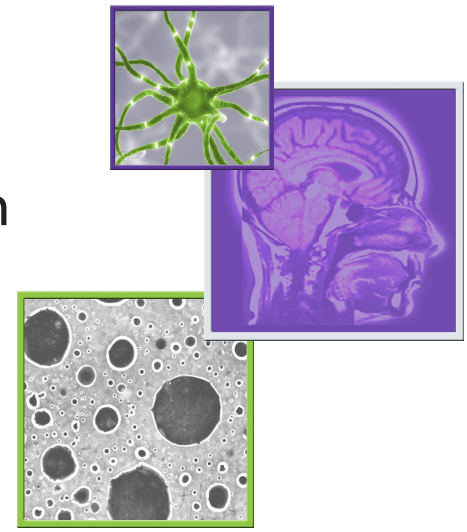
REVIEW

For reprint orders, please contact: reprints@futuremedicine.com

Brain metastases in non-small-cell lung cancer: better outcomes through current therapies and utilization of molecularly targeted approaches



Rimas V Lukas*[1], Maciej S Lesniak[2] & Ravi Salgia[3]

Practice Points

- The Disease-Specific-Graded Prognostic Assessment system for prognostication in patients with brain metastases provides a more nuanced prognosis based on a number of variables that differ based on the histology of the primary tumor. In non-small-cell lung cancer (NSCLC) these are Karnofsky performance status, age, presence of extracranial metastases and number of brain metastases with a median overall survival, depending on these variables, ranging from 3.02 to 14.78 months.
- The steps involved in brain metastases development include: extravasation of cancer cells from the tumor, travel of the cells through the vasculature, arrest of the cells in the microvasculature, cells crossing the blood–brain barrier and angiogensis. Components of these different steps may serve as future potential therapeutic and prophylactic targets.
- Molecular markers in NSCLC will continue to define potential targets for current and future therapies. These will also be used in combination with traditional therapies.
- Surgical resection followed by radiation therapy plays a role in the management of single brain metastases, including those from NSCLC.
- Radiation is a cornerstone in the treatment of brain metastases. In an effort to limit potential CNS toxicities from whole-brain radiation therapy there has been an increase in the use of stereotactic radiosurgery. When investigated specifically within the context of NSCLC brain metastases, radiation has been evaluated primarily in conjunction with other therapies, particularly systemic therapies.
- Systemic therapies may potentially play a growing role in the management of NSCLC brain metastases.

SUMMARY Non-small-cell lung cancer (NSCLC) patients experience a high incidence of brain metastases, *de novo* and recurrent. We review the mechanisms of brain metastases and promising NSCLC molecular markers to delineate potential future therapeutic targets. Discussed are the current and previously utilized roles of surgery, radiation (both therapeutic and prophylactic), and systemic therapies in the treatment of NSCLC brain metastases. Future directions for treatment of NSCLC brain metastases will conclude our review.

[1]Department of Neurology, University of Chicago, Chicago, IL, USA
[2]Department of Surgery, Section of Neurosurgery, Chicago, IL, USA
[3]Department of Medicine, Section of Hematology & Oncology, Chicago, IL, USA
*Author for correspondence: Tel.: +1 773 834 9026; Fax: +1 773 702 7485; rlukas@neurology.bsd.uchicago.edu

Future Medicine part of fsg

CNS metastases are associated with substantial morbidity and mortality in patients with solid tumors. Treatment of brain metastases is made difficult by the symptoms caused by the neuroanatomic location of the metastases, the difficulty of achieving efficacious concentrations of systemic therapies in the target organ, and the sensitivity of said organ to the therapies administered. The majority of CNS metastases are brain metastases, with the spinal cord and cerebrospinal fluid (CSF) less frequently involved. Lung cancers represent the solid tumors with the highest incidence of brain metastases [1]. The focus of this review will be narrowed to non-small-cell lung cancer (NSCLC) owing to the higher prevalence of NSCLC brain metastases at the population level as well as the significant differences in the underlying biology, and, in turn, clinical management of NSCLC brain metastases compared with small-cell lung cancer (SCLC) brain metastases. This review will begin by discussing the epidemiology of lung cancer brain metastases. It will then examine the mechanisms of brain metastases as this will broadly influence future directions in the investigation of therapeutic and prophylactic strategies for brain metastases. The developing role of molecular markers in NSCLC will also be addressed, focusing on what is known with respect to brain metastases. This will be followed by review of established treatments for brain metastases, including surgery and radiation, and how they pertain to NSCLC in particular. Finally, the evolving role of systemic therapies in potentially addressing brain metastases from NSCLC will be discussed.

Epidemiology

While national databases providing detailed information on the incidence of primary brain tumors exist, an analogous system is not present for brain metastases. In turn, the true incidence rates of brain metastases are less clearly established. Estimates of 8–11 per 100,000 individuals in the USA are frequently reported [2]. Lung cancer is thought to be the underlying primary tumor in approximately 15 to >50% of these cases, with NSCLC representing over a quarter of brain metastases patients in contemporary cohorts [1–5]. A discrepancy appears to exist between genders for the incidence of lung cancer brain metastases with the incidence being higher in women [2,3,6]. This, however, has not been consistently noted across all studies [7]. With respect to age, there appears to be a wide distribution in the incidence of lung cancer brain metastases with the highest relative incidence in patients in their 40s, and a notably decreased relative incidence (although higher absolute incidence) in patients older than 70 years of age [2,4]. This may be influenced, at least in part, by less aggressive work-ups in older patients with brain metastases in comparison with younger patients. The relative incidence and prevalence is shifting since many patients are undergoing brain imaging even for presumed early-stage disease, as well as in follow-ups.

The prognosis of patients with lung cancer brain metastases can be gauged via the contemporary Disease-Specific-Graded Prognostic Assessment. Factors influencing prognosis in NSCLC patients with brain metastases include: performance status, age, presence of extracranial metastases and number of brain metastases. The current median overall survival (OS) for patients with NSCLC brain metastases in is 7.00 months, compared with the median OS of 4.90 months for SCLC patients with brain metastases. Depending on the presence of specific prognostic factors median OS for NSCLC can range from 3.02–14.78 months [8]. With this wide range in OS, prognostic factors of the patients enrolled in therapeutic trials will influence the interpretation of study results and will need to be taken into consideration in the design of future clinical trials.

While not employed in the Disease-Specific-Graded Prognostic Assessment, and to our knowledge not evaluated in a histology-specific manner, the overall aggregate volume of brain metastases is another important prognosticator, one which may prove to be of greater importance than the number of metastases [9].

Mechanisms of brain metastases

Overview

The overwhelming majority of brain metastases from NSCLC arrive via a hematogenous route, classically growing at the interface between the cortical gray matter and underlying white matter and initially arresting in the microvasculature, particularly at branch points, where flow is slow. While brain metastases can occur anywhere within the brain, there appear to be differing incidences between histologies with regard to sites of local involvement within the brain. This may reflect either a tropism of specific malignant cell histologies for specific CNS locations independent

of the pattern of blood flow to the CNS or an increased facility for growth in specific locations within the CNS. Recent imaging-based studies demonstrated NSCLC may have a predilection for the parieto-occipital region and cerebellum [10]. This differs somewhat from earlier imaging work demonstrating predominantly supratentorial involvement, particularly at the watershed zones between arterial supplies [5]. Chemokines appear to play a role in the regulation of tumor cell migration through the vasculature to target organs [11]. Understanding the location of tumor cell arrest and growth within the CNS holds importance in helping form an understanding of why specific tumor histologies grow within specific areas in the CNS; a progressively more nuanced delineation of the 'soil' of Paget's 'seed and soil' hypothesis of metastases [12].

While a complete understanding of the mechanisms underlying solid tumor spread to and growth in the brain has not yet been elucidated, a general view of the key sequential steps exists. This understanding arises predominantly from preclinical studies investigating a wide range of tumor histologies, particularly breast, melanoma and lung adenocarcinoma. After extravasation from the primary tumor or other metastases and travel through the arterial vasculature, tumor cells must arrest their flow in the vasculature. Both size restriction of the vasculature and a cancer cell–endothelial cell adhesion cascade have been proposed as potential mechanisms. It is possible that different mechanisms are of varying importance in different histologies.

