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Review article

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Stereotactic radiosurgery for patients with brain metastases: current principles, expanding indications and opportunities for multidisciplinary care

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Abstract

The management of brain metastases is challenging and should ideally be coordinated through a multidisciplinary approach. Stereotactic radiosurgery (SRS) has been the cornerstone of management for most patients with oligometastatic central nervous system involvement (one to four brain metastases), and several technological and therapeutic advances over the past decade have broadened the indications for SRS to include polymetastatic central nervous system involvement (>4 brain metastases), preoperative application and fractionated SRS, as well as combinatorial approaches with targeted therapy and immune-checkpoint inhibitors. For example, improved imaging and frameless head-immobilization technologies have facilitated fractionated SRS for large brain metastases or postsurgical cavities, or lesions in proximity to organs at risk. However, these opportunities come with new challenges and questions, including the implications of tumour histology as well as the role and sequencing of concurrent systemic treatments. In this Review, we discuss these advances and associated challenges in the context of ongoing clinical trials, with insights from a global group of experts, including recommendations for current clinical practice and future investigations. The updates provided herein are meaningful for all practitioners in clinical oncology.

Sections

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Key points

- Advances in imaging, patient immobilization techniques and radiotherapy-planning software have expanded the scope of stereotactic radiosurgery (SRS) for the treatment of brain metastases.
- Paradigms for determining suitability for SRS are gradually shifting away from strict thresholds of number and size of brain metastases to total intracranial tumour volume along with increased consideration of the influence of tumour histology.
- Fractionated SRS can increase efficacy while minimizing the risk of adverse radiation events, particularly for larger brain metastases; however, the optimal fractionation schedule and dosing remains to be established.
- Reliable detection of adverse radiation events, specifically distinguishing radionecrosis from tumour recurrence, remains challenging, although trials using advanced imaging approaches are under way.
- Neoadjuvant SRS might minimize the risk of leptomeningeal dissemination and simplify radiation-dose planning. Ongoing trials will better define strategies for patient selection (for example, amenable tumour types) as well as the optimal dosing, schedule and timing of SRS before surgery.
- Immune-checkpoint inhibitors and brain-penetrant targeted therapies have added to our armamentarium of treatment for brain metastases. However, further research is needed to determine the optimal sequencing of these systemic therapies in relation to SRS — or potentially whether SRS can be omitted altogether.

Introduction

Brain metastases occur in nearly 20% of all patients with cancer and are associated with substantial neurological morbidity[1,2]. Improvements in systemic cancer therapy have prolonged overall survival (OS), which has in turn led to an increase in the incidence of brain metastases owing to the extended disease course. Treatment advances have also substantially improved local intracranial control in patients with brain metastases[3–9], although the development of brain metastases still portends a poor prognosis. A collaborative priority-setting effort under the auspices of the National Cancer Institute has highlighted several unmet needs for patients with brain metastases, as well as the continued requirement for a multipronged approach for their management[10] — the current ideal being a multidisciplinary approach aimed at preventing or delaying neurological deterioration, whereas extracranial oncological care continues uninterrupted[11,12]. Of the recently developed specific indicators of the quality of interdisciplinary care for patients with brain metastases (the Brain Metastases Quality-of-Care measure, BMETS-QC)[13], three pertain to stereotactic radiosurgery (SRS). SRS has been established as a first-line treatment modality for brain metastases owing to its favourable risk–benefit profile demonstrated in randomized controlled trials (RCTs), especially for oligometastatic central nervous system (CNS) disease (one to four brain metastases), and is recommended across various clinical guidelines[3–5,8,12,14–16]. However, high-quality evidence informing the clinical management of patients with larger brain metastases[3], polymetastatic CNS involvement (≥5 brain metastases)[15] and those at high risk of development of leptomeningeal disease (LMD)[17] remains limited[12].

Advances in imaging and radiation delivery technologies have enabled fractionated SRS for brain malignancies, expanding the indications for SRS, especially for large brain metastases or those proximal to key CNS organs at risk (such as the brainstem[18] or optic pathway). These approaches, together with the potential synergy of SRS with novel systemic targeted therapies and immune-checkpoint inhibitors (ICIs), are promising[14] but require further evaluation with respect to the optimal dose and fractionation schedule, timing, treatment combinations and their sequencing. These and other avenues of investigation have been a major focus of annual meetings of several major neuro-oncology and radiation oncology societies over the past few years. Herein, we provide a comprehensive synthesis and appraisal of landmark RCTs, ongoing investigations and emerging frontiers pertaining to SRS discussed at these meetings in the context of the available literature, and provide expert insights to forge a balanced approach to integrating the evolving roles of SRS in the modern-day management of brain metastases, including in particular (1) the management of polymetastatic brain disease, (2) the advances in the diagnosis and management of adverse radiation events (AREs), (3) the potential role and optimal timing of neoadjuvant SRS, and (4) the current evidence and gaps in our understanding related to the optimal sequencing and combination of SRS with ICIs and/or brain-penetrant targeted therapies. Emphasizing the multidisciplinary nature of this disease, the goal of this Review is to present the evidence in a manner that is contextually relevant for all clinical specialities involved in the care of patients with brain metastases.

