Multiple Brain Metastases

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16.1 Selecting Optimal Indications for Radiosurgery in a Rapidly Evolving Landscape

Since 2014, ASTRO contributed, by a "choosing wisely" publication policy, to identifying radiosurgery (RS) as the preferred option for patients presenting *a* "*limited number*" of brain metastases (BMs), namely, *up to four lesions* [1]. In contrast, for patients with multiple BMs, whole-brain radiotherapy (WBRT) continues to be a "first option" for most oncologists, even if this attitude is clearly decreasing [2, 3]. Furthermore, most neuro-oncologists suggest the role of many other parameters, such as the general and neurological status, extracranial disease control, size and/or volume of BMs, molecular profile of the primary and secondary tumors, and the expected outcome in the decision-making process.

Actually, over the past decade, a series of key events have occurred. Firstly, because of the large dissemination of "radiosurgery" systems, an increasing number of cancer centers had the possibility to propose an alternative to whole-brain radiotherapy (WBRT) for their patients presenting multiple BMs; not only Gamma Knife (GKN) or CyberKnife (CKN) devices, which were fully developed for RS, but also LINAC-based machines "dedicated" to stereotactic radiotherapy (SRT) are now available, even in hospitals of small-intermediate size. At the same time, more asymptomatic patients will present with multiple BMs, due to the increased access to MRI for neurological symptoms or simply as a "checkup," or before inclusion in clinical trials.

Secondly, since the "enrichment" of diagnostic and treatment opportunities of BM patients is now available with the routine use of molecular profiling and frontline immunotherapies, the outcome of an increasing part of them has been significantly improved, mostly in melanoma patients. Mainly immune checkpoint inhibitors (ICIs) have dramatically changed their prognosis, with durable intracranial overall response rates (ORR) almost comparable to extracranial results [4]. This positive trend is going to be translated, at a lower level, in "targetable" metastatic lung cancer patients with EGFR mutation [5] and ALK rearrangement [6], with impressive results. ICIs are also evaluated in retrospective and prospective studies as first-line therapy for metastatic lung cancer patients [7, 8]. As a consequence of the increased efficacy of these systemic treatments, more metastatic patients will be "long-term survivors" and consequently exposed to the risk of developing (new) and, mostly, multiple BMs for longer.

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Thirdly, beyond the basic calculation of the number of BMs and the RPA (Recursive Partitioning Analysis) index [9, 10], several new prognostic scores and tools are now available to better approach the outcome of metastatic patients, defining subgroups of different prognosis more precisely, from less than 3 months to more than 2 years of expected median survival. Indeed, this possibility to better predict the outcome for each type of primary, with a margin of error still recognized as too wide, is essential in the "choosing wisely" decision process [11]. Delivering WBRT to a patient with slowly evolving multiple BMs and an expected median survival of 18 months is as questionable as delivering an SRS to a patient who will present an explosion of new BMs or a leptomeningeal invasion in 3 months. Consequently, beginning with the RPA index and then refining the *Graded Prognostic Assessment index (GPA)* [12–15], new "Diagnosis-Specific" GPA indexes were published, dedicated for each histomolecular subgroup of patients, from melanoma, breast, colorectal, and lung cancers to renal cell carcinomas and sarcomas [16–20]. In parallel, the "*Velocity index*" could better predict the risk of an early indication of WBRT after an initial SRS delivery, making the latter questionable in some rapidly evolving cases [21–23]. Finally and for an optimal compromise between efficacy and toxicity, the recent concept of "*Cumulative intracranial tumor volume*" was proposed and evaluated [24, 25], not only for a prognostic evaluation but also to better exclude some RS indications: this category of patients with multiple and bulky BMs would possibly suffer more from neurological toxicities than "benefit" from RS.