■ Arrest within the vasculature

Mechanical restriction of malignant cell movement has been demonstrated with lung carcinoma and melanoma cell lines in mouse models. Multiphoton laser-scanning microscopy has been used to demonstrate real-time arrest of malignant cell movement at branch points of narrow microvessels with diameters comparable to those of single cells [13]. It is not yet clear what exactly occurs to the multiple cancer cell aggregates or cancer cell–stromal cell aggregates that have been shown to more readily evade the immune response while travelling through the vasculature, which in turn improves metastasis efficacy [14], it may be possible that they lodge in slightly larger vessels in a similar fashion to their single cell analogs. Demonstration of mechanical arrest of malignant cells in the microvasculature does not exclude the role of cell surface receptors in anchoring the cells and their extravasation from the luminal side of the vessel into the brain parenchyma. Anchoring and arrest of cells is not adequate for the development of brain metastases, as has been demonstrated in animal models using injections of nanoparticle-labeled tumor cells [15].

In the classic cell adhesion cascade, the first step in this process is the binding of selectin ligands located on cancer cells to selectins, a family of transmembrane glycoproteins, on the luminal endothelial surface. This leads to a rolling and slowing of the cancer cells on the endothelium. This process may be influenced by leukocytes and platelets that also exhibit selectins and selectin ligands [16]. The next step in anchoring of cells is the binding of integrins, a family of obligate heterodimer transmembrane receptors, and their respective ligands. Increased expression of specific integrin subtypes has been noted in lung cancer cell lines and the inhibition of specific integrins has led to prevention of brain metastases in animal models. For example, the $\alpha 3$ subunit has been shown to have increased expression in brain metastases NSCLC cell lines. Blockage of this integrin was associated with a decreased risk of brain metastases in a mouse model [17]. Integrin subtype expression correlates with pattern of growth in the brain parenchyma. Well demarcated growth, as opposed to diffusely infiltrating or vascular co-opting growth, is associated with increased expression of $\alpha v \beta 5$. In a contemporary autopsy study, squamous cell NSCLC appeared to predominantly grow in a well-demarcated fashion, while NSCLC adenocarcinoma appeared to grow equally in a well-demarcated pattern or a diffusely infiltrating one, similar to SCLC [18]. Different growth patterns may influence clinical management in the future. In addition to the direct effect of cell adhesion to the endothelial surface, binding of integrins to their ligands increases cytokine activity, including upregulation of VEGF, a key driver of angiogenesis, which will be discussed in greater detail below [19].

■ Extravasation from the vasculature & growth in the brain parenchyma

Upon anchoring to the endothelium, malignant cells need to cross from the luminal side of the vasculature to the parenchymal side. The process whereby malignant cells cross the blood–brain barrier (BBB) is not completely understood. It may have similarities to the normal process of

diapedesis, whereby immune cells cross the BBB. Factors that influence and regulate this process may differ between histologies. A complicated series of interactions between metastasis-inducing and metastasis-suppressing gene products is likely necessary for brain metastases to develop. Matrix metalloproteinases, heparinases and other enzymes degrade the extracellular matrix facilitating tumor cell invasion. A closely related step in the metastatic cascade is angiogenesis. In intra-arterial tumor cell injection mouse models, while tumors such as melanoma appear to grow by co-opting existing brain vasculature, NSCLC appears to grow its own vessels early on. This has been demonstrated with adenocarcinoma and large-cell carcinoma cell lines. The diffusely infiltrating pattern of tumor growth noted in some autopsy specimens was not seen. Single NSCLC cells have been shown to potentially remain dormant in a perivascular niche for weeks in mouse models before growing into macrometastases. This transition from micrometastatic to macrometastatic growth may be a potential target for future therapies, and in mouse models the process has been inhibited via a blockade of VEGF-A with bevacizumab [13]. When angiogenesis does occur in NSCLC mouse models, large vessels with dilated lumens (angioectasia) and transverse bridges create multiluminal structures, but a decreased mean vessel density within the tumor is noted. This is thought to be the result of nonsprouting angiogenesis leading to vascular remodeling [20]. This finding, however, has not been consistently reproduced [21]. In a comparison of human lung primary and brain metastases, when using coverage of endothelial cells by pericytes as a sign of vessel maturity, the brain metastases exhibit a significantly higher proportion of mature vessels when compared with their matched primary tumors. The vascular patterns also differ between the primaries (alveolar, basal and diffuse) and the brain metastases (diffuse and papillary). No correlation in VEGF expression between the primaries and their matched brain metastases was found [22]. Modulation of the patterns of angiogenesis may serve as additional therapeutic targets for impeding growth of brain metastases.

It has been demonstrated that NSCLC cells travel through the vasculature with fibroblasts that subsequently extravasate into the brain parenchyma with them. These tumor-associated fibroblasts detected in human brain metastases (including lung carcinoma) may play a key role in creating the appropriate microenvironment metastases growth [14]. In addition to aiding travel through the vasculature, these stromal cells may augment aspects of tumor growth, including angiogenesis, at the metastatic site. It is possible that the importance of stromal cells towards the development of brain metastases varies between tumor histologies. The mechanisms of binding between tumor cells and their stromal cotravelers may serve as potential targets for decreasing the risk of metastases, including those to the CNS.

In addition to fibroblasts, the main stromal cell of the CNS, astrocytes appear to be involved in establishing a niche for brain metastases. Recent evidence suggests that lung cancer cells and astrocytes stimulate each other through the expression of specific inflammatory cytokines, MIF, IL-8, PAI-1, IL-6, TNF-α and IL-1β [23]. Moreover, the astrocytes elevated gene (*AEG-1*) exerts its effect by activating the NF-κB pathway and is a downstream target of Ha-ras pathways, playing an important role in Ha-ras tumorigenesis. AEG-1 is thus a crucial regulator of tumor progression and metastasis [24]. Of note, data from CNS melanomas has also shown that reactive astrocytes can actually protect melanoma cells from chemotherapy by sequestering intracellular calcium through gap junction communication channels [25]. These findings suggest that metastatic brain tumors can utilize the neuroprotective effect of astrocytes for their own survival, and elucidating the mechanisms by which tumor cells interact with astrocytes represents an important area of research and one that may allow us to develop future therapeutic targets.

While in small brain metastases the BBB appears to be robust, as the metastases increase in size, greater permeability may be evident [20]. As understanding of the unique histology-specific structure of brain metastases vasculature, as well as the permeability of the BBB and blood–tumor barrier improves, our understanding of how best to employ systemic therapies to address CNS tumor will improve in tandem.

Molecular markers in lung cancer

NSCLC is a heterogenous group of disorders, originally subclassified histologically and initially subdivided into adenocarcinoma, squamous cell carcinoma and large cell carcinoma (with or without neuroendocrine differentiation). We now not only consider microscopic

classification, but, more importantly, molecular classification. Recently, adenocarcinomas have been shown to have a number of activating mutations, such as *EGFR* mutations, *EML4–ALK* translocation, *ROS1* translocation, *MET* amplification/expression and *KRAS* mutations, among others [26]. Squamous cell carcinoma can have other abnormalities, such as copy number gains and mutations of the catalytic subunit of PI3K and mutations of DDR2, among others. Based on molecular analysis, large cell carcinomas can be subclassified under adenocarcinomas or neuroendocrine tumors. Our understanding of the heterogenous group of diseases classified as lung cancer continues to progress. Important ongoing work on molecular characterization of subtypes of NSCLC has direct implications on patient management. As this has recently been reviewed elsewhere [26] we will limit ourselves to introducing the key molecular markers, focusing on those with existing targeted therapies, with the goal of creating a broad framework necessary for understanding the potential therapeutic implications in NSCLC brain metastases. Many of the currently targetable oncogenes are implicated in NSCLC adenocarcinomas found in young never or light smokers, a prognostically favorable group more likely to benefit from therapies for brain metastases.

