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Stereotactic Radiosurgery and Targeted Therapies for Brain Metastases from Solid Cancers

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Authors' contributions

This work was carried out in collaboration among all authors. Authors BP and ET designed the study, wrote the protocol and the first draft of the manuscript. Authors AK, DS, YB and US managed the analyses of the study. Authors AK and YB managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Perpetual advances in the diagnostic tools, local plus systemic cancer treatments, and ensued lengthened survival times led to striking increments in the incidence rates of brain metastases (BMs), with a collective incidence range of 20-40% for all solid cancers. Stereotactic radiosurgery (SRS) and innovative molecularly targeted therapies are continuously gaining growing significance in the triumphant management of BMs, as the brain represents a sanctuary site for the vast majority of the conventional cytotoxic chemotherapies. In this scenario, the molecularly targeted agents appear to be an attractive alternative to traditional chemotherapeutics as they can modulate cancer metabolism and progression and exert synergism with radiation therapy. Therefore, the

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present paper intends to sum up the accessible proof on the consolidated utilization of SRS and molecularly targeted agents in the precise management of BMs from certain solid cancers, specifically the non-small-cell lung, breast, and renal-cell carcinomas, and malignant melanomas.

Keywords: Brain metastases; stereotactic radiosurgery; targeted therapy; tumor control; toxicity.

1. INTRODUCTION

Marked advancements in diagnostic tools, as well as the local and systemic cancer treatments, did not only lengthened survival times, but regrettably, they also led to notable increments in the incidence rates of grimly prognostic brain metastases (BMs), with an overall incidence range of 20-40% for all solid cancers considered collectively [1]. The current treatment instructions for patients presenting with BMs typically consolidate various blends of surgery, whole-brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS) depending on the number, size, and localization of the BMs, patients' performance, comorbid conditions, and primary disease status [2-3]. Although it is plausible to achieve local control rates up to 94% with SRS, yet, largely due to the uncontrolled extracranial metastases, the prognosis of such patients is usually bleak with the estimated median and 2-year survival rates of less than 1-year and nearly 8%, respectively [4,5].

Molecularly targeted agents have become an attractive alternative to traditional chemotherapeutics as they can modulate cancer metabolism and progression, and exert synergism with radiation therapy [6,7]. Because the addition of targeted agents increased the locoregional and systemic tumor control rates and ensuant survival outcomes, it suited conceivable to integrate these agents to WBRT and/or SRS of BMs from various tumor primaries. Because such endeavors may substantially enhance the BM control rates and reduce the associated deaths, we planned to review the current status of targeted agents combined with SRS for patients presenting with BMs of particular cancers.

2. DATA COLLECTION METHODOLOGY

We attempted to identify all convenient studies on the subject from January 2000 to December 2020, as this was a comprehensive literature review on the applications and outcomes of concurrent or sequential usage of the targeted agents and SRS. For this purpose, we searched PubMed for 'targeted agents', 'targeted therapies', 'brain metastases', 'radiosurgery', 'stereotactic radiosurgery', or 'SRS' terms, and deliberately surveyed the selected literature to fulfill an objective discussion on the issue.

3. NON-SMALL CELL LUNG CANCER

Sixteen to 34% of all patients with non-small cell lung cancer (NSCLC) experience BMs during the disease course, which may increase up to 54% for patients presenting with adenocarcinoma histology [8,9]. Moreover, about 40-50% of all BMs originate from lung cancers when all pathologies are considered collectively [9]. Of these, almost half of all BMs present at diagnosis, with up to 60% of them being the sole site of distant metastatic disease site [10]. Notwithstanding the disturbing reality that the NSCLC-related BMs are regularly multiple, practically 30% to 35% manifest as solitary lesions [11].