16.2 Predicting Survival at "Individual" Level: Definitions, Thresholds, and Endpoints

Several prognostic tools were evaluated mainly based on RPA and then GPA scores, age, Karnofsky Performance Scale (KPS)/Performance Status (PS) score, number of brain metastases, and presence/absence of (active) extracranial metastases and either focused on expected survival (a basic "efficacy" marker) or the quality of life, the "toxicity" parameter being very heterogeneously evaluated [26]. For daily practice, the last DS-GPA classification for each histomolecular diagnosis could be proposed, since it evolves continuously over time, is user-friendly, integrates the advances in "personalized" systemic treatments, and clearly divides patients in four categories with different prognosis. Limitations include the retrospective aspect, the rapidly changing landscape of "personalized" treatments (second or third generation of targeted drugs/different anti-PD1, anti-PDL-1 molecules), and, importantly, the high spatial-temporal tumoral heterogeneity, with a possible clonal shift between primary and metastatic sites. BMs could have, in up to 50% of cases, distinctly different phylogenic origins to those of the dominant clones of the primary tumor [27], encouraging to resect operable BMs when it is functionally safe.

An interesting dynamic tool, both predictive and prognostic, was recently described: the "*Brain Metastasis Velocity*" (BMV) index, predicting clinical outcome after initial distant brain failure following upfront SRS alone. It was defined as "the cumulative number of new BMs since initial SRS/Total time between initial SRS and Time of new BMs." The subgroup with a BMV index of less than four new BMs per year presented the lowest risk of salvage WBRT, the best prognosis, and consequently the best indication for SRT [23].

Definition of the 'oligometastatic status' has evolved over time: in the initial RPA index, the "oligometastatic" status was defined by 1–3 BMs, even if the more recent DS-GPA scores consider that a patient presents "multiple" BMs from 5 to 10 BMs which are possibly "treatable" with RS up to 15 or even 20 BMs. Recently, Yamamoto and other authors strongly suggested that, for a highly selected population, patients treated with SRS presenting five to ten BMs seem to have the same prognostic as those with one to five lesions [28–31].

This highlights an important "new" parameter to consider: the "*Cumulative intracranial volume*" *(CIV)* of BMs (in mL or cm^3), which was

introduced more than 10 years ago [32] and more recently suggested as a possibly better independent prognostic indicator than the number or the largest size of BMs (more than 3 cm) [24]. For example, *a threshold of 15 cm³* was an exclusion criterion in the Yamamoto study, and some ongoing trials exclude patients with a CIV superior to 20 cm^3.

Considering only studies including patients with multiple BMs (all but one retrospective) with a median follow-up of at least 6 months, it is interesting to note that older publications reported median overall survivals (mOS) of 4–8 months, in contrast to the more recent one which identified subgroups of patients with mOS as high as 11 months [28, 33]. This could be explained both by more stringent selection criteria with a larger part of asymptomatic patients and by the efficacy of new personalized systemic treatments, particularly for the melanoma group and an increasing proportion of lung cancer patients.

Consequently, with this important part of "long survivors" (more than 9–12 months of expected OS), the choice of primary endpoints is shifting from the local/intracranial control rate to the overall survival item and, furthermore, toward quality of life and neurocognitive evaluations [34]. The longer the expected survival, the more important the items assessing patient-reported outcomes (PRO), and, ideally, both clinical toxicity (as disabling radionecrosis/leukoencephalopathy) and OS should be evaluated as co-primary endpoints. It is the case in one of the most interesting ongoing trials testing RS versus WBRT, the NCT03550391 (Table 16.1).

16.3 Combining SRT with New "Precision Medicine," Is There Still a Place for "Modern" WBRT?

Most patients with multiple BMs are also extracranially metastatic patients and candidates for systemic frontline treatments. Consequently, the question of "do we have to" and "how to combine" targeted drugs and/or immunotherapies with SRT is increasing in our daily practice. Because there is no conclusive solid data based on results of already closed prospective randomized trials, we only have the ability to analyze published heterogeneous series mostly with a limited number of patients [35, 36]. However, available data are favoring the early introduction of SRT, "combined with" the systemic personalized treatments if the latter is necessary. Furthermore, the concurrent administration of immunotherapies with frontline SRS (and a minimal dose/no steroids) for these patients with multiple BMs could not only improve intracranial control (without a significant increase in clinical toxicity) but potentially improve overall survival [37]. Focusing on melanoma brain metastases, the question of introducing SRT frontline with or as salvage after introduction of targeted drugs/immunotherapy is the object of a randomized trial (the "Become-MB" trial NCT04074096).

