Emerging treatment paradigms for brain metastasis in non-small-cell lung cancer: an overview of the current landscape and challenges ahead

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Advances in the last decade in genomic profiling and the identification of druggable targets amenable to biological agents have transformed the management and survival of a subgroup of patients with brain metastasis in non-small-cell lung cancer. In parallel, clinicians have reevaluated the role of whole brain radiotherapy in selected patients with brain metastases to reduce neurocognitive toxicity. Continual progress in this understudied field is required: optimization of the sequence of schedules for therapies in patients with brain metastases of differing genomic profiles, focusing on new strategies to overcome mechanisms of biological resistance and increasing drug penetrability into the central nervous system. This review summarizes the field to date and possible treatment strategies based on current evidence.

Key words: brain metastasis, non-small-cell lung cancer, personalized medicine, radiotherapy

Introduction

Non-small-cell lung cancer (NSCLC) constitutes 85% cases of lung cancer and can be subdivided into a variety of histological subtypes with adenocarcinomas predominating (1). Patients with lung cancer present initially with brain metastases in ~10%–25% of cases, with up to 50% of patients developing brain metastases throughout their disease course (2).

Patients with brain metastases generally have a poor prognosis with a median survival of ~6 months in those receiving whole brain radiotherapy (WBRT) alone (3) and are typically excluded from clinical trials if they are symptomatic (4, 5).

The incidence of patients presenting with brain metastasis is increasing due to improved systemic therapies leading to better control of extracranial disease (6). Advances in the ability to interrogate the genome in recent years have fostered the concept of personalized medicine based on molecular classification of oncogenic addicted tumours. The identification of epidermal growth factor receptor (EGFR) mutations, ROS1 and ALK translocations (ALK+) has uncovered a subset of NSCLC tumours that are responsive to targeted treatment. Concurrently, strategies employed to treat patients with brain metastases have also evolved. Treatment modalities include biologically targeted therapies, chemotherapy, stereotactic radiosurgery (SRS), surgery in selected cases and WBRT. The approach adopted for a particular patient will depend on the performance status, molecular classification of the tumour and the distribution of intracranial and extracranial disease. This review provides a state-of-art overview of strategies to treat brain metastasis in NSCLC patients.

EGFR-mutant tumours

Pathogenic mutations in EGFR are typically associated with exon 19 deletions or L858R mutations in exon 21, accounting for ~90% of activating mutations (7). Activating mutations confer constitutive kinase activity and stimulate downstream signalling cascades. Several generations of small-molecule biologically targeted drugs to target the EGFR have been developed (Table 1).

Case series, early phase studies and more recently subgroup analysis derived from randomized controlled trials (RCTs) have
evaluated the role of these targeted agents in patients with brain metastases (Table 2) (8–18). Favourable intracranial response rates (RRs), 35%–88%, and improved overall survival (OS) have been reported in EGFR-mutant tumours. Iuchi et al. assessed the role of tyrosine kinase inhibitors (TKIs) in delaying the commencement of radiotherapy in patients with brain metastases (13). The median time to progression using gefitinib alone was 14.5 months, and the usage of TKIs delayed the administration of brain irradiation by a median time of 17.9 months. Stratification by EGFR mutation status demonstrated differential intracranial RR 100% versus 80% and median OS of 30.3 versus 19.8 months for exon 19 deletions and exon 21 L858R mutations, respectively. Recently a retrospective study evaluating the timing of WBRT and SRS in EGFR-mutant brain metastases reported the longest median OS benefit (46 months) in patients receiving upfront SRS followed by TKI therapy, in comparison with patients receiving delayed radiotherapy (19). A systematic review and meta-analysis of 12 non-comparative observational studies reported some benefit from upfront cranial radiotherapy (SRS or WBRT), with improved intracranial disease control and survival than with TKI treatment alone (20). RCTs are required to determine the optimal timing of radiotherapy in EGFR-mutant tumours.