NSCLCs should not be noticed as an indivisible disease entity even in the same histologies, as it is conceivable to distinguish many oncogenic mutations with differential effects on the results. A comprehensive study by Kris et al. [12] illustrated the availability of actionable oncologic driver mutations in 64% of the study cohort presenting with BMs of lung adenocarcinomas. In light of such pertinent proof, the National Comprehensive Cancer Network 2019 guidelines recommended the extensive testing of NSCLC tissues for EGFR, KRAS, HER2, ALK, ROS1, MET, BRAF, RET, and NTRK mutations [13].

The first and the most frequently studied mutation is the EGFR, which is overexpressed in 15% to 50% of NSCLCs [14]. EGFR mutation status is of specific significance regarding the effectiveness of tyrosine kinase inhibitors (TKIs). Radiotherapy may potentially disrupt the blood-brain barrier (BBB) and increase the ability of EGFR-TKIs to penetrate through the BBB, which may augment the radiosensitivity of tumor cells, with EGFR-mutant cells being more radiosensitive than their wild-type counterparts. Hypothetically, the mutual use of RT and TKIs might be exceptionally productive because of these synergistic effects. In support, TKIs were

shown to be more effective in EGFR mutant NSCLC patients who underwent WBRT and erlotinib for BMs [9]. The phase III RTOG 0320 trial has reported significantly increased grade 3 to 5 toxicity after the addition of erlotinib to WBRT and SRS, without any survival advantage [15]. Nevertheless, Magnuson et al. [16] reported that the patients with NSCLC BMs with EGFR mutations who received SRS followed by EGFR-TKI had the best overall survival times contrasted with those receiving WBRT followed by EGFR-TKI or EGFR-TKI followed by SRS/WBRT.

Another vital target for NSCLCs is the anaplastic lymphoma kinase (ALK) gene rearrangement that is detectable in nearly 2-7% of the NSCLC patients [17]. Because the ALK inhibitors prolong the survival times, it has been indicated that the cumulative BM rate in ALK-positive NSCLC patients (58.4% at 3 years) was higher than the ALK-negative cases [18]. ALK inhibitors can efficiently treat BMs as they are, in general, small molecular drugs that can competently pass the BBB. Johung et al. [19] indicated that the combined utilization of ALK-targeted therapy and radiotherapy was able to lengthen the median overall survival durations up to 49.5 months in ALK-positive NSCLC patients with BM. The first generation ALK-TKI crizotinib is an inhibitor of ALK, Met, and Ros1 that is recommended as the first-line treatment for ALK-rearranged or Ros1 mutated metastatic NSCLCs. Nonetheless, on the grounds that the efficacy of crizotinib in intracranial lesions was weaker than in extracranial lesions [20], the second (ceritinib, alectinib, and brigatinib) and the third generation ALK-TKI (lorlatinib) have been studied for ALK-rearranged or Ros1 mutated NSCLC BMs, with overall intracranial response rates of 35% to 73% [21,22]. Costa et al. [20] found that compared with crizotinib alone, the combination of radiotherapy and crizotinib significantly increased the overall response rate (18 versus 33%) and prolonged the median time-to-tumor progression of BMs (7 versus 13.2 months). Furthermore, other studies showed that the progression-free survival was improved from 3-4 months with crizotinib alone to 7-27 months with ALK-TKI and RT combinations [22,23]. Despite prospective randomized proof is still lacking, yet, available evidence advises the combination of ALK-TKIs and SRS as a safe treatment option with durable brain control rates [19,21,24,25]. However, to conclude more wisely, the results of large-scale studies addressing the efficacy and toxicity of various TKIs and SRS combinations should be waited to uncover the genuine worth of such treatment strategies for BMs of NSCLCs with oncogenic driver mutations.