EGFR, a member of the human epidermal receptor (HER) family, is perhaps the best studied molecular target in NSCLC. Specific mutations within the intracellular domain have been associated with favorable responses to EGFR-targeted therapies in patients with extra-CNS NSCLC [27,28]. These include exon 19 deletions and exon 12 L858R mutations. Lung cancer *EGFR* mutations do not have EGFRvIII alteration, as found in glioblastomas. Unfortunately, while patients with these mutations initially respond, most subsequently develop additional mutations, such as the T790M point mutation, which confer resistance to EGFR-specific tyrosine kinase inhibitors (TKIs). Efforts are being made to circumvent this resistance with pan-HER inhibitors. More recently, it has been demonstrated in a single institution cohort study that patients with NSCLC with *EGFR* mutations and brain metastases have improved survival from the time of their brain metastases diagnosis compared with those without mutations. These patients when they develop metachronous brain metastases do so later than non-*EGFR*-mutated patients. *EGFR*-mutated patients demonstrated better responses to whole-brain radiation therapy (WBRT) than non-mutated patients. More optimal control of both intra-CNS and extra-CNS disease is thought to contribute to improved OS in *EGFR*-mutated patients [29].

VEGF, as stated earlier, is a key driver of angiogenesis, an important step in the development of brain metastases. In addition to its effects on neovascularization, it plays a role in altering the function of existing vasculature, which can lead to edema in the surrounding tissues. The development of cerebral edema can have distinct neurologic consequences depending on the neuroanatomic location where it occurs.

There has been significant recent interest in the subset of NSCLC with *ALK* translocations due to the oncogene addiction of these tumors, which is associated with marked clinical and radiographic systemic responses in patients treated with TKIs targeting ALK. Crizotinib recently received full US FDA approval for this subset of patients [30]. Limited information exists regarding CNS concentrations of crizotinib.

Additional important receptor tyrosine kinases currently being evaluated in the clinical setting for NSCLC include: HGFR, ROS1 and KRAS. HGFR is encoded by the proto-oncogene *MET*. Activation of HGFR leads to downstream activation of PI3K, RAS and STAT-3. KRAS, which activates the Raf–MEK–ERK pathway, is mostly activated in NSCLC adenocarcinomas and is associated with a potentially poorer prognosis. *ROS1*, a gene encoding a tyrosine kinase is a member of the insulin receptor family. ROS1 is activated via translocation in some lung cancers.

There are other abnormalities in lung cancer, and as we begin to understand the genomics, proteomics and microenvironment, we will have a better understanding of the molecular mechanisms of brain metastases.

Surgery

The role of surgical resection in single brain metastases has been well described and predominantly based on the results of three randomized clinical trials investigating its role in combination with WBRT [31–33]. The representative number of patients in these studies with NSCLC ranged from 52 to 77%, with the highest percentage in the earliest of the trials. In turn, results from these trials should be viewed as generalizable to patients with NSCLC. In all three trials an attempt was made at a complete surgical resection of the metastasis. This approach is

supported by the understanding that the majority of brain metastases, including many NSCLC, demonstrate a minimal amount of invasion into the surrounding brain parenchyma. In the first two trials surgical resection was associated with improved OS (40 vs 15 weeks; $p < 0.01$; 10 vs 6 months; $p < 0.04$, respectively) as well as improvement in other end points, including duration of functional independence [31,32]. These findings were not replicated in the third trial (OS: 5.6 vs 6.3 months; $p = 0.24$) [33]. In all three studies surgical intervention was followed by WBRT administered at various dosing schedules (30–40 Gy). When evaluated in separate randomized trials, postoperative WBRT (50.4 Gy in the earlier study, 30 Gy in the more contemporary) after resection of a single brain metastasis was associated with decreased recurrence at the resection site, decreased recurrence elsewhere in the brain and decreased risk of neurologic death, but no significant change in OS [34,35]. Lower doses and focal approaches to radiation therapy (RT) are more frequently used currently to limit the potential toxicities from WBRT. With the lack of improvement in OS, observation without RT is an alternate management plan that, although not common practice, is sometimes considered. Focal approaches to postoperative radiation appear to provide good local control, and unsurprisingly do not address intracranial failure further from the resection cavity [36,37]. Comparable outcomes have been noted in patients with a single brain metastasis treated with resection followed by WBRT versuss stereotactic radiosurgery (SRS) alone [38]. In patients without significant mass effect, with single smaller lesions amenable to SRS or those who are poor surgical candidates this less invasive approach is reasonable to consider.

To the best of our knowledge, only one prospective trial specifically evaluating the role of surgical resection in solitary brain metastases from NSCLC has currently been published. A Phase II trial conducted from 1992 to 1999, enrolling 23 patients with newly diagnosed NSCLC and a synchronous solitary metastasis, including single brain metastasis, investigated the role of neoadjuvant and adjuvant chemotherapy in conjunction with surgery. Fourteen of the 23 patients (60%) had a brain metastasis. Patients received three cycles of mitomycin, vinblastine and cisplatin followed by surgical resection of all disease sites including the brain. This was followed by two cycles of vinblastine and cisplatin. The long accrual interval likely reflects the rarity of synchronous solitary metastases patients. Mitomycin, vinblastine and cisplatin proved to be a poorly tolerated induction chemotherapy regimen and median OS (11 months) did not appear superior to historical data employing surgery without neoadjuvant chemotherapy [39].

Retrospective studies lend further support to the role of surgical resection for NSCLC single brain metastases. The largest of these is a multicenter study conducted in France collecting data on 103 patients from 1985–1998, many of who likely did not undergo MRI to screen for additional brain metastases that, if detected, would have been associated with a poorer prognosis. The vast majority (91%) underwent craniotomies prior to thoracic surgeries with an interval of less than 1 month between procedures in approximately a third of patients. Most patients who went on to receive chemotherapy did so after their two surgeries. Median OS was 12.4 months. The 1-year survival rate was 56%, 2 years was 28% and 5 years was 11% [40]. Similar results in this large NSCLC cohort and in the prospective trials evaluating various histology favorably argue for surgical resection of single brain metastases from NSCLC as a reasonable management option.

Radiation

Radiation therapy has a role both in conjunction with other interventions, such as surgery, as well as an independent treatment for brain metastases. WBRT has long served as a key treatment modality for brain metastases [41]. It is often administered to a dose of 30 Gy in 3 Gy fractions. SRS, a distinct method of delivering single large fractions of ionizing radiation via the expertise of a multidisciplinary team, including neurosurgeons, radiation oncologists and radiation physicists, has been an important advance in the management of brain metastases, particularly when a limited number of lesions are present. Tumor control, OS and cognitive side effects from radiation are all being actively studied with respect to more clearly defining the role for SRS in patients with brain metastases [42]. Results from numerous studies suggest that WBRT is associated with an increased risk of neurocognitive symptoms when compared with more focal treatments of brain metastases [43]. It has been specifically shown in NSCLC patients with brain metastases that the risk of developing

leukoencephalopathy is significantly greater when WBRT is used in combination with SRS as opposed to SRS alone [44]. These concerns have lead to a trend of limiting radiation treatment to more focal approaches when possible, most often with the use of SRS without the inclusion of WBRT. The maximum number of lesions that can be safely treated with SRS has not yet been clearly defined. While randomized studies have treated up to four metastases, reports of the safe treatment of much larger numbers exist [45,46]. It may be that aggregate tumor volume, as opposed to number of brain metastases, may be the more appropriate determinant of feasibility regarding the use of SRS [9]. While the majority of trials evaluating the role of fractionated radiation include numerous histologies and those of SRS include either numerous histologies or are specific for radioresistant histologies, we will direct our focus on those studies that are specific to NSCLC. We will first discuss the therapeutic trials **(Table 1)** and then the prophylactic cranial irradiation (PCI) trials **(Table 2)**.

While there is a growing trend towards the use of focal radiation, the preponderance of NSCLC-specific brain metastases prospective radiation trials have employed WBRT, often in combination with various chemotherapy regimens [47–60]. A few studies have investigated other radiation modalities including the addition of SRS to WBRT [48,61], the use of brachytherapy [62] or the use of motexafin gadolinium as a radiation sensitizer [63]. Varying inclusion/exclusion criteria, study designs and methodology make direct comparison between trials very difficult. One of the overriding themes in these trials is the choice of chemotherapy regimens. In five studies a small molecule TKI of EGFR, either erlotinib or gefitinib, were used [48–50,55,56]. In three the alkylating agent, temozolomide was used [48,50,52]. Interestingly, in all of the studies in which patients were randomized to WBRT versus WBRT plus chemotherapy, there was a trend towards inferior outcomes with the addition of chemotherapy [52–54,58]. Some of the most favorable OS outcomes were in trials enrolling patients with a limited number of brain metastases, a favorable prognostic factor [48,61,62].

