ONLINE FIRST

REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY

ISSN: 1507-1367

e-ISSN: 2083-4640

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Authors: Margarita Martin, Raúl Hernanz, Carmen Vallejo, Leonardo Guerrero, Xabier Mielgo, Ana Lopez, Juan Carlos Trujillo-Reyes, Felipe Couñago

DOI: 10.5603/RPOR.a2022.0050

Article type: Review paper

Published online: 2022-04-07

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Margarita Martin[1], Raúl Hernanz[1], Carmen Vallejo[1], Leonardo Guerrero[1], Xabier Mielgo[2], Ana Lopez[3], Juan Carlos Trujillo-Reyes[4], Felipe Couñago[5]

[1]*Radiation Oncology, Hospital Universitario Ramon y Cajal Servicio de Oncologia Radioterapica, Madrid, Spain*

[2]*Medical Oncology, Hospital Universitario Fundación Alcorcón, Alcorcon, Spain*

[3]*Medical Oncology, Hospital Severo Ochoa, Leganes, Spain*

[4]*Thoracic Surgery, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

[5]*Universidad Europea de Madrid, Madrid, Spain*

Address for correspondence: Margarita Martín, Hospital Universitario Ramon y Cajal Servicio de Oncologia Radioterapica, Radiation Oncology, Carretera de Colmenar Viejo Km 9,100, 28034 Madrid, Spain, tel: 0034 628476830; e-mail: oncomarga@gmail.com

Abstract

Background: The development of brain metastases is a common problem in patients diagnosed with non-small cell lung carcinoma (NSCLC). Technological advances in surgery and radiotherapy have allowed greater local control. Moreover, the emergence of targeted therapies and immunotherapy with greater activity on the central nervous system than classical chemotherapy have given way to new strategies in the treatment of brain metastases.

We review the current role of local treatments, surgery and radiotherapy, and the most effective combination strategies with the new systemic treatments.

Relevance for patients: Brain metastases frequently occur during the course of NSCLC. In recent years, a range of treatments have appeared, such as targeted

treatments or immunotherapy, with greater activity at the brain level than classical chemotherapy. Radiotherapy treatment is also now much more conformal and ablative doses can be delivered to the volume of the metastatic area, providing greater local control and less neurological toxicity. However, surgery is still required in cases where anatomopathological specimens are needed and when compressive effects appear. An important challenge is how to combine these treatments to achieve the best control and minimise patients' neurological impairments, especially because of limited experience with the new target drugs, and the unknown toxicity of the different combinations. Future research should therefore focus on these areas in order to establish the best strategies for the treatment of brain metastases from non-small cell lung cancer.

Core tips: In this work, we intend to elucidate the best therapeutic options for patients diagnosed with brain metastases of NSCL, which include: surgery, WBRT, radiosurgery or systemic treatment, and the most effective combinations and timings of them, and the ones with the lowest associated toxicity.

Key words: non-small cell lung cancer; brain metastases; immune checkpoint inhibitors

Introduction

The central nervous system (CNS) is, together with the lung and bone, one of the most frequent sites of metastatic growth in non-small cell lung cancer (NSCLC). Up to 18% of patients present with brain metastases at the time of diagnosis of NSCLC [1] and in 11% of patients brain is the only site of metastases [2]. The rate of brain spread increases over the course of the disease eventually affecting more than 40% of these patients [3]. Treatment has traditionally consisted of surgery for single metastases or those at risk of complications, and whole brain radiotherapy (WBRT). With technological developments, ablative doses of irradiation can be administered to one or multiple metastases by stereotactic radiosurgery (SRS) in a single session, or stereotactic radiotherapy (SRT) in several sessions. In addition, an increased molecular knowledge of tumours has given rise to new systemic treatments, such as tyrosine kinase inhibitors (TKIs), in patients with ALK (anaplastic lymphoma kinase), rearranged EGFR (epidermal growth factor receptor), or proto-oncogene tyrosine-protein kinase (ROS1) mutation. In these patients, the onset of brain metastases occurs

later and survival is better than in patients without these genetic alterations. Programmed cell death receptor (PD1) and programmed cell death ligand (PD-L1) inhibitors, which impede immune evasion by tumour cells, have been approved for the treatment of NSCLC. The efficacy of these drugs has also been demonstrated at the CNS level [4] and the next challenge is how to combine them with radiotherapy. With these novel combined treatments, the median survival of patients with brain metastases has improved over the last two decades, now standing at between 3 and 46.8 months, depending on clinical, histological and molecular prognostic factors. The median survival for adenocarcinoma and non-adenocarcinoma is now 15.2 and 9.2 months, respectively [5]. In patients alive after 2 years of brain metastases diagnosis, the probability of being alive 5 years after treatment is 26% [6].

We decided to conduct a literature review to determine the current role of surgery and radiotherapy, and the combination of these treatments with novel systemic therapies. We used the following search terms in Pubmed: non-small cell lung cancer and brain metastasis with surgery, radiotherapy, targeted therapy and immunotherapy.

Radiotherapy treatment

Whole brain radiotherapy

Since 1950, WBRT has been the standard palliative treatment for patients with multiple brain metastases with the aim of improving quality of life (QoL) and prolonging survival by a few months.