Latterly, Yomo et al. researched the influence of post-SRS EGFR-TKI use on the efficacy and toxicity of SRS for BMs from lung adenocarcinomas through using the Japanese Leksell Gamma Knife (JLGK) 0901 study dataset [26]. The authors employed the propensity score matching (PSM) analysis to discover the influence of concurrent or post-SRS EGFR-TKI use on intracranial disease recurrence, OS, neurological death, and SRS-related complications. A total of 608 lung adenocarcinoma patients were eligible, of whom 238 (39%) had received EGFR-TKI concurrently or after the SRS. There were 200 patient pairs with/without post-SRS EGFR-TKI use in the PSM analysis. The median BM volume was larger (0.8 versus 0.6 mm^3; $P < 0.001$) in the TKI group, while both groups received a median dose of 18 Gy SRS prescribed to the 50% isodose line. Although the distant intracranial recurrences were more likely in the EGFR-TKI cohort (HR: 1.45; $P = 0.005$), the authors concluded that EGFR-TKI usage exhibited significantly superior median OS (25.5 versus 11.0 months; HR: 0.60; $P < 0.001$), with comparable SRS-related complication rates between the two groups. Similar results were additionally confirmed by Cho and colleagues' recent analysis in a cohort of 496 patients who received TKIs or immunotherapies. The authors reported significantly longer OS times with Gamma Knife SRS and one of TKIs or immunotherapies than the Gamma Knife SRS alone [27].

Osimertinib is a third-generation EGFR-TKI that targets activating EGFR mutations as well as the T790M resistance mutations. Osimertinib has exhibited more vigorous systemic activity than the first and second-generation TKIs and better BBB penetration, which is of basic imperativeness for the treatment of NSCLC-related BMs. Osimertinib was approved as first-line therapy for EGFR-mutant NSCLCs in April 2018 after the announcement of the results of the phase III FLAURA trial [28]. Although the FLAURA trial's results demonstrated significantly superior median progression-free survival times with osimertinib (18.9 versus 10.2 months; $P < 0.05$) than with the first-generation drugs gefitinib or erlotinib, yet, this trial included only the patients with stable or treated BMs at the time of randomization. Recently Xie et al. [29] compared the clinical outcomes of patients experiencing progressive BMs treated with osimertinib alone

with those treated with cranial radiotherapy plus osimertinib. Receiving radiotherapy before the commencement of osimertinib for patients with progressive BMs did not prolong either of the time-to-failure-, progression-free survival and OS endpoints in this study. However, contrasting with these results, Park et al. [30] prospectively evaluated the efficacy of osimertinib 160 mg in T790M-positive NSCLC patients and showed significantly improved overall response and overall survival rates for patients with progressed BMs on past EGFR TKI treatment, particularly those previously managed with cranial radiotherapy (p= 0.04). The ongoing phase II OCEAN trial will include 65 patients (T790M cohort, 40 patients; first-line cohort, 25 patients) with radiotherapy-naïve EGFR mutant NSCLC BMs [31]. The primary and secondary endpoints are determined as the response rate of BMs and progression-free survival and the response rate of the brain, respectively. If the eagerly awaited results of the OCEAN study are positive, then avoidance of radiotherapy may be recommended to patients harboring EGFR mutant NSCLC BMs.

4. BREAST CANCER

Breast cancers (BCs) represent the second most prevailing cause of cancer-related BMs following the lung cancers [32]. The very recent report from the Epidemiological Strategy and Medical Economics (ESME) research program in a gathering of 16,703 metastatic BCs revealed that the 4,118 (24.6%) patients presented with (7.2%) or developed (17.4%) BMs with a median BM-free survival of only 10.8 months [33]. Results of this examination uncovered that the incidence, kinetics, and prognosis of BM in such patients were firmly influenced by the tumor molecular subtypes. The cumulated 24 months BM incidence rates were 14.4%, 29.2%, 49.0%, and 44.8% for patients with HER2-/HR+, HER2+/HR+, HER2+/HR−, and triple-negative tumors, with continued incidence increment for all four tumor subtypes without any time-dependent incidence flattening. The multivariate analysis results indicated an independent connection between the BC molecular subtype and BM-free survival, where HER2+/HR- and triple-negative tumors badly had 2.01- and 1.57-times higher risk of BM-related deaths contrasted with their HER2-/HR+ counterparts.