In this context of early delivery of "precision medicine" therapies to most patients with multiple BMs, the place of WBRT seems more debatable, even for those with more than ten BMs. Due

Table 16.1 Clinical trials comparing SRS versus WBRT in patients with more than four brain metastases

Trial number	Group	Arms	Number of lesions/ Number of patients planned	HA	Opening/end expected	Primary endpoint(s)
NCT03550391	CCTG	SRS/WB*	5–15/206	*All* HA-WB	2018/2022	Survival and neurocognition
NCT01592968	MDACC	SRS/WB	4–15/100	No HA	2012/2020	Local control and neurocognition
NCT03075072	B & W	SRS**/WB	5–20/196	HA *if possible*	2017/2022	Quality of life at 6 months

SRS stereotactic radiosurgery, *SRS*** 1 to 5 fractions, *WB* whole-brain radiotherapy, *WB** with memantine, *HA* hippocampal avoidance, *CCTG* Canada Cancer Trials Group with Alliance and NRG groups, *MDACC* MD Anderson Cancer Center, *B & W* Birgham and Women's Hospital

to the justified fear of unnecessary added neurotoxicity and the necessity of delivering WBRT during a period of 2 weeks, many oncologists are reluctant to stop or delay their systemic treatment, particularly if it is effective on extracranial metastatic disease. They will favor a shorter treatment such as SRT, with one to three fractions in a week, which will always spare more normal brain white matter than any hippocampal-avoiding (HA) modern WBRT, even if this technique seems to limit (marginally) its negative impact on some important neurocognitive functions [38]. Finally, and outside ongoing prospective trials, HA-WBRT could be proposed in some highly selected and more palliative indications (see Table 16.2 and Fig. 16.1), but clearly not as a "last option" for frail patients, in light of the QUARTZ study [39].

16.4 Ongoing Trials, Daily Practice, and Perspectives: A Case-by-Case Multidisciplinary Decision

Among the very few ongoing trials (see Table 16.1) still proposing WBRT as the "reference arm" for patients with multiple BMs (with or without memantine, with or without HA), the NCT03550391 trial seems to be the one that could best answer the two coupled questions that are still topical: What impact will a modern HA-WBRT choice have on survival and neurocognition? Other registered trials are either not yet recruiting or don't propose HA systematically in the WBRT arm or are slowly recruiting. Consequently, because there is no "level 1 evidence-based" data to definitively conclude pro or against HA-WBRT versus RS in patients with multiple BMs, a case-by-case interdisciplinary discussion will be the best option.

In daily practice, outside including patients in ongoing trials, the individual decision should integrate several key factors including clinical, radiological data (volumetric and dynamic) and also the histomolecular profile, if possible based on the more recent tissue available, as proposed in Table 16.2. For example, the "best candidate" for exclusive RS/hFSRT will meet both the following characteristics: a symptomatic patient with a favorable/intermediate expected survival and a low velocity index with "non-targetable" lesions of a "non-bulky" total cumulative volume (Fig. 16.2). Combination of RS/hFSRT and targeted drugs/immunotherapies could be preferably proposed for multiple BM patients who also present a favorable/intermediate prognostic, but needs to be controlled rapidly both intra- and extracranially with "targetable" lesions.

Table 16.2 Choosing between systemic treatments vs RS ± HFSRT vs a combination of both vs WBRT

	Systemic treatment (ST)	RS/HFSRT	Combination of ST and SRS/HFSRT*	Modern WBRT with HA
Molecular profile	Targetable	Non-targetable	Targetable	Non-targetable
Number of BMs	More than 10	4–10	4–10	More than 10
Total cumulative volume of BMs	More than 15–20 cc	Less than 15–20 cc	Less than 15 cc	More than 20 cc *(surgery if needed)*
BM velocity index	>13 new BMs/year	<4 new BMs/year	4–13 new BMs/year	>13 new BMs/year
Survival^T	>3 months	>3 months	>6 months	3–12 months
Neurological status	No symptom	Symptomatic	+/− Symptomatic	Symptomatic

Survival^T expected median overall survival based on DS-GPA dedicated index, *DS-GPA* disease-specific Graded Prognostic Assessment, *ST* systemic treatment, essentially targeted drugs and/or immunotherapies as checkpoint inhibitors, *RS* radiosurgery (1 fraction), *HFSRT* hypofractionated stereotactic radiotherapy (3–5 fractions/1 week), *HSFRT** if possible, *before* ST or "*concomitant*" with ST (within 1 half-life of the drug)