Many prognostic factors affect the survival of patients with brain metastases of pulmonary origin such as: the number of metastases, location, histology, ECOG, control of primary disease, patient’s age and presence of extracranial metastases. Karnofsky Performance Status (KPS) < 70 has been found as independently predictive of death within 30 days of treatment for patients who received at least 10 fractions [7]. Over the years, prognostic classification systems have been designed to attempt to predict survival outcomes. In 1997, the Radiation Therapy Oncology Group (RTOG) introduced the Recursive Partitioning Analysis (RPA), but this system is only based on age, KPS presence of extracranial brain metastases, and control of the primary tumour, without taking into account the number of brain metastases, presence of liver or lung metastases,

or the previous treatments received [8]. In 2008, Sperduto established another classification system, Graded Prognostic Assessment (GPA), after analysing data from 5 randomised RTOG studies. This scoring system takes into account age, Karnofsky scale, number of brain metastases, and the presence or absence of extracranial metastases [9]. This was followed by the Disease Specific Graded Prognostic Assessment (DS-GPA), which maintains the same prognostic factors for patients diagnosed with lung cancer but is different for other diagnoses [10]. In 2017, this classification was updated with the molecular characteristics of the tumours, Lung-molGPA, adding two new prognostic factors: EGFR and ALK genetic alterations in patients with adenocarcinoma. Overall, survival was 12 months for the entire cohort, but patients with mutations had a median survival of nearly 4 years [5]. The QUARTZ trial questioned the indication for WBRT in patients with lung carcinoma with a poor prognosis. In these patients, fractionation of 4 Gy into 5 sessions did not improve ~~on~~ survival or QoL achieved with optimal supportive care [11]. WBRT ~~would~~ still ~~be~~ is indicated in patients with a good general health and multiple brain metastases, and ~~be~~ is equally effective in those with supra- or infratentorial locations [12]. The standard dose is 30 Gy delivered in 10 fractions of 3 Gy, as studies testing dose escalation failed to improve the results of this scheme [13, 14]. However, similar results were also obtained in another study with 20 Gy in 5 fractions [15]. By contrast, the results in terms of neurological palliation were worse with ultra-short regimens of a 10 Gy single fraction or two fractions of 6 Gy [16]. It should be noted that the influence of hypofractionation on long-term toxicity has not been evaluated.

Stereotactic radiotherapy

With the development of new technologies, WBRT is being replaced by radiosurgery (SRS) or fractionated stereotactic radiotherapy (SRT), in an attempt to limit neurological toxicity and improve QoL and metastatic control. Initially, these new techniques were only considered for patients with few brain metastases, generally 1 to 4, and of less than 3 cm in size, in patients with a good general condition and controlled primary disease. However, results of administering radiosurgery alone are similar in patients with 5 to 10 metastases and in those with 2 to 4 [17], without differences in neurological toxicity between the two groups [18]. Even in selected patients with 10 or more metastases treated with radiosurgery, there was no difference in either outcome or

neurological side effects compared to those with 2 to 9 metastases [19]. Therefore, there is no consensus on limiting the treatment in relation to the number of metastases [20].

Studies comparing SRS with WBRT combined with SRS in patients with NSCLC found no differences in OS, but a greater interval of cerebral-free disease [21–24]with SRS + WBRT. However, a post-hoc analysis of the JROSG-99 trial suggested a benefit in OS in the WBRT group in patients with NSCLC of favourable prognosis, DS-GPA > 2.5. This supports the hypothesis that in these patients the risk of death from brain progression is greater than from systemic progression, in that case, whole brain irradiation could provide an additional benefit [22]. This is the only study that reported this benefit of adding WBRT to SRS. The second analysis of the European Organisation For Research And Treatment Of Cancer EORTC 22952 trial and North Central Cancer Treatment Group NCCTG N0574 did not find this improvement in OS in the same subgroup of patients with good prognosis and controlled extracranial disease [21, 25]. These inconsistent results may be caused by etiological differences in lung tumours in the Asian population, which has a higher incidence of the EGFR mutation that confers better prognosis. However, the mutational status of the population of patients in whom the subanalyses were performed is unknown. It is also likely that rescuing brain progression with a further radiosurgery will result in a similar OS. A meta-analysis of the NCCTG N0574 and Japan Radiation Oncology Study Group JROSG 99-1 studies also conclude that there is no difference between the GPA ≥ 2 and GPA < 2 subgroups for the two treatments (SRS and WBRT vs SRS alone). When WBRT was included, the time free from brain relapse improved in both groups. Salvage treatment was more frequent in the SRS only group and the rates of grade 3 and 4 toxicity were similar in GPA ≥ 2 and GPA < 2 [24].

Therefore, evidence is inconclusive for an improved OS with WBRT combined with SRS vs exclusive SRS. Moreover, several randomised studies have concluded that SRS alone can improve QoL with less impaired memory and neurological dysfunction. For both these reasons, exclusive SRS and close follow-up are currently preferred for early treatment of brain metastases [26, 27]. However, WBRT is still indicated in patients with a good performance status who are not candidates for surgery or treatment with SRS. In these cases, the preservation of the hippocampus reduces the risk of neurological dysfunction, especially of verbal memory. The hippocampus is a structure of between 3–4 cm, and the risk of metastases in this area in patients with non-small cell

lung carcinoma is about 2.8%. The rate increases by 0.2% when it is protected from irradiation [28], so lowering the dose in the hippocampus seems to be a safe strategy with no differences in PFS or OS. Compared with WBRT in the randomised study by Brown [29], neurological decline is reduced when the average dose in the hippocampus is below 10 Gy and the maximum dose is less than 17 Gy.

Surgery followed by stereotactic radiotherapy

With regards to the combination of surgery and SRS-SRT, a retrospective study comparing 66 patients treated with SRS alone *vs.* 157 treated with surgery and SRS reported lower local recurrence at one year (36.7% *vs.* 20.5%, p: 0.007) and OS at two years (38.9% *vs.* 19.8%, p:0.01) with the combination of treatments. There was no difference in radiation necrosis between the combined treatment and SRS alone, but differences were observed between SRS administered before surgery vs postoperative SRS, 5.5% vs. 26.6%, respectively [30].