Trastuzumab, the first anti-HER2 antibody, was proved to enhance the extracranial disease control and survival rates in HER2+ metastatic BCs [34]. Albeit roughly 55% of all HER2+ BC patients will incur BM with an overall 4-fold higher BM risk compared to HER2- patients [35,36], yet, BBB penetration capacity of trastuzumab is extremely limited due to its large molecular weight (~148kDa), such that the cerebrospinal fluid level was shown to be 300-fold lower than its serum levels [37]. Nevertheless, preclinical data propose augmented penetrability for trastuzumab after fractionated and high-dose single-fraction radiotherapies, with changes persisting for days to months. In support, Stemmler et al. reported that the cerebrospinal fluid levels of trastuzumab were raised from 420:1 to 76:1 after either WBRT or SRS [38].

Trastuzumab emtansine (T-DM1) is an FDA approved targeted therapy for metastatic HER2+ BC patients who previously underwent taxanes and trastuzumab, which promoted the objective response and median survival rates by 12.8% and 5 months, individually [39]. T-DM1 is an antibody-drug conjugate that uses the trastuzumab antibody to deliver the mysantine (DM1) to antigen-expressing tumors, which provokes mitotic catastrophe and apoptosis in a 25- to 4,000-fold more potent manner than presently accessible chemotherapeutics [40-44]. However, regrettably, accessible proof proposes that the utilization of T-DM1 with SRS increases the symptomatic radiation necrosis rates from 6%-11% [41,42] to 39.1%-50%, which appears to be more prominent with concurrent SRS and T-DM1 usage than their sequential administration (50% vs. 28.6%) [45]. Likewise, T-DM1 may lead to severely symptomatic brain edema when combined to the SRS either concurrently or sequentially [46,47]. Subsequently, in light of the fact that the correlation between the severe brain edema/necrosis and the utilization of SRS plus T-DM1 is quite salient, excessive care ought to be consumed for their usage in patients presenting with BC BMs.

Better BBB penetrating HER2-targeted TKIs have been additionally researched in clinical trials, like lapatinib, afatinib, epertinib, neratinib, tucatinib, and pyrotinib. Among those, lapatinib is an orally administered small-molecule dual tyrosine kinase inhibitor that targets EGFR-1 and HER2 pathways simultaneously. Even though the overall response rate of lapatinib is only 6% in BC BMs [48], yet, this rate was shown to increase to 38% when combined with capecitabine [49]. The LANDSCAPE trial was a phase II study that examined the efficacy of lapatinib plus capecitabine in HER2+ patients

presenting with previously untreated BMs [50]. The results of this trial suggested up-front lapatinib plus capecitabine combination as a feasible first-line treatment option alternative to cranial radiotherapy for HER2+ BC BMs. Essentially dependent on these outcomes, Parsai et al. analyzed the results for patients undergoing SRS for HER2+ BMs who also received lapatinib, and reported that the addition of concurrent lapatinib to SRS was associated with significantly increased BM control rates in BMs ≥ 1.10 cm^3, but not those < 1.10 cm^3 [51]. Any use of lapatinib was not only associated with significantly extended survival times (27.3 versus 19.5 months for SRS-alone; P = 0.03), but additionally, the 12-month risk of radiation necrosis was likewise consistently more favorable in the lapatinib group (1.3% versus 6.3% for SRS-alone; P < 0.01). In general, the results of accessible studies on the efficacy of other BBB penetrating HER2-targeted TKIs are favorable. Yet, the results of large-scale prospective studies are required to reveal their actual value on the BMs of HER2+ BCs before reaching remark conclusively.