Amongst the TKIs, there are limited data regarding central nervous system (CNS) penetrability. Erlotinib CNS penetrability appears the greatest with concentrations reported as 66.9, 8.2, 1 and 7.51 nM achieved for erlotinib, gefitinib, afatinib and osimertinib, respectively (14, 21, 22). Osimertinib demonstrated

**Table 1. Summary of current TKIs in clinical use**

<table>
<thead>
<tr>
<th>Generation of TKI</th>
<th>Drugs</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Gefitinib • Erlotinib • Icotinib</td>
<td>Reversibly binds to the ATP-binding site of the EGFR kinase domain and inhibits activity</td>
</tr>
<tr>
<td>Second</td>
<td>Afatinib • Dacomitinib</td>
<td>Irreversibly binds to the ErbB family of receptors through covalent bonding preventing homodimer/heterodimer formation</td>
</tr>
<tr>
<td>Third</td>
<td>Osimertinib</td>
<td>Inhibitor targeting both EGFR sensitizing and T790M resistance mutations</td>
</tr>
</tbody>
</table>

TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor.

**Table 2. Intracranial response rates in patients treated with TKI with brain metastasis**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug</th>
<th>Study</th>
<th>Line of treatment</th>
<th>Number of patients with brain metastases</th>
<th>Response rate %</th>
<th>Survival months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. (2009)</td>
<td>Gefitinib or Erlotinib</td>
<td>Case series</td>
<td>First line</td>
<td>23</td>
<td>70</td>
<td>OS = 18.8</td>
</tr>
<tr>
<td>Hotta et al. (2004)</td>
<td>Gefitinib</td>
<td>Case series</td>
<td>Prior chemotherapy exposure</td>
<td>14</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Porta et al. (2011)</td>
<td>Erlotinib</td>
<td>Case series</td>
<td>Some patients had prior WBRT exposure</td>
<td>69</td>
<td>82</td>
<td>OS = 12.9</td>
</tr>
<tr>
<td>Park et al. (2012)</td>
<td>Gefitinib or Erlotinib</td>
<td>Phase II</td>
<td>Some patients had prior chemotherapy exposure</td>
<td>28</td>
<td>83</td>
<td>OS = 15.9</td>
</tr>
<tr>
<td>Wu et al. (2013)</td>
<td>Erlotinib</td>
<td>Phase II</td>
<td>Prior chemotherapy exposure</td>
<td>48</td>
<td>58</td>
<td>PFS = 15.2</td>
</tr>
<tr>
<td>Iuchi et al. (2013)</td>
<td>Gefitinib followed by sequential Erlotinib</td>
<td>Phase II</td>
<td>First line</td>
<td>41</td>
<td>88</td>
<td>OS = 21.9</td>
</tr>
<tr>
<td>Hoffknecht et al.</td>
<td>Afatinib</td>
<td>Efficacy from compassionate usage program</td>
<td>Prior chemotherapy and TKI exposure</td>
<td>100</td>
<td>35</td>
<td>–</td>
</tr>
<tr>
<td>Mok et al. (2017)</td>
<td>Osimertinib</td>
<td>Subgroup analysis from RCT</td>
<td>Prior TKI exposure</td>
<td>93</td>
<td>–</td>
<td>PFS = 8.5</td>
</tr>
<tr>
<td>Yang et al. (2017)</td>
<td>Icotinib</td>
<td>Phase III</td>
<td>First-line comparison of WBRT and chemo versus Icotinib</td>
<td>85</td>
<td>65</td>
<td>PFS = 10</td>
</tr>
<tr>
<td></td>
<td>Dacomitinib</td>
<td>To date, to our knowledge, there are no data with regards to intracranial efficacy. Recent phase III trials have not reported intracranial outcomes or have excluded patients with brain metastasis in their design. ARChER 1009/1050.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TKI, tyrosine kinase inhibitor; OS, overall survival; WBRT, whole brain radiotherapy; PFS, progression-free survival; RCT, randomized controlled trial.
improved progression-free survival (PFS) (8.5 versus 4.2 months) in patients with brain metastasis who had progressed following first-line TKI therapy and were randomized to receive either osimertinib or platinum/pemetrexed chemotherapy (15). A recent study shows osimertinib given as first-line treatment improves PFS compared to standard first-generation TKIs (18.9 versus 10.2 months) including patients with brain metastases. (93)