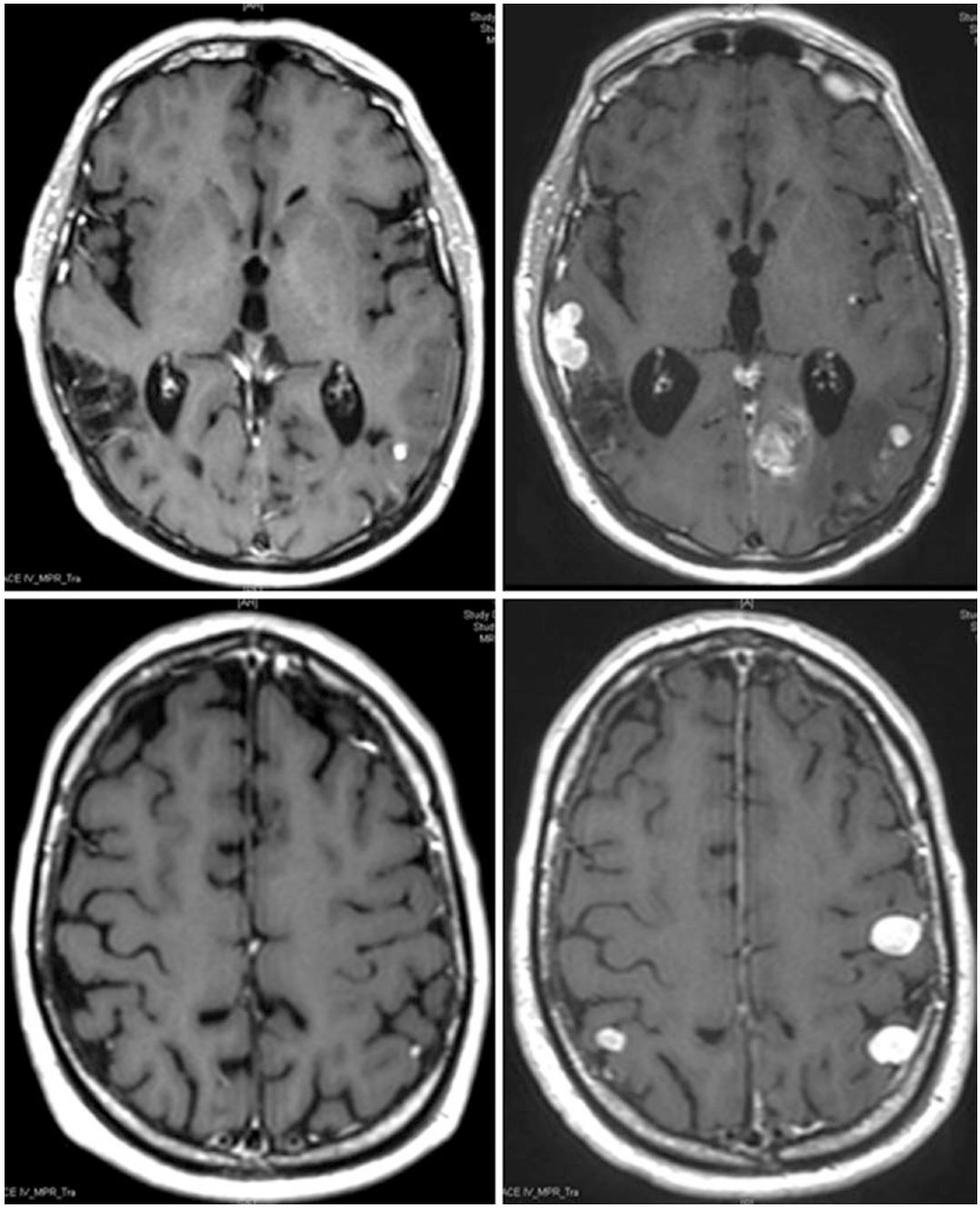

Fig. 16.1 A healthy 55-year-old patient, recently metastatic from a melanoma, progressing extracranially with an anti-BRAF anti-MEK treatment who switched to a checkpoint inhibitor (pembrolizumab). Contrary to a previously normal investigation obtained 3 months ago, the MRI showed rapid emergence of nine new lesions, some of which are not well defined. The cumulative volume was 20 cm^3 but without a definitive sign of leptomeningeal invasion. The patient underwent whole-brain radiotherapy, and ten fractions of 3 Gy were delivered in 2 weeks (between two cycles of pembrolizumab). However, the patient died quickly 3 months later due to intracranial progression