5. MALIGNANT MELANOMA

About 50% of all advanced malignant melanoma (MM) patients inevitably develop BMs, where the its prevalence soars to 75% in autopsy series [52,53]. BMs from MMs usually present as multiple manifest lesions accompanied by many more microscopic foci, and such patients have a grim prognosis with an estimated survival of fewer than six months [54]. Because the MM cells are relatively resistant to regular doses of WBRT, SRS has become the universally appreciated treatment choice, even for multiple BMs, if worthwhile [55,56].

The gene transcription and mRNA translation regulator BRAF is a proto-oncogene that is mutated in nearly 50% of all MMs [57]. It has been clearly shown that BRAF-mutant melanoma patients have a 2-fold (24% versus 12%) increased risk of BM development contrasted with their BRAF wild-type counterparts [58]. Because patients presenting with active BMs were prohibited from the vast majority of the clinical trials, our information about the viability of BRAF-inhibitors in MM originated BMs is restricted. Results of past retrospective investigations utilizing single-agent therapies with dabrafenib and vemurafenib exhibited intracranial overall response and intracranial disease control rates ranging between 42-50% and 66%-83%, respectively [59-62]. In 2019, Holbrook and colleagues announced that the combination of encorafenib and binimetinib was capable to achieve a new response in 8 (33%) of 24 patients, with a median response duration of 22 weeks [63]. This study is of particular importance as 21 (88%) of the 24 subjects treated with the novel combination had previously received BRAF/MEK inhibitors, which underlines the potential viability of rechallenge with BRAF/MEK inhibitors in such patients.

Hitherto, 3 phase II trials investigated the efficacy of BRAF/MEK inhibitors in previously treated and treatment naïve MM BMs [64-66]. The BREAK-MB study was a phase II trial that enrolled 172 BM patients with BRAF V600 mutated MM: 89 and 83 patients with and without previous BM-directed local therapies, respectively [64]. The authors reported that dabrafenib had a significant activity with an acceptable safety profile on BMs irrespective of whether they were treatment-naive or progressive BMs after past local treatments. McArthur et al. reported the results of another phase II trial evaluating the efficacy of vemurafenib in patients with/without prior treatments for BMs from BRAF mutated MMs [65]. The results of this study revealed clinically meaningful response rates to vemurafenib without excessive neurological toxicity. The COMBI-MB was a phase II clinical trial designed to assess the safety and efficacy of dabrafenib combined with trametinib in 125 patients with BRAF V600 mutated MM BMs [66]. In this study, Davies et al. announced that dabrafenib plus trametinib combination was active with a manageable safety profile in BRAFV600-mutant MM BMs, although the median response duration was relatively short.

Inhibition of BRAF has been associated with radiosensitization in vitro through increased the G1 cell cycle arrest rates by the interference of the MAPK/Erk signal transduction pathway in V600E mutant MM cell lines [67,68]. Besides, radiation therapy may enhance the uptake of BRAF inhibitors by transiently disrupting the BBB. Although various researchers examined the clinical efficacy and safety of radiotherapy and BRAF inhibitors in BMs from BRAF V600 mutated MM patients, yet, almost all are small-scaled retrospective studies rendering the achievability of conclusive remarks quite difficult. Narayana et al. reported that 48% of BMs had a complete response after vemurafenib plus WBRT or SRS in 12 patients with 48 BMs, with a median overall survival of 13.7 months [69].