**Pulsatile/high-dose EGFR-TKI therapy**

Despite improved tumour control with EGFR-mutant tumours treated with TKIs, all tumours will eventually develop resistance. Several pathways of resistance have been reported with the *T790M* mutation development as the predominant mechanism (23). Interestingly several reports showed *T790M* mutations were rare for intracranial progression in contrast to extracranial synchronous metastatic sites (24, 25). Researchers postulated that this is due to inadequate CNS drug penetration. The possibility of ongoing TKI sensitivity in the CNS has engendered the strategy of dose escalation with pulsatile/high-dose treatment for progressive brain metastasis or leptomeningeal disease previously treated with standard-dose TKI. Although still largely experimental, several case reports have demonstrated activity and tolerability by using high-dose erlotinib and gefitinib (24, 26–28).

Despite the need for RCTs to define the optimal TKI drug and cranial radiation timing (both SRS and WBRT), based on the current evidence, we propose the use of erlotinib alongside SRS at initial presentation to treat symptomatic EGFR-mutant brain metastases given its increased CNS penetrability. A repeat tissue biopsy should be considered on disease progression. Osimertinib can be considered upon disease progression for *T790M*-mutant tumours, whereas erlotinib dose escalation with radiotherapy (SRS and/or WBRT) can be considered for patients with CNS disease progression alone.

**ALK rearranged tumours**

Genomic rearrangements in a subset of NSCLC have been identified involving the ALK fusion oncogene, resulting in ligand-independent constitutive tyrosine kinase activity of ALK, induced through oligomerization with *ELM-4* (29). These genomic rearrangements are typically mutually exclusive with *EGFR* and *KRAS* mutations (30). Advanced ALK+-NSCLC is characterized by a high frequency of brain metastases at diagnosis and also a high lifespan risk of developing brain metastases, with the brain being the most common site of disease progression (31).

Crizotinib, a first-generation ALK inhibitor, suppresses signal transduction resulting in G1-S phase cell cycle arrest and apoptosis (32). Despite initial disease control, tumour progression inevitably develops mediated through different pathways of resistance (33). Mutations in the tyrosine kinase domain of ALK drive resistance, the most frequent being *L1196M* (gate keeper) and *G1269A* (30). Steric hindrance disrupts the ability of the drug to bind to the ATP binding pocket.

Ceritinib, a second-generation ALK inhibitor, demonstrates activity in crizotinib-resistant tumours (*L1196M*, *G1269A* *I1171T* and *S1206Y ALK* somatic mutations) (34). Alectinib, another second-generation TKI, has been developed to target ALK+ tumours and can overcome crizotinib resistance. Several other ALK inhibitors (brigatinib and lorlatinib) are also currently undergoing clinical trials (35). Table 3 summarizes intracranial outcomes with ALK inhibitor therapy and the line of treatment at which they have been used (36–41).

Many patients treated with crizotinib alone eventually develop CNS relapse (42). This may be attributable to ineffective CNS drug penetration (43). The low levels of CNS penetration may relate to crizotinib serving as a substrate for P-glycoprotein–mediated efflux (44). Alectinib has greater CNS bioavailability compared with crizotinib, 2.69 nmol/l and 1.4 nmol/l, respectively (43, 45). To our knowledge, the CSF concentration of ceritinib in humans has not been published.

Ceritinib and alectinib have demonstrated activity in both crizotinib-resistant and -naive tumours (37–39, 46, 47). The ASCEND-4 trial demonstrated promising intracranial RR (69%) with ceritinib compared with chemotherapy (28%) (37). Alectinib also demonstrated promising intracranial RR of 57% in crizotinib-resistant patients and 81% in crizotinib-naive patients with measurable CNS lesions (38, 47). The Japanese ALEX trial reported significantly more durable intracranial responses with alectinib when compared with crizotinib (48). They reported a hazard ratio (HR) of 0.16 for time to progression of brain metastatic lesion/death and an HR = 0.41 for time to onset of brain metastatic lesion/death. These results were confirmed recently by the global ALEX trial that reported an HR of 0.16 for time to CNS progression compared with crizotinib (47).