Two other randomised studies reported that postoperative SRS-SRT decreased the risk of cognitive impairment with respect to WBRT and improved local control compared to observation. The first of these studies was conducted by the NCCTGN/CEG. This study compared WBRT with 30 Gy delivered in 10 fractions or 37.5 Gy in 15 fractions vs single dose radiosurgery of 15–20 Gy. A total of 194 patients were randomised and the study found more cognitive impairment in the patients receiving WBRT, with no differences in OS [31]. The second randomised study compared postsurgical SRS, 12–16 Gy *vs.* observation in 132 patients treated with surgery for 1 or 3 brain metastases with a maximum diameter of 4 cm. Local control was better in patients treated with postsurgical SRS, 72% *vs.* 43%, HR 0.46, p: 0.01. The main risk factor for local recurrence was metastasis size of over 2.5 cm [32]. There was no difference in the median OS between the two groups, 17 vs 18 months. Death from neurological causes was 64% in the observation group and 48% in the group receiving radiosurgery, with no statistically significant differences between the groups. There was no grade 3 or higher toxicity in either arm. These studies are summarised in Table 1.

Therefore, after surgery for brain metastases, postoperative radiotherapy on the surgical bed is indicated. The use of a single or several fractions will depend on the location and size of the metastases.

Stereotactic radiotherapy prior to surgery

Delineation of the irradiation volume after surgery is imprecise, making it necessary to increase the margins to include normal brain tissue. The planning volume (PTV) for metastases corresponds to the gross tumour volume, with a margin of 1–2 mm of normal brain tissue. Because of this, many centres now prefer to perform SRS treatment prior to surgery. Another potential advantage is that before surgery, radiotherapy acts on a tumour with an intact blood supply, whereas when delivered postoperatively the patient must first recover from surgery. A retrospective study compared stereotactic radiosurgery applied pre- *vs.* post-surgery and reported no differences in local recurrence, distant brain recurrence or OS, but lower rates of symptomatic radiation necrosis and leptomeningeal disease in the preoperative SRS cohort [33].

Status of prophylactic whole brain irradiation in NSCLC

Prophylactic cranial irradiation (PCI) is performed to prevent the appearance of brain metastases. It is the standard therapy in patients with limited-stage small cell lung carcinoma (LS-SCLC), where it improves OS [34]. However, its role is less clear in the case of NSCLS, where it is not yet known whether any subgroup of patients could benefit from this strategy. Patients diagnosed with NSCLC with a higher risk of developing brain metastases are those with Pancoast tumours, who develop brain metastases in 40% [35], patients with histology other than squamous stage IIIA-N2 [36], those operable or with complete response after chemoradiotherapy [37], and those under 60 years of age.

Since the 1970s, attempts have been made to define the value of PCI in NSCLC (Tab. 2).

In 1981, VALG [38] conducted their first prospective study which also included SCLC. They reported a potential benefit of PCI in patients with NSCLC, with a reduced incidence of metastasis of approximately 6% but no impact on OS. In 1984 [39], the MD Anderson Cancer Center (MDACC) studied 97 patients diagnosed with locally advanced non-small cell lung cancer (LA-NSCL), and reported a significant control in brain metastases (4% *vs.* 23% for the PCI and observation group, respectively) without differences in OS. Similarly, the most recent randomised phase III studies presented similar results (Tab. 2), reporting that PCI reduced the incidence of brain metastases and

significantly improved disease-free survival (DFS), although with no impact on OS. Only the study by Li et al. showed a marginal and not statistically significant benefit in median OS of 31 *vs.* 27.4 months in the control group, with a p value of 0.13, although the study did not complete recruitment [40]. As an exception, the Southwest Oncology Group, SWOG [41, 42], observed a significant reduction in OS in the PCI group, although this was probably due to the simultaneous administration of thoracic RT, and the high brain dose administered (37.5 Gy). Although the RTOG 84-03 study did not report a significant reduction in the incidence of brain metastases, 9% *vs.* 19% p ns, there was a delay in their appearance [43].

The first systemic review on PCI in NSCLC was the one by Cochrane published in 2005. It reported a decrease in the incidence of brain metastases with no improvement in OS and no conclusions about the impact on QoL. The basic limitation of this first review is that meta-analysis was not performed because the studies were too heterogeneous. Also, the most recent studies were not included as they have not been updated since 2010 [44].

Three meta-analyses of randomised studies have been published in the last two years. The one conducted by Feghali et al. [45] shows a 70% reduction in the incidence of brain metastases and an improvement in DFS in stage III patients, with no difference in OS (HR = 1.08, 95% CI: 0.91–1.27) or QoL. They did not perform subgroup analyses because most studies included in the meta-analysis were not stratified by variables such as histology, stage or response to induction chemotherapy. However, one of the included studies using surveillance, epidemiology and end results data found no benefit either in the subgroup of patients under 60 years of age with adenocarcinoma histology and stage IIIB [46].

The one published by Witlox, also in 2018 [47], shows a reduced incidence of brain metastases with PCI of 13% (RR: 0.33; 95% CI: 0.22–0.45). Although there were no statistically significant differences in OS or QoL, the authors consider the results to be inconclusive. In respect of OS, because the studies had a very short follow-up, and for QoL, data were only collected in a few studies. The most recent systematic review published by Precival et al. [41] shows identical results with a reduced incidence of metastases with PCI but no differences in OS.

This lack of difference in OS may be due to methodological deficiencies in the studies, some of which were conducted on small series of patients or had incomplete recruitment. On the other hand, the increasing radical treatment of metastases with surgery or ablative doses of irradiation, or disease progression at the systemic level may also contribute to this.

In terms of side effects, PCI is well tolerated and associated with a relatively low toxicity [48]. The most common acute toxicity presents with asthenia, skin toxicity, nausea or vomiting and alopecia, while somewhat later, at 6 months, headache, drowsiness and cognitive impairment with recent memory loss may occur. Some randomised studies reported discrete cognitive and memory impairments, such as the De Ruysscher [49] study and the RTOG 0214 study which found an impaired cognitive function assessed by the Hopkins Verbal Learning Test-Revised, HVLT-DR with PCI, and worse neurological function at three months of treatment but not at one year, which was one of the objectives of the study. Moreover, there was no difference in QoL at 6 or 12 months between patients who received PCI and those who did not [50]. However, some retrospective studies also showed cognitive impairment in patients who had not received WBRT, suggesting that other factors could also come into play [51]. None of the three meta-analyses found differences in toxicity or QoL with the use of PCI.