Ahmed et al. administered vemurafenib and SRS concurrently in a group of 24 patients and reported 92% and 75% BM control rates at 6- and 12-months, respectively [70]. Xu and colleagues examined the impact of BRAF mutation status and the use of BRAF inhibitors in conjunction with brain SRS [71]. The median largest dimension of treated BM and the median margin radiation dose were 6 mm (range 1.1–59.7 mm) and 20 Gy (range 13–23 Gy), respectively. The authors divided 65 eligible patients into 3 three groups: Group A, those with mutant BRAF without BRAF inhibitor treatment (13 patients); Group B, those with mutant BRAF with BRAF inhibitor treatment (17 patients); and Group C, those with wild-type BRAF (35 patients). The local control rate was improved in the patients treated with SRS in conjunction with BRAF inhibitor (Group B) compared with patients with wild-type (Group C) or with BRAF mutation but no BRAF inhibitor (Group A) as an adjunct treatment for BMs. At 1 year, the local tumor control rate in Groups A, B, and C was 82.4%, 92%, and 69.2%; P = 0.022, respectively. Ly et al. hypothesized that BRAF inhibitors would improve local control in previously treated BMs from MMs those undergoing a single fraction SRS of a median dose of 20 Gy [72]. Patients with a proven BRAF mutation were treated with a BRAF inhibitor. Fifty-two patients were managed for 185 BMs and 13 tumor beds. The 1-year local control rate for BMs was significantly higher in the patients with BRAF mutation plus BRAF inhibitor plus SRS contrasted with those without BRAF treatment (85.0% versus 51.5%; P= 0.0077). Latterly, Martins et al. analyzed BRAF/MEK inhibitors initiated during the 9-weeks before or after SRS in MM patients presenting with newly diagnosed BMs [73]. The authors demonstrated that the addition of BRAF +/-MEK inhibitors to SRS was associated with significantly lengthened median overall survival times (24 versus 7 months; P= 0.0001). Additionally, the results of a recently reported systemic review by Weaver et al. showed that BRAF/MEK inhibitor was well tolerated with substantially improved local control, distant control, and overall survival rates in the absence of notable toxicity increments when joined with SRS for the treatment of BMs from MMs [74].

Although the toxicity is of considerable concern for the concurrent or sequential use of BRAF/MEK inhibitors and SRS, neurologic symptomatic intracranial toxicity risk appears low, which is accounted for to be comparable with SRS alone toxicity rates [75]. Brain necrosis and hemorrhage comprise the specific worries for SRS alone and SRS plus BRAF/MEK inhibitors-related toxicity. Ahmed et al. [70] reported only one case with intracranial hemorrhage requiring craniotomy two months after the SRS in a group of 24 patients with 80 BMs. Although intracranial hemorrhage is frequently associated with melanoma metastases, Ghia et al. found no SRS-related alterations on the risk of intracranial hemorrhage [76]. Despite the leading cause of neurologic death was intracranial hemorrhage in their series, Ly et al. reported that 60% of such patients never received BRAF inhibitors [72]. However, Gaudy-Marqueste et al. reported no toxicities from the combination, despite most patients (20 of 30) receiving concurrent BRAF inhibitors and SRS [77]. Therefore, in general, the accessible SRS and BRAF/MEK inhibitors data do not indicate an increased risk of clinically significant hemorrhage. Considering the brain necrosis, Narayana et al. [69] reported one case of potential radionecrosis among 6 patients who received vemurafenib before or after SRS. In another study, Peuvrel et al. [78] reported revealed perilesional edema and radionecrosis in two patients who received 20 Gy SRS and vemurafenib started in the past 3 months. Similarly, Liebner et al. [79] likewise reported 2 patients with radionecrosis after SRS and vemurafenib combination. Consequently, depending upon the current proof, the risk of brain radionecrosis does not appear to increase beyond that of SRS alone with the addition of BRAF/MEK inhibitors to SRS in such patients.

6. RENAL CELL CARCINOMA

The 5-year cumulative incidence of BM for renal cell carcinoma (RCC) patients is 7-13%, which exhibited a significant increment in the most recent twenty years as a result of the wide accessibility of more salutary imaging tools and implementation of survival enhancing systemic agents to the therapeutic algorithm [80,81]. Because RCC is radiobiologically resistant to conventionally fractionated and mildly hypofractionated WBRT, considering together with the increased WBRT-induced neurotoxicity risk, SRS has become the favored local non-surgical management of RCC BMs [82].