While PCI has a well-established role in SCLC, there is limited evidence to support its use in NSCLC and, in turn, it is currently not the standard of care. Early studies of PCI in lung cancer patients combined numerous histologies. A significant decrease in the development of brain metastases in 'non-small-cell' patients was noted. The non-small-cell category did not, however, include adenocarcinoma, squamous cell carcinoma or large cell carcinoma likely representing a difficult-to-classify category [64]. Early nonrandomized studies that included PCI in stage III NSCLC used doses of 30–36 Gy. These studies noted decreased incidences of brain metastases [65–67]. While an overall improvement in median OS was not reported, improvement was noted in patients with favorable prognostic factors, such as complete or partial responses to upfront therapy. No obvious performance differences were found on a battery of neurocognitive tests, however, evolution of neurocognitive symptoms could not be assessed as pretreatment neurocognitive evaluation was not performed [67].

More recent randomized trials looking specifically at patients with NSCLC have also demonstrated decreased incidence of radiographically evident brain metastases in patients receiving PCI. In these studies the same PCI dosing schedule of 30 Gy in 15 fractions was used. These studies more definitively demonstrated a decrease in the overall incidence of brain metastases, incidence of brain metastases at 1 year, and incidence of the brain as the first site of failure in patients who received PCI. However, no improvement in OS was shown with the addition of PCI [68,69]. In the study by Pottgen *et al.* a limited number (n = 11 out of 112) of long-term survivors underwent neuropsychological testing that revealed no marked differences between those who had undergone PCI and those who did not [68]. The more recent Phase III trial by Gore, *et al.* included neurocognitive and quality of life evaluations at baseline as well as numerous prespecified intervals. At 1 year the PCI group had a significant decrease in performance measures of encoding, retrieval and retention of new information. No significant difference was noted on quality-of-life measures [70]. From the data available, it is reasonable to assume that PCI can cause neurocognitive impairments that would likely be of greatest consequence in the long-term survivors.

In all of the above studies, the PCI patients randomized to observation probably received WBRT in most cases if they subsequently developed brain metastases, creating a significant crossover effect that may have played a role in the outcomes. Specific concerns regarding PCI are the potential neurologic toxicity, which

Table 1. Clinical trials using radiation therapy specifically for non-small-cell lung cancer brain metastases.

Study (year)	Phase	Patients (n)	RT modality	Additional therapies	BM (n)	OS (months)	Ref.
Dinglin *et al.* (2013)	II	42	WBRT	Pemetrexed + cisplatin	NA	12.6 WBRT	[47]
Langley *et al.* (2013)	III	151	WBRT	OSC	NA	49 days WBRT vs 51 days OSC	[96]
Sperduto *et al.* (2013)	III	126	WBRT + SRS	TMZ vs erlotinib	1–3	13.4 WBRT + SRS vs 6.3 WBRT + SRS + TMZ vs 6.1 WBRT + SRS + erlotinib	[48]
Welsh *et al.* (2013)	II	40	WBRT	Erlotinib	NA	11.8 WBRT	[49]
Pesce *et al.* (2012)	II	59	WBRT	Gefitinib or TMZ	NA	4.9 WBRT	[50]
Galetta *et al.* (2011)	II	29	WBRT	Cisplatin + fotemustine	NA	4.7† WBRT	[51]
Minnitti *et al.* (2010)	–	66	WBRT + SRS	NA	2–3	10.3 WBRT + SRS vs 7.2 WBRT	[61]
Chua *et al.* (2010)	II	95	WBRT	TMZ	NA	4.4 WBRT + TMZ vs 5.7 WBRT	[52]
Quantin *et al.* (2010)	II	70	WBRT	Cisplatin + vinorelbine + ifosfamide vs HD ifosfamide	NA	8.5 WBRT + cisplatin + vinorelbine + ifosfomide vs 5.7 WBRT + HD ifosphamide	[53]
Mehta *et al.* (2009)	III	554	WBRT	Motexafin gadolinium	NA	NA	[63]
Neuhaus *et al.* (2009)	III	70	WBRT	Topotecan	NA	NA	[54]
Lind *et al.* (2009)	I	11	WBRT	Erlotinib	NA	133 days WBRT	[55]
Ma *et al.* (2009)	II	21	WBRT	Gefitinib	NA	13.0 WBRT	[56]
Huang *et al.* (2007)	I	16	WBRT	Gemcitabine	NA	NA	[57]
Guerrieri *et al.* (2004)	III	42	WBRT	Carboplatin	NA	4.4 WBRT vs 3.7 WBRT + carboplatin	[58]
Robinet *et al.* (2001)	III	176	WBRT (early vs delayed)	Cisplatin + vinorelbine	NA	24 weeks cisplatin + vinorelbine + delayed WBRT vs 21 weeks cisplatin + vinorelbine + early WBRT	[59]
Bogart *et al.* (1999)	–	15	I^{125} brachytherapy	Surgery	1	14 I^{125} brachytherapy	[62]
Pronzato *et al.* (1995)	–	20	WBRT	Carboplatin + teniposide	NA	7 WBRT	[60]
Chatani *et al.* (1994)	–	162	WBRT	NA	NA	5.4 WBRT (30 Gy) in subjects with normal LDH vs 4.8 WBRT (50 Gy) in subjects with normal LDH vs 3.4 WBRT (30 Gy) in subjects with high LDH vs 2.4 WBRT (20 Gy) in subjects with high LDH	[97]

†Estimated.
BM: Brain metastases; HD: High dose; LDH: Lactate dehydrogenase; NA: Not applicable; OS: Overall survival; OSC: Optimal supportive care; RT: Radiation therapy; SRS: Stereotactic radiosurgery; TMZ: Temozolomide; WBRT: Whole-brain radiation therapy.

it would be preferable to delay, as well as the concern regarding limited treatment options for patients who develop multiple brain metastases after PCI.

Systemic therapies

While there is a lack of strong support for the use of chemotherapy in combination with radiation therapy in newly diagnosed NSCLC brain metastases, the role for chemotherapy for progressive brain metastases after WBRT needs to be more clearly defined. The role of targeted therapies holds significant potential. While we are unable to cover all systemic therapies that have been evaluated in NSCLC brain metastases, we will discuss some central themes. A number of clinical trials have been performed evaluating systemic therapies alone, without RT or surgery, in this specific patient population (Table 3).

Some of the earliest NSCLC-specific brain metastases prospective trials employed platinum-based regimens [71–74]. These were administered as doublets or triplets with a variety of agents including the mitotic inhibitors paclitaxel and vinorelbine; the topoisomerase inhibitor teniposide; the nucleoside analog gemcitabine; and the nitrosourea fotemustine. Overall response rates (RRs) were rarely reported. Cerebral RRs ranged from 20–45%. Median OS was measured in weeks (16–33 weeks).

The next generation of NSCLC-specific brain metastases trials focused either on the use of small molecule TKIs [75–79] or the alkylating agent temozolomide [80,81] that is used in the treatment of primary brain tumors. These

agents have also been studied in conjunction for NSCLC brain metastases, but only in retrospective studies [82]. The small molecule TKI studies predominantly employed EGFR-specific agents such as gefitinib and erlotinib [75–78]. Currently available EGFR-specific TKIs reach the CNS in varying concentrations. While data is limited regarding brain intraparenchymal concentrations, CSF concentrations of erlotinib and OSI-420, its active metabolite, range between 1–7% and 3–9% of serum concentrations [83–85]. CSF concentrations of gefitinib are approximately 1% of serum concentrations [85,86]. There is concern that the CSF and brain parenchymal concentrations may be inadequate. It has been suggested that weekly pulsatile dosing of erlotinib (1000–1500 mg/week) may be able to achieve adequate levels to treat CNS involvement of EGFR-mutated NSCLC [87]. Different end points were used in the various prospective trials making comparisons difficult. Some patients that were treated experienced cerebral responses when treated with EGFR-specific TKIs and median OS (5–19.9 months) appeared promising in this patient population, most of whom had progressive CNS disease.