Current role of SRS in the management of brain metastases

Oligometastatic brain disease

In patients for whom surgical resection or biopsy sampling is considered unnecessary or infeasible, upfront SRS alone is currently the de facto standard-of-care (SOC) treatment for most patients with oligometastatic brain disease[3–5,8,12,14,19]. The evidence supporting this strategy is reviewed in the Supplementary Information. The clear utility of SRS in the upfront setting in patients with oligometastatic disease was first established in early RCTs (notably the Radiation Therapy Oncology Group 9508 trial) that investigated the addition of SRS to whole-brain radiation therapy (WBRT)[20–23]. Later, several RCTs, along with an individual patient-data meta-analysis[24], demonstrated superior neurocognitive and quality-of-life outcomes, as well as similar OS, in comparisons of SRS with either WBRT alone or WBRT plus SRS in patients with oligometastatic CNS involvement[20,25–28], including the JROSG 99-1 trial ($n = 132$)[26], the EORTC 29952 trial ($n = 359$)[25] and the ALLIANCE N0574 trial ($n = 213$)[28].

For surgically accessible brain metastases, particularly larger lesions and those causing neurological deficits[29], or when biopsy sampling is necessary for an updated molecular analysis of the brain metastatic cancer cells[30], the SOC is surgical resection or biopsy of the lesion of interest, followed by postoperative SRS[3,4,6,7,12,31] (Fig. 1), with the evidence reviewed in the Supplementary Information. Several RCTs have demonstrated the therapeutic roles of SRS delivered to the resection cavity, both versus observation alone[32] (with the goal of improving local control, as noted in the MD Anderson trial[32]) and versus WBRT[33,34] (with the goal of sustaining local control while reducing cognitive decline, as in the ALLIANCE/CCTG N107C trial).

Overall, substantial consensus exists between recommendations from different professional society guidelines for patients with