Remarkable improvements in the systemic therapy of metastatic RCC let the combinations of immune checkpoint inhibitors (ICIs) or ICI + TKI as the current standard first-line treatments for metastatic RCC patients. However, TKI monotherapy still remains as an efficient therapy

for patients presenting with refractory disease and as a first-line treatment for immunosuppressive or frail patients. To date, numerous agents have been approved for the metastatic RCC, yet, their BBB penetration capacities are limited, including the sorafenib, sunitinib, and pazopanib: namely the VEGF-TKIs. Hypothetically, the utilization of TKIs with RT may enhance RT efficacy through inhibiting the angiogenesis factors Ang-2, Ang-1, and Tie-2, and tumor growth factor TGFα, and mitogen-activated protein kinase (MAPK) pathways.

Only three comparative retrospective studies investigated the efficacy of TKIs on RCC BMs when combined with the SRS or WBRT [83-85]. Bates et al. reported that addition of concurrent TKI to radiotherapy was not linked to any improvement in local control or overall survival rates in a small cohort of only 25 patients [83]. Starkly conflicting with these results, Verma et al. found that the usage of TKI was associated with significantly improved median overall survival of 23.6 months as opposed to 4.41 months with no-TKI use (P = 0.0001) in 81 RCC patients with 216 BMs [84]. The median BM size was 5 mm (2-23 mm) in this study. Likewise, Cochran et al. examined the outcomes of 61 patients with RCC BMs who underwent Gamma Knife SRS and suggested that the addition of TKI to SRS was connected to significantly improved median overall survival (16.6 versus 7.2 months; P=0.04) and 14-year freedom from local failure (93% versus 60%; P = 0.01) rates respectively [85]. Additionally, the multivariate analysis results unveiled the addition of targeted agents (HR: 3.02, P = 0.003) as the unique predictor of enhanced survival results.

Cabozantinib is a novel effective multitargeted TKI that is active on the VEGF, MET, and AXL axis in metastatic RCCs [86]. Cabozantinib can easily penetrate through the BBB and exert direct actions on BMs as MET expression is significantly higher in BMs than the index RCC site [87-89]. Peverelli et al. examined the results of 12 patients with RCC BMs treated with cabozantinib and reported that all 5 patients who received cabozantinib plus brain-directed approach enjoyed the controlled BMs with no additional severe toxicity [90]. Recently, Negrier et al. announced the results of two cases with recurrent RCC BMs after SRS plus targeted agents and immunotherapies [91]. Underscoring the demand for the conduction of prospective trials with cabozantinib for patients presenting with treatment-resistant and/or treatment-naive RCC BMs, the authors reported that orally administered cabozantinib was able to regress RCC BMs that were resistant to past SRS radiation and angiogenic TKIs.

7. DISCUSSION

The addition of the targeted therapies to the treatment algorithms of certain advanced cancers produced significant improvements in the disease control, survival, and quality of life parameters, particularly in those patients presenting with extracranial metastases. As a distinct difference, despite the proof is quickly aggregating, yet, our present information on the safety and efficacy of targeted therapies in the treatment of BMs from various solid cancers remains to be limited. But accessible data emphatically propose that targeted agents achieved noticeable progress in augmenting the BM control rates and the associated reduction in the neurologic deaths (Fig. 1), chiefly in the scenario of combined use of targeted agents and the SRS.

Though overall promising, still, there is too much work to be done to achieve the most favorable outcomes with the combination of targeted agents and SRS. For example, no strong consensus exists on the administration timing of the targeted agents relative to SRS. Likewise, we do not possess enough evidence to recommend the use of fractionated or single fraction SRS together with such agents, which may lead to the best BM control and survival outcomes. Because of their molecular size and chemical structure, better penetration of the BBB remains to overcome to achieve more effective cerebrospinal fluid concentrations for most, if not all, targeted agents. Unfortunately, to date, most targeted agents and SRS combinations have been assessed for their efficacy after failures to past WBRT, which unquestionably represents a poor-outcome group. Different blends of SRS plus targeted agents and novel immunotherapies deserve to be researched in the immunotherapy era. Finally, although the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) has been recommended for routine usage, still, we do not have a current and established response criterion for BMs. Therefore, universally validated response assessment tools need to be urgently developed for comparing the results of different studies with a standard method and reveal their precise scientific values.