In summary, despite the decreased incidence of brain metastases, PCI cannot be recommended as a standard therapy in patients with NSCLC, owing to the lack of evidence for an improved OS, and the need for further research to determine its impact on cognitive function. However, with the emergence of new and more effective systemic treatments, such as TKIs or immunotherapy, which better control extracranial disease and improve patient survival, there is renewed interest in prophylactic ~~head~~ brain irradiation in patients with NSCLC. In addition, hippocampal protection techniques and medications, such as memantine, which decrease side effects at the neurological level, are also being studied. The benefits of PCI compared with close monitoring with MRI in high-risk patients should also be assessed.

Role of surgery

Three randomised studies compared WBRT *vs.* WBRT with single brain metastasis. Two of them reported an improvement with the combined treatment [52, 53], but the third study by Mintz et al. [54] found no benefit. These studies were performed on a

small number of patients two decades ago when systemic treatments were less effective. Moreover, WBRT would not be the treatment of choice in patients with a single brain metastasis today.

Surgery for brain metastases is currently used in two main settings. The first is for treatment with radical intent in patients with a single metastasis, controlled or controllable extracranial disease, and good performance status. In these patients the 5-year survival is 7.6% when both locations are treated radically[55]. The role of surgery is especially important when SRS or SRT are not an option, in some cases due to the size of the brain metastases, over 5 cm in diameter, or when they are located close to organs at risk such as the brain stem. The second setting for surgical treatment is for symptomatic relief, when eloquent areas are involved, or for tumours causing compressive effects. Another advantage of surgical treatment is the possibility of carrying out histopathological studies. Some studies have reported different molecular patterns for the primary tumour and brain metastases and this information would allow for a better adaptation of systemic treatments [56]. On the other hand, postsurgical complications have decreased with improved surgical techniques, with morbidity and mortality rates at around 17.7% and 2.4%, respectively [57].

The incidence of recurrence after surgical resection is approximately 50–60% in the 12 months following surgery. WBRT may reduce the risk of recurrence both locally and in different brain locations, but does not improve OS and is associated with increased cognitive and QoL impairments[25,58]. As we have seen previously, it is now being replaced by SRS-SRT.

Combining radiotherapy treatment with new systemic treatments

Radiation therapy and targeted therapies

In patients with lung adenocarcinoma, the presence of EGFR and ALK alterations confer a better prognosis [5]. The discovery of targeted therapy against these alterations in NSCLC has significantly changed the treatment options, with increased survival in this patient group. There is, therefore, more time in which to develop brain metastases, which are much more common (50–60% *vs.* 15–20% in patients with tumours without mutation) [59–61], and also to observe the cognitive deficits resulting from some local

treatments, such as WBRT. For this reason, use of WBRT should be avoided or delayed in these patients [62, 63] and SRS is preferred over WBRT whenever possible, depending on the size and location of the metastases.

When radiation therapy is performed in the course of TKI treatment, the medication is usually discontinued until completion of the radiation therapy to reduce the risk of cognitive damage. However, the data are not conclusive, with one study suggesting an increase in cognitive decline [64], but another claiming that they can be administered together safely [65], although in most studies it was not even mentioned. Whenever possible, it is recommended that medication in these cases should be suspended, except when the tumour burden is so high that it increases the risk of patient's condition worsening significantly. Although cognitive decline is associated with WBRT, and most patients are currently treated with SRS, medications are also usually discontinued until completion of RT. The most relevant studies are summarised in Table 3.

Brain metastases in patients with EGFR mutations

The EGFR mutation is present in approximately 15% of cases of primary NSCLC. The first EGFR inhibitors studied were gefitinib and erlotinib, and on the development of resistance to these (usually the T790M mutation in EGFR mutant tumours), the second and third generation inhibitors afatinib and osimertinib were developed [66, 67].

Evidence of their efficacy in brain metastases from EGFR-positive primary NSCLC was initially described in small case series that showed good response rates for intra and extracranial metastases[68]. Prospective trials with first generation tyrosine kinase inhibitors (TKI) showed cranial responses of up to 80% [69–71].

The question of whether patients with EGFR mutation and brain metastases can be treated with TKIs alone without radiotherapy remains open. A meta-analysis of 12 observational studies, including 363 patients with EGFR-positive NSCLC and brain metastases, suggested that cranial RT compared to an initial treatment with a first-generation EGFR TKI achieved an improvement in PFS for intracranial disease at 4 months (RR = 1.06, 95% CI: 1.00 to 1.12) and also in OS at two years (OS; RR = 1.33, 95% CI: 1.00–1.77), although it caused more neurological toxicity than TKI alone. The authors acknowledge methodological flaws and conclude that, despite evidence that initial cranial radiation therapy can improve control of intracranial disease and survival

outcomes compared to TKI alone, the quality of the evidence is poor [72]. A later study [73], also retrospective, including 351 patients from 6 institutions diagnosed with NSCLC with the EGFR mutation and brain metastases compared the treatments: SRS followed by EGFR-TKI, WBRT followed by EGFR-TKI and EGFR-TKI followed by SRS or WBRT at the time of intracranial progression. The median OS (measured from the date of brain metastases) for the groups treated with SRS (n = 100), WBRT (n = 120) and EGFR-TKI (n = 131) was 46, 30 and 25 months, respectively ($p < .001$). These data show that initial use of EGFR-TKI and delayed radiation therapy is associated with lower OS in patients with EGFR mutant NSCLC with brain metastases. SRS followed by EGFR-TKI resulted in the longest OS and allowed patients to avoid possible neurocognitive sequelae from WBRT.