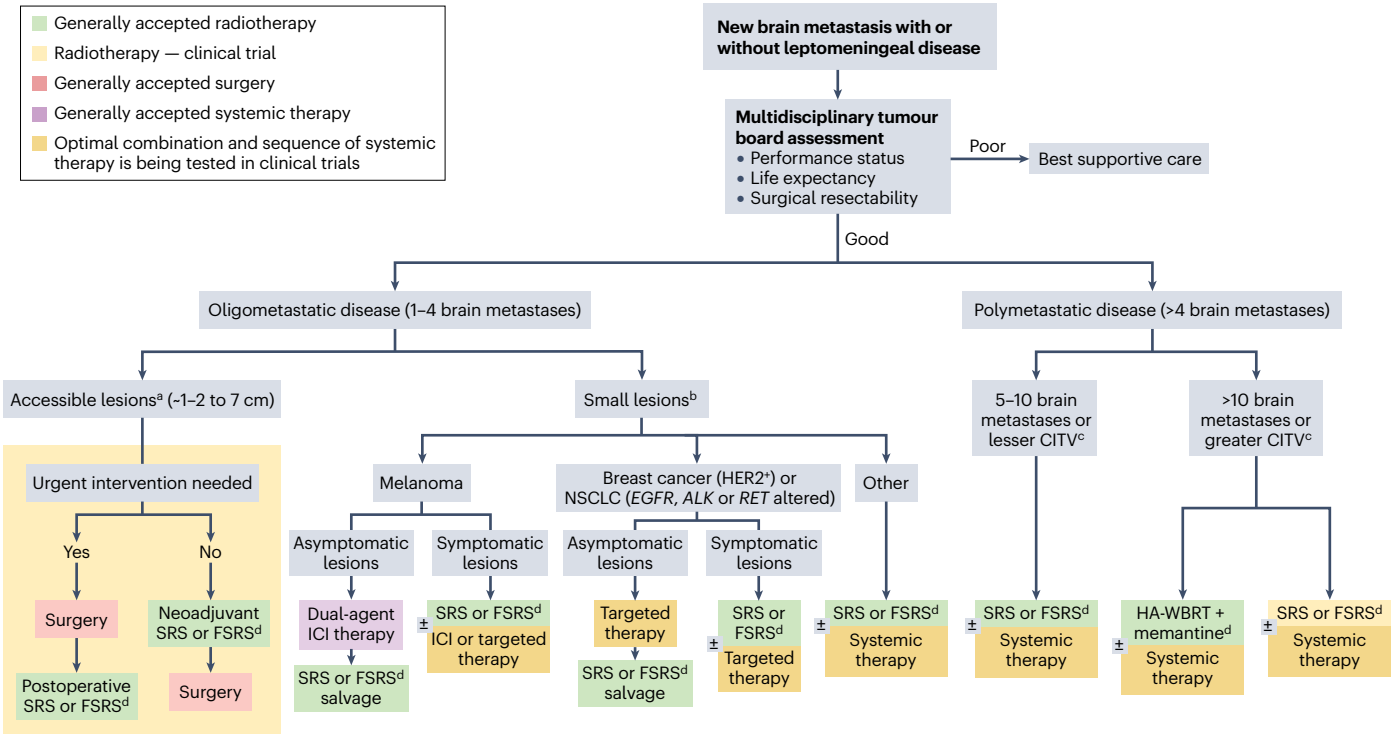

Fig. 1 | Emerging concepts challenging the current treatment paradigm for brain metastases. In selecting the optimal management approach for a patient with brain metastases, consideration must first be given to the overall performance status and life expectancy of the patient, ideally in a multidisciplinary tumour board setting. Those with poor performance status (such as Karnofsky Performance Scale score <70 or Eastern Cooperative Oncology Group Performance Status 3–4) or limited life expectancy (defined as ≤3 months in many trials) would benefit most from best supportive care. The paradigm for polymetastatic central nervous system involvement (>4 brain metastases) is different from that for oligometastatic disease (1–4 brain metastases). However, this distinction, based on number of lesions, is being challenged based on considerations of cumulative intracranial tumour volume (CITV). For patients with larger accessible lesions (approximately 1–7 cm in diameter) not requiring urgent surgical intervention, the concept of neoadjuvant radiosurgery is being evaluated against the current approach of postoperative radiosurgery. In patients with smaller brain metastases, accumulating evidence might support upfront dual immune-checkpoint inhibitor (ICI) therapy for those with melanoma (especially if asymptomatic), or upfront molecularly targeted central nervous system-active therapy for certain patients with oncogene-driven non-small-cell lung cancer (NSCLC) or HER2+ breast cancer, with stereotactic radiosurgery (SRS) reserved for salvage therapy — ongoing trials are evaluating this approach. The evidence for other histologies and/or molecular subtypes is not strong enough and ongoing investigations are limited. For local or distant intracranial tumour recurrence and/or progression, consideration should be given to advanced imaging modalities (local recurrence), possible biopsy (to confirm tumour recurrence and/or rule out tumour molecular evolution) in the setting of a multidisciplinary tumour board discussion. For all treatment options, where feasible, appropriate systemic therapy should continue uninterrupted, unless it is affecting the patient's overall health. FSRS, fractionated stereotactic radiosurgery; HA-WBRT, hippocampal-avoidance whole-brain radiotherapy. [a]Accessibility determined by the treating surgeon. [b]The exact size cut-offs for defining smaller lesions have not been established; current evidence supports these approaches for lesions <1 cm in diameter or volume <2 ml, although ongoing clinical trials are evaluating larger cut-offs (for example, CITV <15 ml, largest brain metastasis volume <14.2 ml or largest brain metastasis diameter <4 cm). [c]CITV threshold has not been firmly established, with some ongoing trials allowing up to 30 ml. [d]Regardless of the timing of radiosurgery, if the lesion or resection cavity is deemed large or is too close to organs at risk, consideration should be given to FSRS over SRS; the optimal FSRS schedule and total dose currently being investigated.

oligometastatic CNS involvement[3–5,8,12,14,19], given the high-quality evidence supporting the role of SRS for patients with most solid tumours, except lymphomas, germ-cell tumours and, historically, small-cell lung cancer (SCLC)[35] — although promising results with SRS have now also been reported for the latter[36–38]. Other, although still emerging, exceptions include certain subgroups of patients receiving CNS-active systemic targeted therapies, as discussed in depth later in this Review.

Considerations in hindsight

Together, the RCTs described above helped to construct a framework, with a proven role of SRS, for the management of oligometastatic brain disease. However, given their 'all-comers'-based enrolment approach, these RCTs set the precedent for a 'one-size-fits-all' approach, treating brain metastases from all primary tumour types in the same fashion. For example, most of the trials comparing SRS versus WBRT pooled all tumour types together but with an over-representation of non-small-cell lung cancer (NSCLC)[25–27]; yet their conclusions were broadly applied across all histologies. Later RCTs attempted to provide histology-specific and molecular profile-specific comparative outcomes[39,40].

Another consideration with the landmark trials of SRS is that they were conducted before the modern era of ICIs and CNS-active molecularly targeted therapies, which have substantially improved the disease course, not only prolonging OS, but also decreasing CNS-related

mortality and increasing the number of long-term survivors[41–43]. With improved molecular classifications, prognostic subgroups and more-effective systemic therapies, increased priority has been placed on treating brain metastases according to the tumour histology[36,37] and molecular profile[36,44,45], thereby creating a divide between the more-personalized management principles that are rapidly being integrated into current practice[46,47] and the more-generalized, histology-agnostic evidence supporting the established management framework and guideline recommendations for intracranial disease[31].

The radiation dose used in many of the RCTs of SRS is another consideration, given that intracranial progression post-SRS is still seen to occur in 10–30% of patients, and more commonly with larger-sized lesions[4,5]. The classical size-based thresholds of SRS dose (single fraction) were defined in the Radiation Therapy Oncology Group 90-05 trial, which enrolled patients with prior cranial WBRT[48]. In this trial, maximum tolerated doses of 24 Gy, 18 Gy and 15 Gy for tumours of <2 cm, 2–3 cm and 3–4 cm in maximum diameter[48], respectively, were reported in the year 2000, with minor dose modifications recommended since then based on accumulating evidence[3–5,8,12,14,19]. Considerable interest has been focused on further dose escalation, given the advances in SRS and associated technologies, as well as the clear establishment of SRS in front-line treatment of oligometastatic disease, a setting in which patients tend to have greater radiation dose tolerance[49]. This approach could potentially further improve local control, if found to be safe in several ongoing or unpublished trials (such as NCT02645487 and NCT02390518). Interestingly, in a trial in which 35 patients with large (>2 cm in diameter) brain metastases received dose-escalated neoadjuvant SRS followed by resection, the maximum tolerated dose was not reached in the cohorts with 2–3 cm tumours, and was 18 Gy in both 3–4 cm and 4–6 cm cohorts[50]. The 1-year local control rate was 76.6% overall, with only one grade 3 ARE seen[50], suggesting promise for investigation in later-phase trials. Additionally, the findings of early molecular and genomic-profiling studies, which have rapidly become crucial to medical management approaches, remain to be clinically translated and meaningfully integrated into SRS decision-making[51], although a new genomic scoring system (based on a next-generation sequencing panel) for the prediction of local control post-radiation has been reported[52].