Given the impressive cranial CNS activity reported for alectinib in the J-ALEX and global ALEX trials, its good CNS penetrability and the absence of first-line ceritinib versus crizotinib efficacy data, we recommend that alectinib should be considered as the first-line treatment in patients with cranial and extracranial metastases in ALK+ tumours. Extrapolating from EGFR-mutant NSCLC treated with cranial irradiation, patients may also derive benefit from additional up front SRS, although an RCT is required to validate this approach.

**Patients without driver mutations**

Systemic treatment options for patients with NSCLC presenting with brain metastases that are *EGFR* and *ALK* wild type are limited. Temozolomide, an alkylating agent, can penetrate the blood-brain barrier (BBB) in therapeutic concentrations (49). Intracranial RR ranging from 0% to 10% with temozolomide has been observed (50, 51). The TACTIC study evaluated the role of erlotinib with concurrent radiotherapy in patients with brain metastases which were predominantly *EGFR* wild type (52). There was no significant benefit from the addition of erlotinib.

Barlesi et al. reported their findings from a phase II study in patients with inoperable brain metastases (93% non-squamous histology) challenged with first-line pemetrexed and cisplatin chemotherapy with WBRT given upon disease progression or completion of chemotherapy. In total, 63% of patients received WBRT. The overall cerebral RR was 41.9% by intent-to-treat analysis with a median PFS and OS of 4 and 7.4 months, respectively.

In the absence of driver mutations in inoperable brain metastasis, our practice has been to consider either localized radiosurgery
or WBRT in the first instance with reevaluation of the role of chemotherapy after an interval depending on the performance status and symptomatology of the patient.

**Immunotherapy**

Immune checkpoint inhibitors (IO) are now rapidly being used to treat advanced NSCLC particularly for tumours expressing PD-L1 protein (53, 54). However, its role for brain metastases is yet to be established. In an open-label phase II trial using pembrolizumab in patients with asymptomatic brain metastases in PD-L1 expressing NSCLC, an intracranial RR of 33% was observed (55). Currently, all reported IO trials excluded patients with symptomatic brain metastasis and/or requiring corticosteroid. One of the challenges in treating brain metastases is the management of neurological symptoms, which might be from tumour growth due to treatment failure or from complications of the IO treatment including oedema, tumour necrosis or haemorrhage seen most frequently in previously irradiated lesions. Nevertheless, clinical studies are needed to determine whether IO will play any role to treat NSCLC patients with multiple brain metastases with or without SRS or WBRT.

**Localized treatment**

Patients with few brain metastases with controlled extracranial disease may be considered for either surgery or SRS. There is no strong rationale with regards to the choice of local treatment, but the decision should be guided by a combination of clinical factors (Table 4).

**Neurosurgery**

Three RCTs compared surgery plus WBRT with WBRT alone in the treatment of a single brain metastasis, and none of these studies were specific to lung cancer (56–58). There was an OS advantage in two of the trials (56, 57) with an increase in local control and in the length of functionally independent survival in the Patchell trial (56). A subsequent trial examined the role of postoperative WBRT by comparing surgery plus WBRT with surgery alone (59). No difference in OS was demonstrated, but WBRT reduced both the risk of intracranial recurrence and the risk of patients dying of neurologic causes. Therefore, postoperative WBRT is generally recommended in this setting (60).

In an attempt to avoid adjuvant WBRT, SRS to the postoperative cavity has been proposed with promising results on local control (61, 62). However, retrospective data have suggested an increase in distant intracranial relapse with adjuvant SRS as compared with adjuvant WBRT (63). An RCT presented in abstract form in 2016, comparing SRS and WBRT after resection, showed less cognitive decline and better quality of life in the SRS group (64).