Two single-arm Phase II studies evaluated single-agent temozolomide in patients with NSCLC brain metastases [80,81]. The first of these studies included patients with (n = 12) and without (n = 13) brain metastases. Patients with brain metastases were WBRT naive and asymptomatic or had completed WBRT at least 4 weeks prior to study entry. A regimen of temozolomide 200 mg/m^2 for 5 out of 28 days was used. The patients with brain metastases received a median number of one cycle (range one to six) with most patients discontinuing due to progressive disease. No objective responses were observed [80]. In the second study patients with NSCLC brain metastases previously treated with WBRT and at least one prior line of chemotherapy for brain metastases received temozolomide (150–200 mg/m^2 for 5 out of 28 days). A 10% cerebral RR was noted with complete response in two patients (6.7%). Another 10% of patients demonstrated stable disease in the brain. Median OS was 6 months in this heavily pretreated group [81]. Prolonged responses in a subset of patients hold promise for the use of temozolomide as a salvage chemotherapy. A number of trials, mentioned earlier, used temozolomide in conjunction with WBRT in patients with NSCLC brain metastases [48,50,52]. Other

Table 2. Clinical trials of prophylactic cranial irradiation for non-small-cell lung cancer.

Study (year)	Phase	Patients (n)	Stage	WBRT dose	OS (months)	1-year OS (%)	5-year OS (%)	Time to developing brain mets (weeks)	Probability of brain as first site of failure (%)	Actuarial incidence of brain mets (%)	Ref.
Gore *et al.* (2011)	III	356	IIIA/IIIB	30 Gy/15 fractions	NA	75.6 PCI vs 76.9 Obs	NA	NA	NA	NA	[69]
Pottgen *et al.* (2007)	NA	112	IIIA	30 Gy/15 fractions	NA	NA	18 Obs vs PCI 16	NA	7.8 Obs vs 34.7 PCI at 5 years	23.7 Obs vs 8.8 PCI (2 years) 30.7 Obs vs 15.8 PCI (5 years)	[68]
Stuschke *et al.* (1999)	II†	75	IIIA (N2)/IIIB	30 Gy/15 fractions	NA	NA	NA	NA	30 Obs vs 8 PCI at 4 years	48 Obs vs 8 PCI (2 years) 54 Obs vs 13 PCI (4 years)	[67]
Albain *et al.* (1995)	II†	126	IIIA (N2)/IIIB	36 Gy/18 fractions	NA	NA	NA	NA	NA	NA	[66]
Strauss *et al.* (1992)	II†	41	IIIA	30 Gy/15 fractions	NA	NA	NA	NA	NA	NA	[65]
Russell *et al.* (1991)	NA	187	Inoperable T1–4, N1–3, M0 or resected T1–3, N1–2, M0	30 Gy/10 fractions	8 PCI 8 Obs	40 44	NA	NA	NA	19 Obs vs 9 PCI (interval not specified)	[98]
Umsawasdi *et al.* (1984)	NA	100	Locally advanced	30 Gy/10 fractions	NA	NA	NA	NA	NA	4 PCI vs 27 Obs (median follow-up 59 and 55 weeks, respectively)	[99]
Cox *et al.* (1981)	NA	NA	Patients without distant dissemination	20 Gy/10 fractions	NA	NA	NA	29 Obs vs 34 PCI	NA	NA	[64]

†Nonrandomized.
Mets: Metastases; NA: Not available; Obs: Observation; OS: Overall survival; PCI: Prophylactic cranial irradiation; WBRT: Whole-brain radiation therapy.

Table 3. Clinical trials of systemic therapies without radiation therapy for patients with brain metastases from non-small-cell lung cancer.

Study (year)	Phase	Patients (n)	Timing	Agents	Median OS	1-year survival (%)	Intracranial TTP	Overall PFS	Cerebral RR (%)	Overall RR (%)	Ref.
Wu *et al.* (2013)	II	48	Progressive BM	Erlotinib	18.9 months	73	10.1 months	9.7 months	NA	58.3	[78]
Novello *et al.* (2011)	II	64	Progressive BM	Sunitinib	25.1 weeks	NA	15.4 weeks	9.4 weeks	4.3	1.6	[79]
Barlesi *et al.* (2011)	II	43	Initial diagnosis of BM	Pemetrexed + cisplatin	7.4 months	NA	5.7 months	4.0 months	41.9	34.9	[100]
Socinski *et al.* (2009)	II	115	Previously treated nonprogressive BM	Bevacizumab	NA	NA	NA	NA	NA	NA	[93]
Lee *et al.* (2008)	Randomized pilot	48	Initial diagnosis of synchronous BM	Gemcitabine + vinorelbine vs WBRT	9.1 vs 9.9 months	NA	NA	3.6 vs 4.4 months	NA	28.0 vs 39.1	[101]
Wu *et al.* (2007)	II	40	Patients with BM who had received prior chemotherapy	Gefitinib	15.0 months	NA	NA	9.0 months	38	32	[77]
Giorgio *et al.* (2005)	II	30	Progressive BM	Temozolomide	6 months	10	NA	3.6 months	10	NA	[81]
Chiu *et al.* (2005)	–	11[†]	NA	Gefitinib	NA	NA	NA	NA	NA	NA	[76]
Ceresoli *et al.* (2004)	–	41	Newly diagnosed and progressive BM	Gefitinib	5 months	NA	NA	3 months	NA	10	[75]
Dziadziuszko *et al.* (2003)	II	12[‡]	BM with or without RT	Temozolomide	NA	NA	NA	NA	NA	0	[80]
Bernardo *et al.* (2002)	II	22	Newly diagnosed BM	Vinorelbine + gemcitabine + carboplatin	33 weeks	NA	NA	NA	45	NA	[74]
Boogerd *et al.* (1999)	–	13	Newly diagnosed and progressive BM	Teniposide	NA	NA	NA	NA	23	NA	[102]
Minotti *et al.* (1998)	–	23	Newly diagnosed BM	Cisplatin + teniposide	21 weeks	NA	NA	NA	35	NA	[73]
Lee *et al.* (1997)	–	5[§]	Newly diagnosed BM	Paclitaxel + carboplatin	–	–	–	–	20	20	[72]
Cotto *et al.* (1996)	II	31	NA	Fotemustine + cisplatin	16 weeks	NA	NA	NA	NA	NA	[71]

[†]21 patients had BM out of 76 total patients, 11 out of the 21 BM patients had chemotherapy without RT.
[‡]12 out of 25 patients had BM.
[§]Five patients enrolled at time of publication of preliminary results.
BM: Brain metastases; NA: Not available; OS: Overall survival; PFS: Progression-free survival; RR: Response rate; RT: Radiation therapy; TTP: Time to progression; WBRT: Whole-brain radiation therapy.

studies exploring similar regimens have also been performed in other tumor histologies. The largest of the trials specifically for NSCLC brain metastases patients, randomly assigned patients with one to three brain metastases to WBRT plus SRS versus WBRT plus SRS plus temozolomide versus WBRT plus SRS plus erlotinib. OS was better in the RT only arm (13.4 months) compared with the temozolomide-containing (6.3 months) and erlotinib-containing (6.1 months) arms. Grade 3–5 toxicities were much higher in the chemotherapy arms (41–49%) compared with the RT-only (11%) arm [48]. While RT and concomitant temozolomide are tolerable and effective in glioblastoma, this does not appear to hold true for patients with NSCLC brain metastases.

Crizotinib is another targeted therapy that has demonstrated significant success in the treatment of a subset of NSCLC patients with extra-CNS disease. Knowledge of its concentration and potential efficacy within the CNS is limited. While measurement of CSF concentration of crizotinib demonstrates a very low concentration and plasma:CSF ratio [88] there are scattered anecdotes of its effect in the CNS [89,90]. This has not been noted, however, in all patients [91]. In mouse models inhibition of P-glycoprotein with elacridar led to significantly higher brain concentrations of orally administered crizotinib [92]. Understanding of the factors which influence the variability of responses in the CNS between patients treated with crizotinib may improve the benefit of this promising therapy.