Controversies surrounding SRS for brain metastases

Polymetastatic brain disease

Although the superior cognition-preserving profile of SRS has resulted in its establishment as a key part of SOC management of oligometastatic brain disease[23], SRS is only conditionally recommended for patients with 5–10 brain metastases and often not recommended at all for those with >10 brain metastases[4,6,8,9,12,19] (Fig. 1). This situation reflects concerns surrounding the rapidity of further intracranial progression and thus the need for subsequent treatment, the control of extracranial disease, the risk of distant failure and irradiation-related complications, all compounded by a lack of high-quality evidence[5,8]. Nevertheless, extensive effort has been placed on reappraising the role of SRS in polymetastatic disease[8,15,53]. This reappraisal has, in part, been driven by long-term follow-up data from JLGK0901, a Japanese Leksell Gamma Knife Society multi-institutional, prospective observational study (n = 1,194), which provided real-world evidence for the non-inferiority of SRS in patients with polymetastatic brain disease relative to those with oligometastatic disease[54,55]. Specifically, this study evaluated the outcomes of SRS alone with no prior WBRT in patients with five to ten brain metastases (median six lesions; n = 208) compared with patients with two to four lesions (median two lesions; n = 531), and found no significant difference in OS (median 10.8 months in both groups; HR 0.97, 95% CI 0.81–1.18; P = 0.78; $P_{\text{non-inferiority}} < 0.0001$)[54]. Moreover, an updated analysis at 48 months found no statistically significant differences in the incidence of long-term complications, including neurocognitive status and irradiation-related complications[55], suggesting that SRS is a safe and effective alternative to WBRT for patients with up to ten brain metastases.

In patients with >10 brain metastases, or those with 5–10 brain lesions but a high brain metastasis velocity[56] (a measure calculated by dividing the number of new brain metastases by time since initial treatment), consideration of the overall trajectory of the disease is necessary when deciding between SRS and WBRT. Do these patients harbour tumours with an inherently greater propensity for metastatic seeding of the brain (such as melanoma[57])? Is the overall metastatic disease burden higher? Are systemic treatment options with good brain penetrance available for that cancer type (such as for NSCLC[58,59]) and molecular subtype (such as for HER2-positive breast cancer[59])? Is the patient on concurrent treatment with a documented ongoing response of a tumour elsewhere in the body? Is the cumulative intracranial tumour volume (CITV) more important than the number of brain metastases (Fig. 1)? Regarding the latter, several studies suggest that CITV, particularly >2 ml (ref. 60), is a better predictor of OS than the number of brain lesions[15,61,62]. Currently, conventional thresholds primarily based on lesion number and size continue to be implemented in both clinical practice and ongoing trials (such as in the phase III ABC-X trial, NCT03340129), although a shift towards CITV thresholds has emerged. The <30 ml cut-off of CITV, introduced decades ago[20], is being used in several ongoing trials (such as NCT02953717 and phase III USZ-STRIKE trial, NCT05522660). The hesitancy to offer WBRT, owing to the risk of leukoencephalopathy and iatrogenic neurocognitive adverse effects, must also be weighed together with the patient's treatment history, disease course and overall prognosis[63]. For example, the individual could have received numerous lines of chemotherapy, leading to the deleterious effects of 'chemobrain' (cognitive decline noted in patients undergoing chemotherapy) before ever developing brain metastases. Moreover, the patient's extracranial disease course might be the source of functional decline[42]. Thus, a balanced, individualized approach to maximize clinical benefit while preserving brain function is required when choosing between SRS and WBRT[11].

Efforts have also been made to apply novel imaging-based strategies to optimize SRS planning in selected patients for whom WBRT can be omitted or deferred. In the phase II CYBER-SPACE trial, 202 patients with 1–10 brain lesions were randomly assigned to undergo SRS of all metastases (including new lesions emerging after initial SRS) based on either MPRAGE MRI sequences or SPACE MRI, which has higher diagnostic performance for detecting brain metastases, with the primary end point of freedom from WBRT indication (indicated for occurrence of >10 lesions, LMD or exhausted SRS radiotolerance). However, the 12-month rate of WBRT indication was similar: 78.5% with SPACE versus 76.0% with MPRAGE (HR 0.84, 95% CI 0.43–1.63; P = 0.59)[64].

Given the continued risk of intracranial progression after SRS, driven primarily by new distant intracranial disease relapse, another novel approach to consider is the addition of tumour treating fields (TTFields). An international phase III trial (METIS, EF-25) randomly assigned 298 patients with NSCLC undergoing SRS for 1–10 brain metastases to receive either TTFields with best supportive care (BSC) or BSC alone. A clear benefit in the primary end point of median time

to intracranial progression after SRS was observed with TTFields (21.9 months versus 11.3 months; HR 0.67, 95% CI 0.48–0.93; $P = 0.02$)[65]. Adverse events attributed to TTFields were mild (grade ≤2) and mainly skin related[65]. Thus, this combination strategy potentially enables postponement of WBRT to preserve quality-of-life without sacrificing efficacy.

Certain clinical scenarios might still require WBRT, such as in patients with a high number of brain metastases[53] and/or with a high rate of new lesion development over time[56], or those with poor performance status and/or short life expectancy (driven by the extent of systemic disease[53,66]). On multivariable linear regression analyses, an initial high number of brain metastases treated with SRS has been found to correspond with a higher likelihood of distal failure, a higher number of lesions found at the time of distal failure and a greater need to undergo salvage WBRT[53].