**Stereotactic radiosurgery**

SRS refers to the precise delivery of large radiation doses to the target in a few fractions, resulting in an increase in the biological effective dose. To minimize normal tissue toxicity, conformation of high doses to the target and rapid fall-off doses away from the

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug</th>
<th>Study</th>
<th>Line of treatment</th>
<th>Number of patients with brain metastases</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costa et al. (2015)</td>
<td>Crizotinib</td>
<td>Pooled retrospective analysis</td>
<td>Previous chemotherapy exposure</td>
<td>275</td>
<td>Intracranial disease control rate at 12 weeks 56% in asymptomatic brain metastasis</td>
</tr>
<tr>
<td>Ou et al. (2015)</td>
<td>Alectinib</td>
<td>Phase II</td>
<td>Second-line crizotinib resistant</td>
<td>35</td>
<td>Intracranial RR = 57%</td>
</tr>
<tr>
<td>Soria et al. (2017)</td>
<td>Ceritinib</td>
<td>Phase III</td>
<td>First line ALK inhibitor naive or one line of prior chemotherapy</td>
<td>22 Alectinib 14; Crizotinib 29</td>
<td>Intracranial RR = 73% HR = 0.16 for time to progression of brain metastatic lesion favouring alectinib</td>
</tr>
<tr>
<td>Hida et al. (2017)</td>
<td>(J-ALEX) Alectinib versus Crizotinib</td>
<td>Phase III</td>
<td>First line Alectinib 21; Crizotinib 22</td>
<td>Intracranial RR: alectinib = 81%; Crizotinib = 50%</td>
<td></td>
</tr>
<tr>
<td>Peters et al. (2017)</td>
<td>(Global ALEX) Alectinib versus Crizotinib</td>
<td>Phase III</td>
<td>Mixed population</td>
<td>154</td>
<td>Intracranial RR = 53%</td>
</tr>
<tr>
<td>Gettinger et al. (2017)</td>
<td>Brigatinib</td>
<td>Pooled analysis Phase 1/2</td>
<td>Previous ALK inhibitor exposure</td>
<td>39</td>
<td>Intracranial RR = 44%</td>
</tr>
</tbody>
</table>

RR, response rate; HR, hazard ratio.
target are critical. Several SRS platforms including cyberknife, gamma knife and standard linac are available (65). It should be noted again that the studies evaluating SRS were not specific to lung cancer patients.

Two RCTs compared WBRT alone with SRS plus WBRT in patients with 1–4 brain metastases. A study by Kondziolka et al. was stopped early due to an increase of 1-year local failure (100% versus 8%) and a decrease in median time to any brain failure in the WBRT alone arm (66). The RTOG 9508 trial included patients with 1–3 newly diagnosed lesions and showed a survival advantage in the SRS group but only for patients with a single brain metastasis (median OS 6.5 versus 4.9 months, \( P = 0.0393 \)) (67). A Cochrane review evaluating the role of WBRT in addition to surgery or SRS compared with surgery alone for brain metastases reported decreased intracranial progression at 1 year with no impact on OS (68).

Another important question in patients with oligo brain metastases treated with SRS is whether there is a benefit to the addition of WBRT. Table 5 summarizes the results of four RCTs comparing SRS alone with SRS and WBRT (69–72). All four studies show a reduction in the risk of relapse within the brain, but none of them report a benefit for the addition of WBRT to SRS. The outcome in terms of cognitive function is contradictory with one study showing improved Mini Mental State Examination (MMSE) scores and performance status (69), whereas other studies showing decline in cognitive function in the combined arm.

A recent individual patient data meta-analysis conducted by Sahgal et al. (73) evaluated three published RCTs. Age was a significant prognostic factor for both OS and distant brain failure: patients \( \geq 50 \) years of age initially treated with SRS alone had a significantly lower HR of mortality than patients with similar ages treated with SRS plus WBRT, with similar rates of distant failures between both arms, whereas in patients \( > 50 \) years, WBRT reduced the rate of distant failure with no impact on OS. They concluded that SRS alone might be the preferred treatment for patients \( \geq 50 \) years.