The above data seem to indicate that delaying RT may be associated with worse outcomes in patients with brain metastases compared to early RT. But these studies were done with first- or second-generation EGFR TKIs that have shown less intracranial activity than third-generation agents like osimertinib.

Osimertinib is a third-generation EGFR-TKI that selectively inhibits EGFR-TKI-sensitising and EGFR T790M resistance mutations. In a sub-analysis FLAURA study, efficacy was assessed in patients with brain metastases. Of the 556 patients included in the study, 128 (61 in the osimertinib arm and 67 in the standard EGFR-TKI arm) had CNS metastases with measurable and/or non-measurable lesions. The median CNS PFS was not achieved with osimertinib (95% CI, 16.5 months to not calculable) and was 13.9 months with EGFR TKI standard (risk ratio: 0.48; 95% CI: 0.26 to 0.86; $p = .014$). The objective response rate in the brain was 91% with osimertinib and 68% with standard EGFR-TKI. The CNS progression rate among the total of 556 study patients was also lower in patients treated with osimertinib compared to those treated with first-generation EGFR-TKI [74].

Survival in this study (FLAURA) has been updated in a recent publication in the subgroup of patients with brain metastases [75], reporting a PFS at 18 months of 58% in the osimertinib-treated group and 40% in the EGFR-TKI first generation group.

Despite the fact that these data with osimertinib indicate significant activity against brain disease, without the neurocognitive side effects or postoperative complications

that can arise after brain irradiation or surgical removal, we have no studies comparing osimertinib with local therapies for the treatment of brain metastases. For this reason, some experts recommend opting for initial RT followed by osimertinib. Another option, especially in patients with extracranial dissemination and multiple brain metastases, is to delay RT if the brain metastases are small and asymptomatic.

Brain metastases in patients with ALK-translocations

Recent clinical trials have examined the effectiveness of ALK inhibitors and there is increasing evidence for their role in treating brain metastases. Several anaplastic lymphoma kinase tyrosine kinase inhibiting agents (ALK-TKI) have shown activity in brain disease. Most patients with brain metastases, both untreated and treated with crizotinib, will respond to these agents, making it possible to delay surgery and/or RT [76, 77]. Here, we will examine the level of evidence for the new agents: alectinib, brigatinib, ceritinib and lorlatinib.

Two phase III trials have demonstrated the superiority of alectinib over crizotinib as a treatment for patients with brain metastases. J-ALEX was a phase 3 randomised trial with 207 patients with ALK-positive NSCLC. The time to brain progression was significantly longer with alectinib versus crizotinib ($p < 0.0001$). In a later publication of this trial [78], which analysed efficacy in 122 patients with brain metastases (64 in the alectinib group, 58 in the crizotinib group), 43 with measurable lesions (21 alectinib, 22 crizotinib), and 46 with previous RT (25 alectinib, 21 crizotinib), the time to brain progression was significantly longer with alectinib versus crizotinib ($p < 0.0001$), the response rate was 85.7% with alectinib *vs.* 71.4% with crizotinib in patients who received prior RT and 78.6% versus 40.0%, respectively, with no previous RT.

In a phase 3 trial, 275 patients with advanced ALK-positive NSCLC not previously treated with ALK inhibitors were randomised to receive brigatinib or crizotinib. The intracranial response rate among patients with measurable lesions (> 1 cm) was 78% with brigatinib and 29% with crizotinib [79].

The ASCEND-7 clinical trial evaluated ceritinib in patients with newly diagnosed brain metastases, or as tumour progression, including 44 patients with no previous brain radiation therapy or treatment with ALK inhibitors. Results are still preliminary, being

reported at ESMO 2019, and showed a brain response rate of 52%, with an average duration of brain response of 7.5 months [80]. By comparing the results of the ALEX and ASCEND-4 clinical trials, alectinib appears to be the most active, and this has been corroborated in some case series [81].

This intracranial activity has also been documented in patients previously treated with crizotinib. In a multicentre phase III randomised trial (ALUR), 107 patients with ALK-positive / metastatic NSCLC previously treated with chemotherapy (platinum doublet) and crizotinib were randomised to receive alectinib (n = 72) versus chemotherapy (n = 35). In patients with measurable brain metastases (24 with alectinib and 16 with chemotherapy), the response rate was significantly higher with alectinib (54.2%) versus chemotherapy (0%; $p < 0.001$). Alectinib significantly improved both systemic and brain efficacy versus chemotherapy [82].

To further assess this activity, one study pooled efficacy and safety data from two single-arm phase II clinical trials that included 136 patients with ALK-positive NSCLC with brain metastases, 50 of them measurable, previously treated with crizotinib. Of these 136, 70% had previously received brain radiation therapy [76]. For the patients with measurable brain disease, the response was 64.0%, the control rate was 90.0%, and the median duration of response in the brain was 10.8 months. For patients with measurable and/or non-measurable brain disease, the response was 42.6%, the control rate was 85.3%, and the median duration of response, 11.1 months. The response rate was 35.8% for the 95 patients with prior radiation therapy and 58.5% for the 41 patients without prior radiation therapy. Therefore, alectinib showed good efficacy against brain metastases, in crizotinib-refractory ALK-positive NSCLC.

The phase II clinical trial, ASCEND-2, evaluated the efficacy and safety of ceritinib in 140 patients with ALK-rearranged NSCLC previously treated with at least one platinum-based chemotherapy and crizotinib. Of the 140 patients, 100 had asymptomatic or neurologically-stable brain metastases. The brain metastasis response rate was 45.0% [83]. The results of a randomised phase 2 trial (ALTA) evaluating brigatinib in NSCLC positive for anaplastic lymphoma refractory to crizotinib have recently been published [84]. In this study, brigatinib (180 mg once daily) achieved a good response to brain metastases in crizotinib-refractory patients, better than the 90 mg/day dose.