Such scenarios led to a re-evaluation of ways in which WBRT can be integrated into the clinical workflow. To this end, phase III trials involving patients with brain metastases undergoing WBRT have demonstrated a reduction in cognitive decline with the use of radiation delivery techniques intended to reduce neurotoxicity (for example, hippocampal-avoidance WBRT (HA-WBRT))[67,68] and/or concurrent neuroprotective pharmacological agents (such as the glutamate receptor antagonist memantine[69], especially in the NRG CC001 trial[70]); the latter approach provided the rationale for an ongoing trial evaluating glutamate excitotoxicity (NCT04785521). A phase III trial had reported modest cognitive benefit of donepezil (a neurotransmitter modulator) given 6 months after cranial radiotherapy, especially for those with higher baseline cognitive impairment[71].

The ongoing phase III NRG CC009 trial (NCT04804644) is comparing cognitive outcomes with SRS versus HA-WBRT plus memantine in patients with 1–10 brain metastases from SCLC. Several other RCTs are evaluating similar approaches, across diverse ranges of tumour histologies and brain lesions, including 5–15 brain metastases from solid tumours (CCTG CE.7, NCT03550391), 4–15 brain metastases from melanoma (NCT01592968), 5–20 brain metastases from solid tumours (NCT03075072), 4–15 brain metastases from solid tumours (NCT04277403) and 1–10 brain metastases from SCLC (NCT06457906). Meanwhile, the ongoing CyberChallenge trial involving patients with 4–15 brain metastases (NCT05378633), the CAR-study B trial in patients with 11–20 lesions (NCT02953717) and the WHOBI-STER trial in patients with ≥5 brain metastases (NCT04891471) are comparing SRS with conventional WBRT, all enrolling patients with various solid tumours.

However, patient accrual is known to be challenging in head-to-head trial comparisons of SRS versus WBRT[39]. A Dutch multicentre, phase III trial enrolling patients with 4–10 brain metastases was terminated early owing to slow accrual, after randomization of only 29 patients (13% of the enrolment target)[72]. Similarly, a single-institution RCT comparing WBRT plus SRS versus SRS alone for 5–20 brain metastases failed to accrue (the trial permitted >30 brain metastases identified at the time of planning MRI to be treated off-protocol), and has consequently been amended to an observational study with parallel treatment arms (NCT03775330). The phase III NRG-BN009 trial, randomly assigning patients with a brain metastasis velocity of ≥4 new lesions per year (at the time of first or second distant brain relapse following initial SRS) to SRS or HA-WBRT, was also terminated early owing to poor accrual (NCT04588246). This challenge might, in part, be related to limited clinical equipoise among both patients and clinicians. Without a comprehensive understanding of the clinical nuances, patients are more likely to lean towards interventions that 'spare the uninvolved brain'. For clinicians capable of providing both WBRT and SRS, the notion that memory and cognition are not strictly isolated to the hippocampus might deter them from offering WBRT. For example, white matter injury to the brain fornices, amygdala or corpus callosum is also associated with memory disorders[73–75]. As currently performed, HA-WBRT does not reduce radiation dose to the fornices and has limited effects on the risk of diffuse white matter leukoencephalopathy.

Overall, highly conformal radiotherapy (such as SRS or HA-WBRT) leads to a higher cognitive recovery than conventional WBRT, as demonstrated in an individual patient-data pooled analysis of the phase III N107C, N0574 and CC001 RCTs[76]. SRS for polymetastatic disease might also adversely affect cognition, albeit to a much lesser extent, and creative strategies to reduce white matter injury, such as the use of connectomics (through diffusion tractography) to optimize SRS treatment planning, are also under investigation in clinical trials (such as NCT04343157, NCT02277561 and NCT04073966) (Fig. 2). Trials evaluating biomarkers of cognitive decline are also ongoing (for example, NCT03606421 and NCT04073966).

Redefining the management of large lesions with fractionated SRS

Another evolving concept in SRS relates to the largest tumour volume that can be irradiated optimally, balancing the maximization of efficacy (that is, tumour control) and minimization of toxicity (that is, AREs). AREs — often also referred to using the more specific terms 'radiation necrosis' or 'radionecrosis' — are a classic late complication of radiotherapy, typically emerging months to years after irradiation, and can mimic tumour recurrence on MRI. Higher ARE rates have been reported in patients with tumours >3 cm in diameter treated with single-fraction SRS (18–26% at 1 year compared with 6% for smaller lesions)[77]. Thus, dose de-escalation protocols are often used for single-fraction SRS, involving scaled reduction of the radiation dose with increasing lesion volume (that is 16, 14 and 12 Gy for target volumes of <10 ml, 10–15 ml and >15 ml, respectively)[32]. Ensuring that the volume of non-malignant brain tissues receiving ≥12 Gy of radiation (V12Gy) is low (that is, <8–12 ml in total) has been well-recognized to reduce the risk of AREs[49,78]. Lower V12Gy does come with the downside that a lower biologically effective dose (BED) is delivered to the tumour, particularly the tumour margins, which might compromise locoregional control[79].

Fractionated SRS (FSRS) has emerged as an alternative dosing strategy to achieve higher BEDs compared with single-fraction SRS. This approach has been facilitated by frameless patient positioning technologies (Fig. 2). The advent of mask-based head immobilization with Gamma Knife platforms[80] has meant that reliable fractionation schemes can be implemented across different platforms. Common daily dose-fractionation schedules include 3 fractions × 9 Gy (27 Gy total)[81], 5 fractions × 5–6 Gy (25–30 Gy)[82] and 5 fractions × 7 Gy (35 Gy)[83], with the latter providing a higher BED than the 12–18 Gy often used for single-fraction SRS of larger brain metastases in clinical trials[84–86].