Even if intracranial disease progression is a significant factor in worsening of neurocognitive performance (74), the long-term adverse effects of WBRT on neurocognitive function might outweigh the benefit provided by improved local control especially for

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion of lung cancer patients (%)</th>
<th>n SRS</th>
<th>Recurrence rate (%)</th>
<th>Median survival (months)</th>
<th>Cognitive function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoyama et al. 1–4 BM</td>
<td>76</td>
<td>67</td>
<td>76.4</td>
<td>8.0</td>
<td>Improved Mini Mental Scores in WBRT arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65</td>
<td>46.8</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(( P = 0.01 ))</td>
<td>(NS)</td>
<td></td>
</tr>
<tr>
<td>Chang et al. 1–3 BM</td>
<td>55.1</td>
<td>30</td>
<td>73</td>
<td>Not reported</td>
<td>Decline in learning and memory function in WBRT arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(( P = 0.0003 ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown et al. 1–3 BM</td>
<td>72</td>
<td>111</td>
<td>11.6</td>
<td>7.4</td>
<td>Decline in cognitive function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>102</td>
<td>35.4</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(( P &lt; 0.0001 ))</td>
<td>(( P = 0.92 ))</td>
<td></td>
</tr>
<tr>
<td>Kocher et al. 1–3 BM</td>
<td>53</td>
<td>100</td>
<td>19</td>
<td>10.9</td>
<td>WBRT did not improve duration of functional independence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99</td>
<td>31</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(( P &lt; 0.04 ))</td>
<td>(NS)</td>
<td></td>
</tr>
</tbody>
</table>

Underlined entries represent SRS + WBRT patients

BM, Brain Metastases; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy; NS, not significant.

### Table 4. Clinical features favouring either SRS of neurosurgery for the management of brain metastasis

<table>
<thead>
<tr>
<th>Feature</th>
<th>SRS</th>
<th>Neurosurgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4 metastases or total tumour volume (&lt; 20 \text{cm}^3)</td>
<td>Primary disease is controlled or is suitable for radical treatment</td>
<td>Up to 3 lesions accessible through a single craniotomy</td>
</tr>
<tr>
<td>Less than 3 cm in diameter</td>
<td>Mass effect and no response to steroids</td>
<td>Tumour ( &gt; 4 \text{cm} ) in size</td>
</tr>
<tr>
<td>No significant mass effect</td>
<td>Primary disease is controlled or is suitable for radical treatment</td>
<td>Mass effect and no response to steroids</td>
</tr>
<tr>
<td>Primary disease is controlled or is suitable for radical treatment</td>
<td>Need for histological diagnosis</td>
<td></td>
</tr>
<tr>
<td>Metastasis inaccessible for surgical resection</td>
<td>Cystic/necrotic lesion</td>
<td></td>
</tr>
<tr>
<td>Progressive disease after surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients not suitable for general anaesthesia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SRS, stereotactic radiosurgery.
patients with oncogene addicted NSCLC. Indeed, the neurocognitive MMSE-based assessment of patients included in the study of Aoyama et al. (69) was reported in detail in a further paper (74). The use of WBRT was significantly associated with an improvement of the time to neurological deterioration (16.5 versus 7.6 months), highlighting the role of WBRT in preventing the neurocognitive deterioration from brain recurrence in the short term. However, as the deterioration reaches a ‘plateau’ among long-term survivors treated by SRS alone (>12–24 months), patients treated with WBRT continued to deteriorate. In Chang’s trial where the primary end point was the 4-month neurocognitive function as measured with the Hopkins Verbal Learning Test–Revised Total Recall, patients randomly assigned to receive SRS plus WBRT were significantly more likely to show a decline in learning and memory function than patients assigned to receive SRS alone (70). However, the timing of the primary end point was not optimal as a temporary deterioration of neurocognitive functions is common in the weeks following WBRT. In an EORTC trial, comparing adjuvant WBRT with observation after either surgery or SRS, patients in the observation only arm reported better health-related quality of life scores compared with patients who received WBRT, but mostly for the early time points (75).