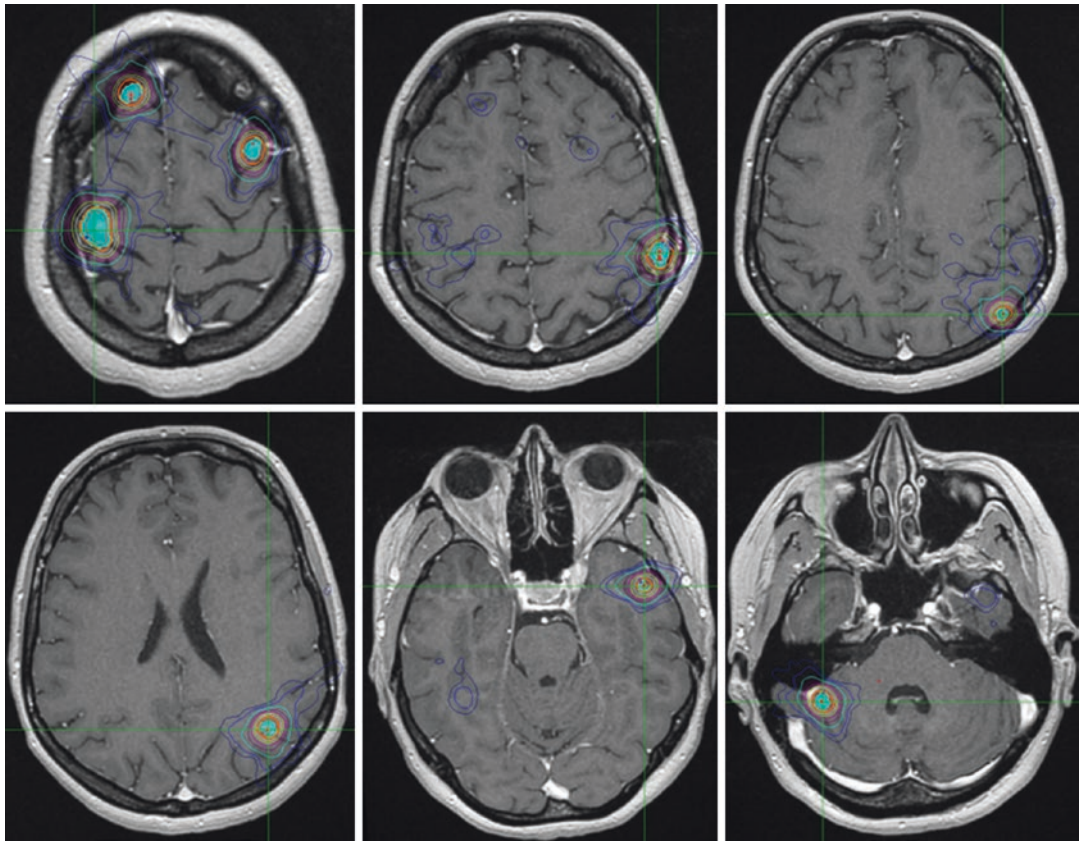

Fig. 16.2 A 35-year-old patient in good health, treated 3 years before for slowly evolving metastatic lesions of a primary carcinoid carcinoma of the lung. Multiple surgeries for "focal" secondary sites in the breast, ovary, and skin; five already known brain metastases (< 5 mm each) controlled with different lines of chemotherapy. Recently: headache, diplopia, and a new MRI showing a progression of BMs and three new BMs, the largest one near the brainstem. Total: eight different BMs but a cumulative volume of 10 cm^3, temozolomide ongoing. CyberKnife treatment was delivered: three fractions for the largest lesion and then one fraction for the other BMs. All lesions are controlled at 2 years with correction of symptoms and excellent general status

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