Bevacizumab, an anti-VEGF antibody used in the treatment of glioblastoma, has been studied in NSCLC patients, including those with brain metastases. Only one trial specifically addressed NSCLC brain metastases patients. The open-label single-arm Phase II PASSPORT trial evaluated the safety of bevacizumab in nonsquamous NSCLC. Concern exists regarding the risk of intracranial hemorrhage with the use of antiangiogenic therapies in patients with CNS tumors. RR, progression-free survival and OS were not reported. Median reported on-study duration was 6.3 months with a median of five cycles of bevacizumab. While a quarter of patients discontinued study treatment due to adverse events no grade ≥2 CNS hemorrhages were reported [93]. Bevacizumab may be safer than initially presumed in nonsquamous NSCLC. Additional studies evaluating efficacy would better define the role for this agent in this patient population.

Finally, studies of surgery followed by local chemotherapy, in the form of Gliadel® (carmustine [BCNU]; Arbor Pharmaceuticals; GA, USA) wafers, have been presented at various meetings. In 2007, Ewend *et al.* reported on the use of BCNU polymer wafer for treatment of solitary brain metastasis in conjunction with radiation therapy [94]. In this report, 25 patients with solitary brain metastasis from various primary malignancies (over half with lung cancer) underwent craniotomy for tumor resection and placement of BCNU polymer wafers followed by WBRT. This was a three-institutional feasibility study, and there was no comparison group. The median survival was 33 weeks with 33% of patients surviving past 1 year, and 25% of patients surviving past 2 years. There was no local recurrence observed at a median follow-up period of over 36 weeks, but four patients did develop recurrence elsewhere in the brain. Since then, over 100 patients who underwent surgical resection with placement of BCNU have been reported in abstracts and meetings. This therapy appears to be safe with only two local recurrences reported to date [95]. However, this form of therapy still awaits a systematic comparison and is reserved for solitary and chemoradiotherapy refractory cases.

Conclusion

NSCLC brain metastases are a significant problem affecting a large group of cancer patients. Over time, our prognostication in this patient population has become more nuanced. This may become more refined, along the lines of breast brain metastases, as work progresses on the molecular subclassification of NSCLC, particularly in relation to treatable molecularly defined targets. Currently, NSCLC brain metastases are managed in a similar fashion to other solid tumor brain metastases. However, as molecular abnormalities become available, we will be able to better tailor therapies. Many of the large trials are applicable to NSCLC as a substantial proportion of NSCLC brain metastases patients composed the study populations. This applies to both the therapeutic surgical and radiation trials. There has been a trend towards the increased use of focal therapies, such as SRS, in an effort to limit the toxicities from WBRT. When focusing exclusively on NSCLC brain metastases, almost all of the prospective radiation trials included another modality, most often a systemic therapy. No definitive recommendations can be made on these mostly noncomparative studies. They do,

however, attest to the interest in and need for improvements in our current therapeutic options in this patient population. Trials evaluating the role of systemic therapies alone in NSCLC patients with brain metastases raise interest in targeted therapies after progression after surgery and/or radiation.

Future perspective

Over the next 5 to 10 years it is likely that our understanding of the processes broadly involved in tumors metastasizing to the CNS will be better understood. In tandem, evaluations of the pharmacokinetics and pharmacodynamics in the CNS of new therapeutic agents will hopefully occur earlier in their development. We will simultaneously see a growing understanding in the optimal employment in the focal administration of ionizing radiation via SRS. This will allow investigators to optimize the efficacy within the CNS for new therapies that prove to be efficacious outside the CNS. Inhibitors of ALK may prove to be such an example in a limited subset of NSCLC patients. The future will incorporate molecular markers, genomics, proteomics and tumor microenvironment to arrive at better therapeutics for brain metastases (true arrival of precision medicine).

Financial & competing interests disclosure

RV Lukas has served on an advisory board for Novocure. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- of interest

1 Posner JB, Chernik NL. Intracranial metastases from systemic cancer. *Adv. Neurol.* 19, 579–592 (1978).

2 Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J. Clin. Oncol.* 22(14), 2865–2872 (2004).

3 Nieder C, Spanne O, Mehta MP, Grosu AL, Geinitz H. Presentation, patterns of care, and survival in patients with brain metastases: what has changed in the last 20 years? *Cancer* 117(11), 2505–2512 (2011).

4 Schouten SJ, Rutten J, Huveneers HAM, Twinjstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer* 94(10), 2698–2705 (2002).

5 Delattre JY, Krol G, Thaler HT, Posner JB. Distribution of brain metastases. *Arch. Neurol.* 45, 741–744 (1988).

6 Yawn BP, Wollan PC, Schroeder C, Gazzuola L, Mehta M. Temporal and gender-related trends in brain metastases from breast and lung cancer. *Minn. Med.* 86(12), 32–37 (2003).

7 Bajard A, Westeel V, Dubiez A *et al.* Multivariate analysis of factors predictive of brain metastases in localized non-small cell lung cancer. *Lung Cancer* 45(3), 317–323 (2004).

8 Sperduto PW, Kased N, Roberge D *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.* 30(4), 419–425 (2012).

9 Kondziolka D. Editorial: multiple metastases. *J. Neurosurg.* 118(6), 1248 (2013).

10 Quattrocchi CC, Erante Y, Gaudino C *et al.* Spatial brain distribution of intra-axial metastatic lesions in breast and lung cancer patients. *J. Neurooncol.* 110(1), 79–87 (2012).

11 Sarvaiya PJ, Guo D, Ulasov I, Gabikian P, Lesniak MS. Chemokines in tumor progression and metastases. *Oncotarget* 4, 2171–2185 (2013).

12 Paget S. The distribution of secondary growths in cancer of the breast. *Lancet* 133(3421), 571–573 (1889).

13 Kienast Y, von Baumgarten L, Fuhrmann M *et al.* Real-time imaging reveals the single steps of brain metastasis formation. *Nat. Med.* 16(1), 116–122 (2010).

- **Report on microscopic imaging of metastatic tumor formation in a mouse model.**

14 Duda DG, Duyverman AM, Kohno M *et al.* Malignant cells facilitate lung metastasis by bringing their own soil. *Proc. Natl Acad. Sci. USA* 107(50), 21677–21682 (2010).

15 Sundstrom T, Daphu I, Wendelbo I *et al.* Automated tracking of nanoparticle-labeled melanoma cells improves the predictive power of a brain metastasis model. *Cancer Res.* 73(8), 2445–2456 (2013).

16 Preusser M, Capper D, Ilhan-Mutlu A *et al.* Brain metastases: pathobiology and emerging targeted therapies. *Acta Neuropathol.* 123(2), 205–222 (2012).

17 Yoshimasu T, Sakurai T, Oura S *et al.* Increased expression of integrin alpha3beta1 in highly brain metastatic subclone of a human non-small cell lung cancer cell line. *Cancer Sci.* 95(2), 142–148 (2004).

18 Berghoff AS, Rajky O, Winkler F *et al.* Invasion patterns in brain metastases of solid cancers. *Neuro Oncol.* 15(12), 1664–1672 (2013).

- **Recent autopsy study describing the patterns of brain involvement of brain metastases from various primary solid tumors.**

19 Lorger M, Krueger JS, O'Neal M, Staflin K, Felding-Habermann B. Activation of tumor cell integrin alphavbeta3 controls angiogenesis and metastatic growth in the brain. *Proc. Natl Acad. Sci. USA* 106(26), 10666–10671 (2009).

20 Fidler IJ, Yano S, Zhang RD, Fujimaki T, Bucana CD. The seed and soil hypothesis: vascularization and brain metastases. *Lancet Oncol.* 3(1), 53–57 (2002).

- **Thorough review on the role of vascularization in relation to the 'seed and soil' hypothesis of metastases, including brain metastases.**

21 Carbonell WS, Ansorge O, Sibson N, Muschel R. The vascular basement membrane as 'soil' in brain metastases. *PLoS One* 4(6), e5857 (2009).

22 Jubb AM, Cesario A, Ferguson M *et al.* Vascular phenotypes in primary non-small cell lung carcinomas and matched brain metastases. *Br. J. Cancer* 104(12), 1877–1881 (2011).

23 Seike T, Fujita K, Yamakawa Y *et al.* Interaction between lung cancer cells and astrocytes via specific inflammatory cytokines in the microenvironment of brain metastasis. *Clin. Exp. Metastasis* 28(1), 13–25 (2011).

24 Emdad L, Sarkar D, Su ZZ *et al.* Astrocyte elevated gene-1: recent insights into a novel gene involved in tumor progression, metastasis, and neurodegeneration. *Pharmacol. Ther.* 114(2), 155–170 (2007).