Consequently, the benefits of adjuvant WBRT must be counterbalanced with the neurotoxicity profile associated with treatment, especially among long-term survivors. Taken together, a reasonable approach supported by ASTRO in patients with few brain metastases definitively treated by surgical resection or SRS would be to monitor patients actively through serial imaging and to offer salvage WBRT upon disease progression (60). On the basis of Sahgal’s meta-analysis, this strategy should be considered particularly in younger patients (<50 years) and could be refined by selecting patients with a lower risk of brain regional failure after local treatment according to specific normograms or scales (76, 77).

Although it is generally accepted that SRS should generally be considered in patients with ≤4 brain metastases, a recent multinational study challenges this prevailing concept (78). In a prospective observational study, OS did not differ between patients treated with SRS with 2–4 tumours (10.8 months) and those with 5–10 tumours (10.8 months). Patients were selected with newly diagnosed brain metastases (longest diameter <10 ml in volume and a total cumulative volume of ≤15 ml) with a Karnofsky performance score >70. These findings may prompt a reconsideration of the eligibility criteria to select patients for SRS treatment for brain metastasis if they are verified in a prospective RCT.

**WBRT alone**

For decades, WBRT has been considered the standard treatment for patients with brain metastases despite the lack of level 1 evidence compared with supportive care, especially in poor performance patients. Most of the clinical research in patients with multiple brain metastases have focused on dose-finding studies to investigate the optimal WBRT regimen (79–81). It should be noted that these trials included patients with malignancies from all solid primary sites and are therefore very heterogeneous. WBRT alone is associated with an overall RR of 60%, a 6-month disease control rate of 50% and an improvement in neurologic symptoms in 70%–90% within 1–3 weeks (82). A Cochrane review reported that altered WBRT dose fractionation schedules when compared with standard dosing (30 Gy in 10 fractions or 20 Gy in 5 fractions) had no benefit in OS (83). Acute side-effects include headache, nausea, hair loss, drowsiness and deterioration of pre-existing neurological deficits. More rarely, some delayed irreversible neurocognitive impairments are reported but with complex and multifactorial pathophysiology, including pre-treatment neurocognitive status (82).

The concept of using WBRT as the main local treatment has been revisited by the introduction of SRS in patients with a limited number of metastases and also by the findings of the QUARTZ trial (84). The QUARTZ trial was started at the same time as the TACTIC trial in the UK (52, 85) and compared optimal supportive care (OSC) including dexamethasone plus WBRT (20 Gy/5 daily fractions) or OSC alone (including dexamethasone) for NSCLC patients with poor prognosis in whom treating clinicians were uncertain about the potential clinical role of WBRT. The primary end point of the study was quality-adjusted life-years with OS being a secondary measure. The study found that WBRT did not offer clinical benefit to NSCLC patients with brain metastases in terms of improved survival, the overall quality of life or reduction in steroid use. The findings, however, require cautious interpretation. The majority of patients had uncontrolled thoracic disease (64%), extracranial metastases (54%), Karnofsky Performance Scale (KPS) ≤70, RPA class 3 (38%) which resulted in an overall median survival of only 2 months for patients treated with WBRT indicating highly selected patients with poor prognosis by treating clinicians. An unplanned subgroup analysis however suggested that male patients, patients <70 years, KPS ≥70, no extracranial metastases or controlled systemic disease benefited from WBRT.

**Minimizing neurocognitive toxicity associated with WBRT**

Several systemic treatments in association with WBRT have been showed to potentially prevent neurocognitive impairment. In an RCT, Mehta et al. reported that motexafin gadolinium in addition to WBRT improved time to neurocognitive progression in lung cancer patients (86). In another RCT, memantine, an inhibitor of the N-methyl-D-aspartate glutamatergic receptor, has also been identified as an agent that could slow the development of neurocognitive deficits in patients receiving WBRT (87). Patients receiving memantine had a significantly longer time to cognitive decline and lower probability of cognitive function failure at 24 weeks.