Lorlatinib is a potent third-generation inhibitor of ALK and ROS1 tyrosine kinases with broad coverage of ALK mutations. In a phase 1 study, activity was observed in patients with ALK-positive NSCLC, most of whom had brain metastases and progression after ALK-directed therapy [85]. Subsequently, in a phase 2 study [86] in patients with advanced ALK-positive, or ROS1-positive NSCLC, with or without brain metastases, the response to lorlatinib was assessed in 276 patients who were assigned to six different cohorts, based on ALK status and ROS1 and previous therapy. Three patients of the 30 in the first cohort (ALK + no previous treatment) had measurable brain lesions and response was observed in 2 of them (66.7%). In ALK-positive patients with at least one prior ALK tyrosine kinase inhibitor (cohorts 2 to 5), a response in measurable brain metastases was observed in 63% of patients (51 of 81). Cerebral response was observed in 87% of patients (20 of 23) with measurable brain metastases of the 59 patients in the cohorts who had received crizotinib with or without chemotherapy; in 55.6% (5 of 9 patients) of the cohort who had received an ALK-TKI with or without CT (28 patients) and in 56% (26 of 49 patients) of the group of 112 patients treated with 2 or 3 ALK-TKI with or without chemotherapy. Hence, in this study lorlatinib showed significant activity in brain metastases and in systemic disease in patients with ALK-positive NSCLC. This activity was observed in patients with no prior treatment and in those who had progressed with crizotinib, a second generation ALK-TKI, and also in patients who had received up to three previous ALK-TKI.

Patients presenting with only brain progression with alectinib, maintaining the systemic response, can be treated locally with SRS if the disease is oligometastatic. Another alternative in these patients is to increase the dose of alectinib to 900 mg administered orally twice a day, in cases of good tolerance to the previous dose, or can be switched to lorlatinib [87]. The choice depends on the preference of the patients and hospitals and the availability of lorlatinib.

Brain metastases in patients with ROS1 translocations

Up to 36% of patients with ROS1 fusion NSCLC have brain metastases at diagnosis. Entrectinib is a ROS1 inhibitor that has been shown to penetrate and be effective in the CNS. Preliminary results of an integrated analysis of three ongoing phase 1 or 2 trials of entrectinib (ALKA-372-001, STARTRK-1 and STARTRK-2) have recently been published. Response was observed in 5 of 7 patients (71%) with measurable brain

metastases who had not received previous RT[88]. In a phase II study of lorlatinib, out of 11 patients with ROS1-positive NSCLC with brain metastases who had not received prior treatment with crizotinib, the response rate for brain metastases was 63%, and of 24 patients with brain metastases previously treated with crizotinib, the response rate was 51% [89].

In conclusion, currently, for the treatment of brain metastases in NSCLC patients with mutations that have drugs for targeted therapy, this targeted treatment is preferred over classical local treatments (RT or surgery), with the intention of reducing the risk of further brain progression and also the side effects of local therapies. However, SRS maintains a key role in the treatment of oligometastatic disease, although targeted therapies are promising treatments for brain metastases from lung cancers with some mutations.

Radiation therapy and checkpoint inhibitors

The risk of pseudoprogression causing the worsening of neurological symptoms, as well as the reduced efficacy due to the steroid treatment, frequently required in patients with brain metastases, are among the concerns regarding treatment with immune checkpoint inhibitors (ICI) for brain metastases. Also, the brain can be considered as an isolated immune organ due to the presence of the blood-brain barrier, the absence of a real lymphatic drainage system, and because macrophages of the microglia are not effective at presenting antigens. The latter is caused by the limited expression of the major histocompatibility complex, the absence of immune system co-stimulatory molecules in the CNS, and the increase in immunosuppressive interleukins such as IL-10, FGF-β. However, in recent years, research has shown that a robust immune response in the periphery can pass the blood-brain barrier, because neuroinflammation caused by metastases and radiotherapy alters the barrier vasculature allowing immune cells to pass. In addition, the microglia can orchestrate interactions with other immune cells and activated T-lymphocytes in the periphery that reach the brain by an alternative route to the blood-brain barrier, via the choroidal plexus. Hence, if there is lymphatic drainage from the brain to the cervical nodes, then T-lymphocytes can be activated by antigens from the CNS. For all these reasons, there is a growing interest in the effects of immune treatments on patients with brain metastases, and their combined use with irradiation. To date, data are scarce on the effects of immune check point inhibitors (ICI) at the brain

level, because patients with uncontrolled or untreated brain metastases have been excluded from clinical trials, and only 6–17% of patients who participated in the trials had controlled brain metastases. In these patients, the percentage response was the same as at the extracranial level [4, 90] (Tab. 4).

Most of the evidence for the combined use of SRS and ICI is obtained from patients with melanoma brain metastases. Two meta-analyses found no increased toxicity at the neurological level with the combination of ICI and radiosurgery. In both meta-analyses, the percentage of symptomatic radionecrosis was around 5% and similar in the concurrent treatment group vs. isolated radiosurgery. As for survival outcomes and local control, OS was better for the combination, but survival free from local and distant progression was similar [91, 92]. Already in patients with brain metastases of pulmonary origin, the Johns Hopkins University has retrospectively published the results of 79 patients with melanoma, renal carcinoma or NSCLC who were treated with nivolumab, ipilimumab or pembrolizumab with or without SRS concomitantly (35%). The median OS was 12.9 months for patients treated with SRS, 14.5 months for those treated with nonconcurrent ICI and SRS, and 24.7 months for those treated concurrently [93].