25 Lin Q, Balasubramanian K, Fan D *et al.* Reactive astrocytes protect melanoma cells from chemotherapy by sequestering intracellular calcium through gap junction communication channels. *Neoplasia* 12(9), 748–754 (2010).

26 Villaflor VM, Salgia R. Targeted agents in non-small cell lung cancer therapy: what is there on the horizon? *J. Carcinog.* 12, 7 (2013).

- **Recent review of molecular markers in non-small-cell lung cancer.**

27 Paez JG, Janne PA, Lee JC *et al. EGFR* mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 304(5676), 1497–1500 (2004).

28 Lynch TJ, Bell DW, Sordella R *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med.* 350 (21), 2129–2139 (2004).

29 Eichler AF, Kahle KT, Wang DL *et al. EGFR* mutation status and survival after diagnosis of brain metastases in nonsmall cell lung cancer. *Neuro Oncol.* 12(11), 1193–1199 (2010).

30 Camidge DR, Bang YJ, Kwak EL *et al.* Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a Phase 1 study. *Lancet Oncol.* 13(10), 1011–1019 (2012).

31 Patchell RA, Tibbs PA, Walsh JW *et al.* A randomized trial of surgery in the treatment of single metastases to the brain. *N. Engl. J. Med.* 322(8), 494–500 (1990).

- **Pivotal trial of surgical resection for single brain metastases.**

32 Vecht CJ, Haaxma-Reiche H, Noordijk EM *et al.* Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann. Neurol.* 33(6), 583–590 (1993).

33 Mintz AH, Kestle J, Rathbone MP *et al.* A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 78(7), 1470–1476 (1996).

34 Patchell RA, Tibbs PA, Regine WF *et al.* Postoperative radiotherapy in the treatment of single metastases to the brain: a randomised trial. *JAMA* 280(17), 1485–1489 (1998).

35 Kocher M, Soffietti R, Abacioglu U *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.* 29(2), 134–141 (2011).

36 Luther N, Kondziolka D, Kano H *et al.* Predicting tumor control after resection bed radiosurgery of brain metastases. *Neurosurgery* 73(6), 1001–1006 (2013).

37 Roberge D, Parney I, Brown PD. Radiosurgery to the postoperative surgical cavity: who needs evidence? *Int. J. Radiat. Oncol. Biol. Phys.* 83(2), 486–493 (2012).

38 Muacevic A, Wowra B, Siefert A, Tonn JC, Steiger HJ, Kreth FW. Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre Phase III trial. *J. Neurooncol.* 87(3), 299–307 (2008).

39 Downey RJ, Ng KK, Kris MG *et al.* A Phase II trial of chemotherapy and surgery for non-small cell lung cancer patients with a synchronous solitary metastasis. *Lung Cancer* 38(2), 193–197 (2002).

40 Bonnette P, Puyo P, Gabriel C *et al.* Surgical management of non-small cell lung cancer with synchronous brain metastases. *Chest* 119(5), 1469–1475 (2001).

41 Borgelt B, Gelber R, Kramer S *et al.* The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int. J. Radiat. Oncol. Biol. Phys.* 6(1), 1–9 (1980).

42 Kirkpatrick JP, Yin FF, Sampson JH. Radiotherapy and radiosurgery for tumors of the central nervous system. *Surg. Oncol. Clin. N. Am.* 22(3), 445–4612 (2013).

- **Recent review of the role of radiation therapy for CNS tumors. This review addresses many of the controversies that exist.**

43 McDuff SGR, Taich ZJ, Lawson JD *et al.* Neurocognitive assessment following whole brain radiation therapy and radiosurgery for patients with cerebral metastases.*J. Neurol. Neurosurg. Psychiatry* 84(12), 1384–1391 (2013).

44 Monaco EA, Faraji AH, Berkowitz O *et al.* Leukoencephalopathy after whole-brain radiation therapy plus radiosurgery versus radiosurgery alone for metastatic lung cancer. *Cancer* 119(1), 226–232 (2013).

45 Hunter GK, Suh JH, Reuther AM *et al.* Treatment of five or more brain metastases with stereotactic radiosurgery. *Int. J. Radiat. Oncol. Biol. Phys.* 83(5), 1394–1398 (2011).

46 Jairam V, Chiang VL, Yu JB, Knisely JP. Role of stereotactic radiosurgery in patients with more than four brain metastases. *CNS Oncol.* 2(2), 181–193 (2013).

47 Dinglin XX, Huang Y, Liu H, Zeng YD, Hou X, Chen LK. Pemetrexed and cisplatin combination with concurrent whole brain radiotherapy in patients with brain metastases of lung adenocarcinoma: a single-arm Phase II clinical trial. *J. Neurooncol.* 112(13), 461–466 (2013).

48 Sperduto PW, Wang M, Robins HI *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.* 85(5), 1312–1318 (2013).

49 Welsh JW, Komaki R, Amini A *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.* 31(7), 895–902 (2013).

50 Pesce GA, Klingbiel D, Ribi K *et al.* Outcome, quality of life and cognitive function of patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy treated with gefitinib or temozolomide. A randomised Phase II trial of the Swiss Group for Clinical Cancer Research (SAKK 70/03). *Eur. J. Cancer* 48(3), 377–384 (2012).

51 Galetta D, Gebia V, Silvestris N *et al.* Cisplatin, fotemustine and whole-brain radiotherapy in non-small cell lung cancer patients with asymptomatic brain metastases: a multicenter Phase II study of the Gruppo Oncologico Italia Meridionale (GOIM 2603). *Lung Cancer* 72(1), 59–63 (2011).

52 Chua D, Krzakowski M, Chouaid C *et al.* Whole-brain radiation therapy plus concomitant temozolomide for the treatment of brain metastases from non-small cell lung cancer: a randomized open-label Phase II study. *Clin. Lung Cancer* 11(3), 176–181 (2010).

53 Quantin X, Bozonnat MC, Pujol JL. Recursive partitioning analysis groups I–III

brain metastases of non-small cell lung cancer: a Phase II randomized study comparing two concurrent chemoradiotherapy regimens. *J. Thorac. Oncol.* 5(6), 846–851 (2010).

54 Neuhaus T, Ko Y, Muller RP *et al.* A Phase III trial of topotecan and whole-brain radiation therapy for patients with CNS-metastases due to lung cancer. *Br. J. Cancer* 100(2), 291–297 (2009).

55 Lind JS, Lagerwaard FJ, Smit EF *et al.* Phase I study of concurrent radiotherapy and erlotinib for multiple brain metastases from non-small-cell lung cancer. *Int. J. Radiat. Biol. Oncol. Phys.* 74(5), 1391–1396 (2009).

56 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* 65(2), 198–203 (2009).

57 Huang YJ, Wu YL, Xie SX *et al.* Weekly gemcitabine as a radiosensitizer for the treatment of brain metastases in patients with non-small cell lung cancer: Phase I trial. *Chin. Med. J. (Engl).* 120(6), 458–462 (2007).

58 Guerrieri M, Wong K, Ryan G, Millward M, Quong G, Ball DL. A randomised Phase III study of palliative radiation with concomitant carboplatin for brain metastases for non-small cell carcinoma of the lung. *Lung Cancer* 46(1), 107–111 (2004).

59 Robinet G, Thomas P, Breton JL *et al.* Results of a Phase III study of early versus delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination in operable brain metastasis of non-small-cell lung cancer: Groupe Francais de Pneumo-Cancerologie (GFPC) Protocol 95–91. *Ann. Oncol.* 12(1), 59–67 (2001).

60 Prozanto P, Bruna F, Neri E *et al.* Radiotherapy plus carboplatin and teniposide in patients with brain metastases from non small cell lung cancer. *Anticancer Res.* 15(2), 517–519 (1995).

61 Minnitti G, Salvati M, Muni R *et al.* Stereotactic radiosurgery plus whole-brain radiotherapy for treatment of multiple metastases from non-small cell lung cancer. *Anticancer Res.* 30(7), 3055–3061 (2010).

62 Bogart JA, Ungureanu C, Shihadeh E *et al.* Resection and permanent I-125 brachytherapy without whole brain irradiation for solitary brain metastasis from non-small cell lung carcinoma. *J. Neurooncol.* 44(1), 53–57 (1999).