Another strategy is to investigate improvements in dose delivery with modern radiotherapy techniques. The hippocampus is a core component of the limbic system and has a key role in short/long-term memory processing and spatial navigation. It has been postulated that radiotherapy damages neural stems cells located in the dentate gyrus of the hippocampus (88). A phase II trial RTOG 0933 has evaluated the role of intensity-modulated radiotherapy (IMRT) to spare the hippocampus to preserve memory and quality of life (89). Patients with brain metastases received hippocampal avoidance WBRT (30 Gy in 10 fractions, with no more than 9 Gy to 100% of the hippocampus), and the control group consisted of a pre-specified historic dataset of patients that received standard WBRT. In total, 113 patients were accrued of
which 42 patients were analyzable. The primary end point of the trial was measured by the Hopkins Verbal Learning Test—Revised Delayed Recall at 4 months. Patients treated with hippocampal avoidance WBRT had a significantly lower mean relative decline in 4-month HVLT-R DR from baseline (7%) in comparison with historic controls (30%) (89). Avoidance of delivering radiotherapy to the hippocampus is time consuming, requires complex planning and treatment with IMRT/volumetric modulated arc therapy. The relative benefits of treatment need to be balanced with the cost-effectiveness of treatment. Given these considerations, patients with a better prognosis (such as patients with EGFR mutation or ALK+ rearrangements) are likely to derive the most benefit from this treatment approach. The findings from RTOG 0933 require confirmatory evidence from a phase III RCT before hippocampal sparing is advocated in patients with multiple brain metastases.

An ongoing phase III trial is testing both systemic and local strategy, thereby combining memantine with either standard WBRT or hippocampal avoidance WBRT to reduce neurocognitive decline in patients with brain metastases (NCT02360215). Notably, the hippocampal avoidance strategy is also under evaluation in oligometastatic patients in the adjuvant setting after surgery or SRS (UK HIPPO trial NCT02147028).

**Future directives**

Molecular classification of tumours has fostered the concept of personalized medicine. For simplicity, patients with brain metastasis with NSCLC can be stratified into three categories: EGFR-mutant, ALK+ and EGFR/ALK wild type. The underlying genetic profile will determine the prognosis and treatment strategy employed. Further studies are required to identify the optimal sequence of treatment schedules in these subgroups of patients. Moreover, the timing at which radiotherapy (SRS and WBRT) is incorporated in the treatment schedule requires further exploration. Despite the development of EGFR and ALK inhibitors, drug resistance still emerged. Newer generations of these inhibitors appear to be active again for first-generation failure patients and will replace the existing first-line treatments. Given the complexity of escape pathways involved in biological resistance, overcoming this obstacle will require repeat genomic testing to identify new mutations developing. Future treatment paradigms may involve utilizing a combination ‘cocktail’ of drugs to target the primary pathogenic mutation and concomitant escape mechanisms promoting tumour proliferation. Penetrability of the BBB remains a challenge hindering the delivery of the drug, and future drug development will require engineering small lipophilic molecules that can cross BBB. In parallel, researchers are attempting to concurrently target P-glycoprotein efflux (42).

The current treatment strategies are guided by genetic profile of the primary tumour or extracranial metastatic site. Requesting a brain metastasis biopsy is technically difficult but this may be overcome in future with liquid biopsy. Efforts have been undertaken to identify driver mutations in brain metastasis (90–92). Paired analysis of primary tumours and brain metastases of lung, breast and renal carcinomas demonstrated clonal heterogeneity between the primary and the metastasis with a branched evolutionary framework. Clonally related paired samples demonstrated a common ancestral relationship, with the development of independent mutations exclusive to the primary and metastasis (92). Future research may focus on sequencing circulating tumour DNA to determine whether this could provide an informative representation of the genetic profile of the brain metastasis (92).

**Funding**

None declared.

**Disclosure**

The authors have declared no conflicts of interest. We thank the support of University College London Hospital Comprehensive Biomedical Research Center (SML).

**References**