Table 1. Studies of targeted agents and stereotactic radiosurgery for brain metastases

Reference	Primary	Patients (N)	Targeted agent	Overall survival (months)
Kim et al. [92]	NSCLC	18	Erlotinib/Gefitinib	37.1
Sperduto et al. [15]	NSCLC	41	Erlotinib	6.1
Parsai et al. [51]	Breast	47	Lapatinib	27.3
Yomo et al. [26]	Breast	24	Lapatinib/trastuzumab	19.5
Xu et al. [71]	MM	17	Vemurafenib	23.0
Wolf et al. [93]	MM	31	Dabrafenib	11.2
Staehler et al. [94]	RCC	51	Sorafenib/Sunitinib	11.1
Cochran et al. [85]	RCC	24	TKI/mTORi/bevacizumab	16.6

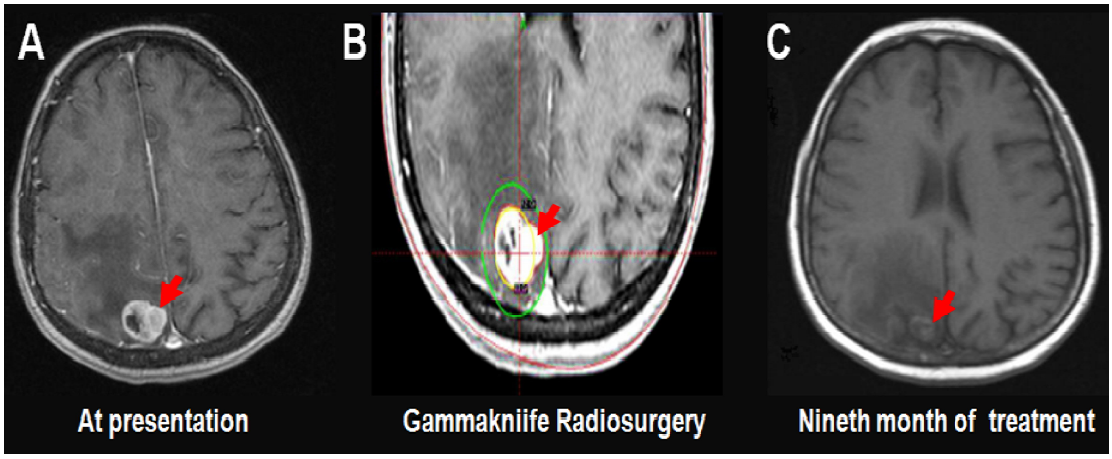

Fig. 1. The pretreatment MRI (A) scan of a 57-year-old female patient with a large right-sided parietal lobe brain metastasis from ALK-mutant non-small-cell lung carcinoma treated with definitive Gamma Knife radiosurgery (B) plus crizotinib. An MRI 9 months after treatment demonstrates significant regression of the brain metastasis (C)

8. CONCLUSION

In conclusion, albeit too much work is assuredly required to be done, in any case, the accessible information counsels a significant role for targeted agents for the improvement of the results acquired with SRS for BMs of various origins [15,26,51,71,85,92-94] (Table 1). Therefore, since the incidence of BMs will continue to grow as a result of more effective systemic and local therapies, both radiation oncologists and medical oncologists should value sustained cooperation as the sole solution to overcome many obstacles and to attain the most beneficial outcomes in patients presenting with BMs from various primaries.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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