Retrospective studies have evaluated various SRS fractionation schedules. In an analysis of 389 patients (a total of 400 brain metastases) treated with FSRS alone or after surgery, no statistically significant differences in local control or ARE rates were found between either of the three commonly used fractionation schedules[83]. Upfront surgery ($P = 0.049$) and smaller lesion size (diameter <2.5 cm; $P = 0.01$) were independent predictors of improved local control. In a series of 294 patients undergoing a total of 360 FSRS procedures, a 30 Gy dose-fractionation schedule (5 × 6 Gy) resulted in a significantly

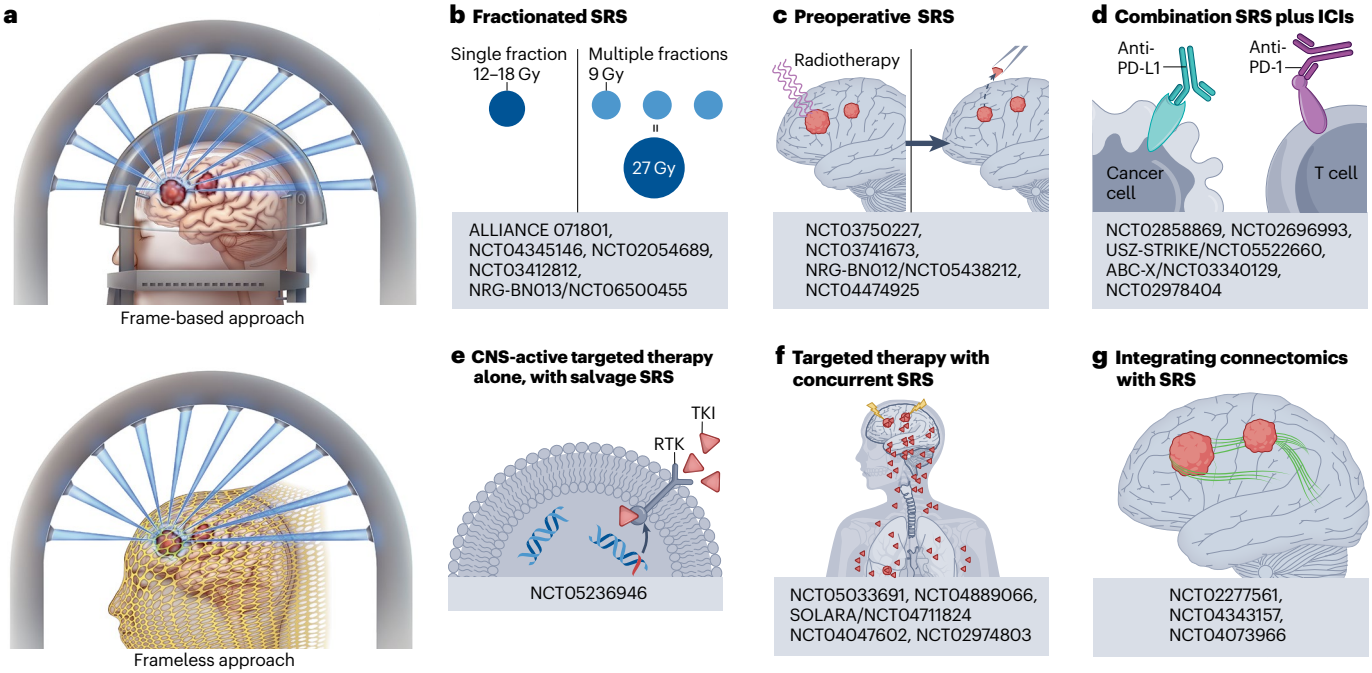

Fig. 2 | Emerging approaches and frontiers in SRS for patients with brain metastases. a, The development and refinement of frameless approaches for patient positioning and treatment delivery have substantially increased the flexibility of stereotactic radiosurgery (SRS) delivery options (for example, enabling fractionated SRS) and patient comfort. **b**, Fractionated SRS is now a part of the standard approach to management of brain metastases, although the optimal fractionation regimen is a focus of ongoing clinical trials, with examples listed in the figure. **c**, An increasing body of evidence indicates the advantages of neoadjuvant SRS, when feasible, but lesion size limitations and timing before surgery are the subjects of ongoing clinical trials. **d**–**f**, Immune-checkpoint inhibitors (ICIs) (**d**), and novel targeted therapies are now being further examined through clinical trials to identify the optimal therapeutic sequence (**e**) and/or combination (**f**) regimens in relation to SRS. **g**, Advanced image-processing strategies such as evaluation of white matter connectivity (connectomics) have the potential to refine SRS treatment planning by enabling improved avoidance of crucial white matter tracts, when feasible; these strategies are also being evaluated in ongoing clinical trials. CNS, central nervous system; TKI, tyrosine-kinase inhibitor; RTK, receptor tyrosine kinase.

lower incidence of AREs compared with the 27 Gy (3 × 9 Gy; $P = 0.03$) or 35 Gy (5 × 7 Gy; $P < 0.01$) schedules on multivariable analysis[87]. A study involving 220 patients with 334 brain metastases treated with upfront FSRS found that any dose regimen delivering less than 30 Gy in 5 fractions is associated with inferior local control (6-month and 12-month local failure rates of 13% and 33%, respectively, versus 5% and 19% in patients receiving ≥30 Gy; HR 1.62; $P = 0.03$), irrespective of lesion diameter[88]. With more modern radiation delivery platforms, however, higher local control rates have been reported with 27.5 Gy in 5 fractions (12-month local failure rate 8.3%), but not with ≤25 Gy in 5 fractions (12-month local failure rate 23.5%; HR 0.59, 95% CI 0.36–0.98; $P = 0.042$), with comparable low ARE rates[82]. Thus, consideration of the optimal dose-fractionation schedules according to the radiotherapy platform being used is important[82].