In another retrospective cohort study, Shepard et al. from the University of Virginia Health System compared the outcomes in 17 patients with brain metastases from NSCLC treated with SRS and ICI administered 3 months before or after SRS with 34 patients treated with SRS without ICI. They found no differences in OS (HR: 0.99, $p = 0.99$), or DFS, HR: 2.18, $p = 0.11$, between the two groups, but the rate of complete brain-level response was higher in the patients receiving the two treatments: 50% vs 15.6% $p = 0.012$. The incidence of radionecrosis, intratumor haemorrhage, or oedema was also similar in both groups. In this study, the group treated with both treatments had more advanced disease according to the RPA scale and previous systemic treatment was not analysed, which could explain the lack of differences in OS [94].

Another retrospective study by Ahmed et al. described the results obtained in 17 patients with brain metastases from NSCLC. They found that patients treated with SRS before or during treatment with ICI had a brain control of 57% *vs.* 0% for patients previously treated with ICI ($p = 0.05$) [95]. For his part, Kotecha, in a retrospective study with a larger series of 150 patients, found that the best responses occur in patients treated

concurrently with SRS and ICI (considering concurrent ± 5 times the half-life of the ICI). These patients had a higher overall objective response and a longer duration of the response, especially if treated within the half-life of the drug. Pre-exposed ICI lesions have a worse response than naïve ones and the incidence of radionecrosis at 12 months was 3.2% in concomitant treatment. They also reported a link between steroid use and a worse response and OS [96]. In another retrospective study of only 37 patients, Schapira found a better OS and lower incidence of brain failure in patients treated concomitantly than in those treated sequentially (OS: 87.3% *vs.* 70.0% *vs.* 0%, p Z .008; 1-year DBF, 38.5% *vs.* 65.8% *vs.* 100%, p = .042). Moreover, local control was better with those treated with SRS before or after the onset of ICI, than those initially treated with ICI (1-year LC, 100% *vs.* 72.3%, p = .016), and no patient presented toxicity of grade 4 or higher [97].

In the study by Hubbeling et al., there was no difference in toxicity with ICI and RT vs ICI without RT [98]. However, Martin in a retrospective study in patients with brain metastases from melanoma or lung did obtain statistically significant differences in the incidence of radionecrosis, especially in melanoma patients treated with ipilimumab [99].

There are still many unresolved issues regarding the combined use of immunotherapy and SRS, such as the neurotoxicity of the combination, the optimal timing of the two treatments and the impact of steroids. A number of studies are attempting to answer these questions. The RADREMI prospective phase I study tried to evaluate SRS dose reduction for brain metastases on immunotherapy, 18 Gy for 0–2 cm lesions, 14 Gy for 2.1–3 cm lesions, and 12 Gy for 3.1–4 cm lesions [100]. In particular, for patients with brain metastases from NSCLC, open studies are NCT02978404 (nivolumab + SRS), NCT02858869 (pembrolizumab + SRS) and NCT02696993 (nivolumab + SRS/WBRT and nivolumab + ipilimumab + SRS/WBRT).

Conclusions

The introduction of new systemic treatments into the therapeutic arsenal and the technological development of surgical and radiotherapeutic treatments have increased the therapeutic options in patients with NSCLC brain metastases. For this reason, the treatment of these patients must be multidisciplinary. In patients with tumour mutations

who are candidates for targeted therapy, local treatment can be delayed provided that the metastases are not symptomatic. The combination of radiosurgery and ICI appears to be safe and effective and the results of ongoing clinical trials will help elucidate the best way to combine treatments.

Table 1. Treatment for non-small cell lung carcinoma (NSCLC) brain metastases (BM) with surgery and radiotherapy

Study, year	**Design**	**Treatment**	**Local recurrence**	**OS**	**RN**
Brown 2016 [26]	Prospective 213 pts	SRS (20–24 Gy) *vs.* SRS (18–22 Gy) + WBRT (30 Gy/12 fr)	HR 3.6	10.4 m 7.4 m p: NS	
Prabhu 2017 [30]	Retrospective 213 pts	SRS 18 Gy S + SRS 15 Gy SRS + S 15 Gy	36% 20% p: 0.007	19.8% (2 y) 38,9% (2 y) p: 0.01	12.3% 22.3% p: 001 5%
Mahajan 2017 [4]	Prospective 132 pts	S S + SRS	67% 28% p: 0.015	18 m 17 m p: NS	None None
Prabhu 2019 [33]	Prospective/retrospective 147 pts	SRS 15 Gy + S	25.1%	17.2 m	.8%

pts — patients; S — surgery; SRS — stereotactic radiosurgery; WBRT — whole brain radiotherapy; HR — hazard ratio; OS — overall survival; RN — radionecrosis; m — months

Table 2. Studies on prophylactic cranial irradiation non-small cell lung carcinoma (NSCLC)

					BM (%)			Median DFS			Median OS/%		
Study/Date	**N**	**Primary treatment**	**Stage**	**Dose [Gy]**	**PCI**	**Obs**	**p**	**PCI**	**Obs**	**p**	**PCI**	**Obs**	**p**
Umsawasdi (MDACC trial) 1984 [39]	97	RT CT	III	30 (3Gy x 10)	4	27	.002	NA			3 y: 22%	23.5%	NA
Russell (RTOG 8403) 1991 [43]	187	RT only	I/III. Inoperable NSCLC	30 (3Gy x 10)	9	19	.1	NA			8.4 m	8.1 m	.36
LI 2014 [40]	156	Sx + CT	IIIA–N2	30 (3Gy x 10)	20.3	50	<0.001	28.5m 5 y: 26.1%	21.2m 18.5%	.037	31.2 m	27.4 m	.310
De Ruysscher (NVALT-11/DLCRG-02) 2018 [49]	175	RT + CT or Sx + RT/CT	III	30 (2.5 Gy x 12)	7	27.2	<0.001	12.3 m	11.5 m	.17	24.2 m	21.2 m	.56
GORE/SUN (RTOG 0214) 2019	340	RT/Sx ± CT	IIIA/B	30 (2 Gy x 15)	16.7	28.3	.004	15 m 5 y: 19%	12 m 16%	.03	28 m 5 y:	25 m 26%	.12