63 Mehta MP, Shapiro WR, Phan SC *et al.* Motexafin gadolinium combined with prompt whole brain radiotherapy prolongs time to neurologic progression in non-small-cell lung cancer patients with brain metastases: results of a Phase III study. *Int. J. Radiat. Oncol. Biol. Phys.* 73(4), 1069–1076 (2009).

64 Cox JD, Stanley K, Petrovich Z, Paig C, Yesner R. Cranial irradiation in cancer of the lung of all cell types. *JAMA* 245(5), 469–472 (1981).

65 Strauss GM, Herndon JE, Sherman DD *et al.* Neoadjuvant chemotherapy and radiotherapy followed by surgery in stage IIIA non-small-cell carcinoma of the lung: report of a Cancer and Leukemia Group B Phase II study. *J. Clin. Oncol.* 10(8), 1237–1244 (1992).

66 Albain KS, Rusch VW, Crowley JJ *et al.* Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group Phase II study 8805. *J. Clin. Oncol.* 13(8), 1880–1892 (1995).

67 Stuschke M, Eberhardt W, Pottgen C *et al.* Prophylactic cranial irradiation in locally advanced non-small-cell lung cancer after multimodality treatment: long-term follow-up and investigations of late neuropsychologic effects. *J. Clin. Oncol.* 17(9), 2700–2709 (1999).

68 Pottgen C, Eberhardt W, Grannass A *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.* 35(21), 4987–4992 (2007).

69 Gore EM, Bae K, Wong SJ *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.* 29(3), 272–278 (2011).

■ **Report of the most recent Phase III trial evaluating the potential role of prophylactic cranial irradiation for patients with non-small-cell lung cancer. A companion paper by Sun *et al.* [70] reports on the neurocognitive end points of this study.**

70 Sun A, Bae K, Gore EM *et al.* Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality of life analysis. *J. Clin. Oncol.* 29(3), 279–286 (2011).

71 Cotto C, Berille J, Souquet PJ *et al.* A Phase II trial of fotemustine and cisplatin in central nervous system metastases from non-small cell lung cancer. *Eur. J. Cancer* 32A(1), 69–71 (1996).

72 Lee JS, Pisters KM, Komaki R *et al.* Paclitaxel/carboplatin chemotherapy as primary treatment of brain metastases in non-small cell lung cancer: a preliminary report. *Semin. Oncol.* 24(4 Suppl. 12), S12–52–S12–55 (1997).

73 Minotti V, Crino L, Meacci ML *et al.* Chemotherapy with cisplatin and teniposide for cerebral metastases in non-small cell lung cancer. *Lung Cancer* 20(2), 93–98 (1998).

74 Bernardo G, Cuzzoni Q, Strada MR *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.* 20(3), 293–302 (2002).

75 Ceresoli GL, Cappuzo F, Gregorc V, Bartolini S, Crino L, Villa E. Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. *Ann. Oncol.* 15(7), 1042–1047 (2004).

76 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* 47(1), 129–138 (2005).

77 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* 57(3), 359–364 (2007).

78 Wu YL, Zhou C, Cheng Y *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.* 24(4), 993–999 (2013).

79 Novello S, Camps C, Grossi F *et al.* Phase II study of sunitinib in patients with non-small cell lung cancer and irradiated brain metastases. *J. Thorac. Oncol.* 6(7), 1260–1266 (2011).

80 Dzidziuszko R, Ardizzoni A, Postmus PE *et al.* Temozolomide in patients with advanced non-small cell lung cancer with and without brain metastases. a Phase II study of the EORTC *Lung Cancer* Group (08965). *Eur. J. Cancer* 39(9), 1271–1276 (2003).

81 Giorgio CG, Giufridda D, Pappalardo A *et al.* Oral temozolomide in heavily pre-treated brain metastases from non-small cell lung cancer: Phase II study. *Lung Cancer* 50(2), 247–254 (2005).

82 Lukas RV, Nicholas MK, Villaflor V, Hoffman PC, Salgia R. Temozolomide and/or erlotinib in the treatment of lung cancer patients with progressive central nervous system metastases. *J. Neurol. Res.* 2(1), 1–9 (2012).

83 Broniscer A, Panetta JC, O'Shaughnessy M *et al.* Plasma and cerebrospinal fluid pharmacokinetics of erlotinib and its active metabolites. *Clin. Cancer Res.* 13(5), 1511–1515 (2007).

84 Buie LW, Lindley C, Shih T *et al.* Plasma pharmacokinetics and cerebrospinal fluid concentrations of erlotinib in high-grade gliomas: a novel, Phase I, dose escalation study. [Abstract]. *J. Clin. Oncol.* 25(18S), 2054 (2007).

85 Togashi Y, Masago K, Masuda S *et al.* Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer. *Cancer Chemother. Pharmacol.* 70(3) 399–405 (2012).

86 Zhao J, Chen M, Zhong W *et al.* Cerebrospinal fluid concentrations of gefitinib in patients with lung adenocarcinoma. *Clin. Lung Cancer* 14(2), 188–193 (2013).

87 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.* 99(2), 283–286 (2010).

88 Costa DB, Kobayashi S, Pandya S *et al.* CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J. Clin. Oncol.* 29(15), e443–e445 (2011).

89 Kaneda H, Okamoto I, Nakagawa K. Rapid response of brain metastasis to crizotinib in a patient with ALK rearrangement-positive non-small-cell lung cancer. *J. Thorac. Oncol.* 8(4), e32–e33 (2013).

90 Kim YH, Ozasa H, Nagai H *et al.* High-dose crizotinib for brain metastases refractory to standard dose crizotinib. *J. Thorac. Oncol.* 8(9), e85–e86 (2013).

91 Maillet D, Martel-Lafay I, Arpin D, Perol M. Ineffectiveness of crizotinib on brain metastases in two cases of lung adenocarcinoma with EML4–-ALK rearrangement. *J. Thorac. Oncol.* 8(4), e30–e31 (2013).

92 Chuan Tang S, Nguyen LN, Sparidans RW, 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* doi:10.1002/ijc.28475 (2013) (Epub ahead of print).

93 Socinski MA, Langer CJ, Huang JE *et al.* Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases. *J. Clin. Oncol.* 27(31), 5255–5261 (2009).

94 Ewend MG, Brem S, Gilbert M *et al.* Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. *Clin. Cancer Res.* 13(12), 3637–3641 (2007).

95 Abel TJ, Ryken T, Lesniak MS, Gabikian P. Gliadel for brain metastasis. *Surg. Neurol. Int.* 4(Suppl. 4), S289–S293 (2013).

96 Langley RE, Stephens RJ, Nankivell M *et al.* Interim data from the Medical Research Council QUARTZ trial: does whole brain radiotherapy affect the survival and quality of life of patients with brain metastases from non-small cell lung cancer? *Clin. Oncol. (R. Coll. Radiol).* 25(3), e23–e30 (2013).

97 Chatani M, Matayoshi Y, Masaki N, Inoue T. [Radiation therapy for brain metastases from lung carcinoma. Prospective randomized trial according to the level of lactate dehydrogenase.] *Strahlenther. Onkol.* 170(3), 155–161 (1994).

98 Russell AH, Pajak TE, Selim HM *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.* 21(3), 637–643 (1991).

99 Umsawasdi T, Valdivieso M, Chen TT *et al.* Role of elective brain irradiation during combined chemoradiotherapy for limited disease non-small cell lung cancer. *J. Neurooncol.* 2(3), 253–259 (1984).

100 Barlesi F, Gervais R, Lena H *et al.* Pemetrexed and cisplatin as first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) with asymptomatic inoperable brain metastases: a multi-center Phase II trial (GFPC-0701). *Ann. Oncol.* 22(11), 2466–2470 (2011).

101 Lee DH, Han JY, Kim HT *et al.* Primary chemotherapy for newly diagnosed non-small cell lung cancer patients with synchronous brain metastases compared with whole-brain radiotherapy administered first: result of a randomized pilot study. *Cancer* 113(1), 143–149 (2008).

102 Boogerd W, van der Sande JJ, van Zandwijk N. Teniposide sometimes effective in brain metastases from non-small cell lung cancer. *J. Neurooncol.* 43(1), 285–289 (1999).