Three separate meta-analyses have evaluated local control and ARE rates based on tumour volume and/or fractionation schedule[84–86]. The first evaluated data from 24 studies encompassing 1,887 brain metastases in total and revealed 1-year local control rates of 76.7% for lesions 4–14 ml (2–3 cm diameter) and 77.6% for lesions >14 ml (>3 cm in diameter) with single-fraction SRS, which were not statistically different from the rates of 92.9% and 79.2%, respectively, with FSRS[84]. The 1-year ARE rates only differed significantly for smaller, 4–14 ml lesions (23.1% with SRS versus 7.3% with FSRS; $P = 0.003$) and not larger lesions (11.7% versus 6.5%; $P = 0.29$). Another of the meta-analyses (encompassing seven studies and 1,100 patients) analysed local control and ARE rates in aggregate, rather than by individual lesion size, and reported superior 1-year local control with FSRS versus SRS (88% versus 81%; $P = 0.018$; $I^2 = 0\%$), with no statistically significant difference in the incidence of AREs (15% versus 7%; $P = 0.70$)[85]. The third meta-analysis (15 studies and 1,049 patients with brain metastases >2 cm in diameter) found significant differences between FSRS and SRS with regard to both 1-year local control (81.6% versus 69.0%; $P < 0.0001$) and ARE rate (8% versus 15.6%; $P < 0.0001$); however, the data were not stratified by tumour volume[86]. These large evidence syntheses provide comparative ranges for local control (79–93% with FSRS versus 69–81% with SRS) and ARE rates (6.5–8.0% versus 12–23%), although the disparities in their outcomes warrant further rigorous and prospective evaluation.

At present, no convincing clinical outcome data can clarify which FSRS fractionation schedule is radiobiologically equivalent or superior to single-fraction SRS, nor the optimal tumour volume threshold for benefit from FSRS versus SRS. In clinical practice, larger brain metastases (>2.5 cm in diameter) and those with associated oedema and/or those located close to critical structures are most often treated with multi-session FSRS.

As alluded to above, imbalances in primary tumour histology and molecular profile, as well as differential use of concurrent therapies, can also confound the results of studies comparing radiotherapy approaches for brain metastases owing to inherent differences in

prognosis as well as radiosensitivity[89]. In addition to fractionation, low-dose strategies might be an option for certain histologies in the modern systemic therapy era. In a retrospective cohort study involving 102 patients with a total of 688 brain metastases originating from various solid tumours, treatment with a median margin dose of 14 Gy (range 10–14 Gy) had low local failure rates of 6% at 1 year and 12% at 2 years, with ARE rates of 0.8% and 2%, respectively[90]. In this study, melanoma brain metastases were found in competing risk analyses to be associated with a higher risk of local failure, suggesting a need for higher radiation doses for this tumour type. Indications for low-dose SRS included large-volume lesions, critical locations, prior adjacent SRS or WBRT, and multiple small or adjacent tumours[90].

RCTs evaluating FSRS versus SRS are being conducted in both patients with resected and those with intact brain metastases. The phase III ALLIANCE-071801 trial is comparing postoperative FSRS (27 Gy in three fractions or 30 Gy in five fractions) and SRS (12–20 Gy) in patients with resected brain metastases 2–5 cm in diameter (allowing ≤3 unresected lesions <4 cm) using a primary end point of surgical bed recurrence-free survival (NCT04114981). The phase III NRG-BN013 trial (NCT06500455) and others are being performed to evaluate three-fraction FSRS versus single-fraction SRS for intact large brain metastases (at least one and up to eight lesions of 1.0–3.0 cm in diameter in NRG-BN013) using similar end points, whereas the phase II SAFESTEREO trial (NCT05346367) is comparing one-fraction SRS or three-fraction FSRS (15–24 Gy) with a five-fraction FSRS (35 Gy) schedule with a composite primary end point of local tumour failure or radionecrosis at 2 years[91]. The phase III SATURNUS trial (NCT05160818) is randomly assigning patients with one to three brain metastases (with resection cavity diameter ≤4 cm) to one-fraction SRS (12–20 Gy) or six-to-seven-fraction FSRS (total 30–35 Gy), with a primary end point of 12-month local control. However, at present, the therapeutic benefit of FSRS versus SRS for tumours <2 cm in diameter remains unclear, as does the effectiveness of hypofractionation as a means of reducing the risk of AREs[92]. As these trials mature, we look forward to seeing histology-specific data related to SRS (Table 1), considering that emerging clinical experience and data from retrospective analyses suggest substantial differences in SRS dose requirements and outcomes across primary tumour types, for example, the high local failure rates reported in patients with melanoma[90,92,93].

Trials are also investigating the safety of greater dose escalation in FSRS for large brain metastases (NCT02054689 and NCT03412812), with the optimal higher dose level potentially enabling better local control. Beyond fractionation, the use of radiosensitizers such as AGuIX, a gadolinium-based nanoparticle[94], to improve local control is also being investigated in an RCT (NCT04899908).