[101, 102] 24.7%

10 y: 7.5% 10 y: 13.3%

12.6% 18%

N — number of patients; PCI — prophylactic cranial irradiation; Obs — observation group; BM — incidence of brain metastases; DFS — disease free survival; RT — radiotherapy; Sx — surgery; CT — chemotherapy; y — years; m — months; NA — not available

Table 3. Brain metastasis from oncogenic driver mutation tumors

Author/type	**No pts/Treatment**	**IC response % or ORR**	**IC PFS months**	**Toxicity**
EGFR mutation: 1st and 2sc TKIs generation				
Ceresoli 2004 [69] Prospective	41 Gefitinib (44% previous WBRT)	27%	13.5	No toxicity > G 2
Iuchi 2013 [71] Phase II	41 Gefitinib	87.8%	14.5	Skin G3 14.6% Liver G3 12.2%
Welsh 2013 [65] Phase II	40 Erlotinib + WBRT	89% with EGFR mutation 63% without mutation	NA	No toxicity ≥ G4
Gerber 2014 [103] Retrospective	63 Erlotinib 32 WBRT 15 SRS	NA	16 24	NA
Magnuson 2017 [73] Retrospective	131 EGFR-TKI follow WBRT/SRS		17 24	NA

	120 WBRT follow TKIs 100 SRS follow TKIs		23	
Jiang 2016 [104] Meta-analysis	RT + TKIs RT	13–77.1 13.3–70.7	HR: 0.55 favour RT + TKIs p < 0.000	More rash and dry skin with RT+TKIs
3rd generation TKIs				
Reungwetwattana 2018 [74] Phase III FLAURA	67 Standard TKIs 61 Osimertinib	91 68	13.9 Not reached	
Soria [68] 2018 Phase III	63 Standard TKIs 53 Osimertinib	84 75	8.3 13.8	
Wu YL [105] 2018 Phase III AURA3	Platinum Pemetrexed Osimertinib	ORR 31 ORR 70 p: 0.015	5.7 8.9 p: 0.004	
ALK translocation				
Hida 2017 [106] Phase III J-ALEX	31 Crizotinb 16 Alectinib		HR time to brain progression: 0.16	
Peters 2017 [78] Phase III ALEX	58 Crizotinib 64 Alectinib	50 81	5.5 17	
Camidge 2019 [107] Phase III ALTA-L1	Crizotinib Brigatinib	26% 78%		

Soria JC 2017 [108] Phase III ASCEND-4	62 Platinum Pemetrexed 59 Ceritinib	23.3% 72.7%	– 16	
Chow 2019 [80] Phase II ASCEND-7	Ceritinib in those settings 42 prior RT prior ALKi 40 no prior RT prior ALKi 12 prior RT no prior ALKi 44 no prior RT no prior ALKi	 66.7 62.5 100 Global response 59% 70.6	Global median intracranial response 7.5	
Shaw 2020 [109] Phase III CROWN	13 Crizotinib 17 Lorlatinib	23 82		Adverse events G3-4 56% Adverse events G3-4 58%
Novello 2018 [82] Phase III ALUR (pts resistant crizotinib)	16 QT: pemetrexed or docetaxel 24 Alectinib	0 54		G3 ≥ 41.2 G3 ≥ 27.1
Huber 2020 [84] Phase II ALTA (pts resistant crizotinib)	79 Brigatinib 90 mg 74 Brigatinib 180 mg	50% 67%	9.4 16.6	
Salomon 2018 [86] Phase 2 (pts resistant crizotinib)	81 Lorlatinib	63%	14.5	
Crinò 2016 [83] Phase II ASCEND-2 (pts resistant crizotinib)	100 Ceritinib	45		

ROS1 translocation				
Drilon 2020 [88] Phase 1-2 trials	23 Entrectinib	Non previous RT or more than 2 two months before 71% Previous RT 80%	7.7	
Lim 2017 [110] Phase II	8 Ceritinib	63		
Shaw 2017 [85] Phase II	11 Lorlatinib, crizotinib naïve 24 Lorlatinib, previous crizotinib	63 51		

EGFR — epidermal growth factor receptor; TKI — tyrosine kinase inhibitors; RT — radiotherapy; WBRT — whole brain radiotherapy; SRS stereotactic radiosurgery; ALKi — anaplastic lymphoma kinase inhibitors; IC — intracranial; PFS — progression free survival; ORR — objective response ratio

Table 4. Studies about immune checkpoint inhibitors (ICI) and radiotherapy (RT) for non-small cell lung carcinoma (NSCLC) patients with brain metastases (BMs)

Author	Design	Treatment	Local control	OS	RN
Chen, 2018[93]	Retrospective 260 pts	SRS SRS + ICI sequential SRS + ICI concomitant		12.9 m 14.5 m 24.7 m p: 0.021	
Shepard, 2019[94]	Retrospective 51 pts	SRS SRS + ICI	HR: 2.18 p:0,11	HR: 0.99 p:0.99	p: NS
Ahmed, 2017[95]	Retrospective 17 pts	SRS pre ICI SRS post ICI	57% 0%	 HR: 9.2 p: 0.006	p: NS
Kotecha, 2019[96]	Retrospective 150 pts	SRS + ICI concomitant SRS + ICI delayed	86% 65%	32 m 29 m p: 0.012	
Schapira, 2018[97]	Retrospective 37 pts	SRS+ICI concomitant SRS+ICI sequential	100% 72,3% p: 0.016	48% Prior 35% After 0% p: 0.08	No toxicities grade ≥ 3
Hubbeling, 2018[97]	Retrospective 163 pts	SRS SRS + ICI			p: NS

Pts — patients; SRS — stereotactic radiosurgery; HR — hazard ratio; m — months

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