Influence of the radiosurgery platform used

Commercial platforms for SRS delivery include, but are not limited to, Gamma Knife, CyberKnife and various linear accelerator (LINAC)-based SRS platforms, including ZAP-X, Versa HD, Edge and TrueBeam, among others[95]. These platforms can be stereotactic frame-based or frameless (instead, for example, using a mask-based approach), with some incorporating real-time MRI guidance (such as Unity and MRIdian) or optical guidance (such as Triology)[96]. Direct comparisons of the performance of such platforms have historically been difficult owing to heterogeneity in technological approach, planning protocols and patient cohorts across different centres and/or studies, as well as user preferences towards specific platforms for particular indications and owing to familiarity. Furthermore, dosimetric comparisons are limited by preferences in energy selection, dose rate, treatment planning using an isocentric

Table 1 | Key clinical challenges and associated implications relating to SRS for major histological subtypes of brain metastases

Primary tumour (sub)type	Current clinical challenges	Implications for clinical practice
Melanoma	Higher rates of local failure with standard SRS dosing than other radiosensitive histologies.	Ongoing trials to evaluate failure rates by histology, molecular profile and concurrent systemic therapy. Dose selection to be individualized.
	Potential for upfront immune-checkpoint inhibitor therapy in patients with smaller, asymptomatic brain metastases.	Can consider delaying SRS for lesions <1 cm in diameter in asymptomatic patients.
Small-cell lung cancer	Owing to the high propensity for brain metastasis (with potential polymetastatic disease), WBRT or even prophylactic cranial irradiation has typically been offered for patients with this disease; however, these approaches carry high risk of neurotoxicity.	In patients with limited intracranial disease, consideration can be given to SRS and serial surveillance.
Non-small-cell lung cancer	The availability of brain-penetrant targeted therapies is a key advance, but their optimal position in the therapeutic sequence is not known, and some evidence suggests an increased risk of ARE when used concurrently with SRS.	Until results from clinical trials emerge, the optimal sequence and dosing of the various therapies needs to be discussed at multidisciplinary tumour boards on a case-by-case basis.
Renal cell carcinoma	Higher risk of AREs than many other histologies.	The radioresistant nature of brain metastases from this disease presents a challenge in balancing the dose needed for efficacy while reducing the risk of AREs.
HER2-positive breast cancer	Drugs such as trastuzumab-based antibody–drug conjugates have promising intracranial activity as they are brain penetrant, but they have been associated with a potential increase in the risk of AREs.	The optimal timing of the various treatments remains to be determined. Multidisciplinary team discussions involving the primary oncologist are crucial.

ARE, adverse radiation event; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

or non-isocentric technique, one or multiple isocentres, co-planar or non-co-planar beams, or beam modulation, and the method used to prescribe the dose (isocentre or to a specific isodose line) and expand dose contouring beyond the contrast-enhancing tumour margins to define target volumes, and the planning algorithm used[97,98].

Unlike Gamma Knife-based SRS, which uses a cobalt-60 radiation source that needs to be replaced periodically, treatment delivery times for LINAC-based SRS are not reliant on the remaining activity of cobalt radiation sources by virtue of generating the radiation through electron acceleration, which has logistical advantages. LINAC-based SRS is planned with volumetric modulated arc therapy (VMAT), using multiple convergent dynamic treatment arcs to achieve high radiation beam conformality similar to that of other SRS delivery methods while decreasing treatment times owing to the absence of the sequential set-up processes required for approaches involving multiple static fields. The rapid treatment delivery times with LINAC-based SRS, enabled by VMAT, also minimize the risks associated with involuntary patient movement, and therefore this method is appealing when treating multiple metastases; however, considerations for the treatment of targets <1 cm in diameter must be made as outlined by the International Stereotactic Radiosurgery Society[97,99]. Overall, benchmarking exercises across technologies demonstrate the utility of the different SRS platforms for the treatment of oligometastatic or polymetastatic brain metastases, and randomized trials comparing platforms have not demonstrated differences in tumour control or ARE rates[100,101].

Dose heterogeneity continues to be an area of active interest, given that selectively increasing the dose (creating a 'hotspot') within a target volume can enable a higher dose to be delivered to radioresistant intratumoural regions, with the intention of improving local control without substantially increasing the risk of AREs[102–105]. Briefly, with the Gamma Knife system, cobalt-60-generated radiation is delivered with typical prescriptions to the 50% isodose line[106] (for an example of isodose lines see Fig. 3); thus, prescribing 20 Gy to the 50% isodose line yields a maximum intratumour dose of 40 Gy. LINAC-based SRS has traditionally resulted in homogeneous dose distributions; however, selective dose escalation and simultaneous-integrated boost techniques enable increased dose heterogeneity (for example, an entire lesion can be treated with 20 Gy of radiation while simultaneously delivering a dose of 40 Gy to a specific contoured inner portion of the lesion). The inherent differences in delivery systems have been shown to potentially result in differing post-SRS transcriptomic profiles and, interestingly, differences in gene expression between the core and peripheral regions of the tumour[107], although these mechanistic insights have not yet been linked to variations in clinical outcomes.

Diagnosis and management of symptomatic AREs

In patients with radiographic evidence of intracranial disease progression (with corresponding clinical deterioration) following SRS, determining whether the radiographic findings reflect a true tumour progression or AREs is required to guide downstream clinical decision-making but remains a major challenge[108,109]. Certain tumour types (for example, melanoma and renal cell carcinoma (RCC)), molecular markers (including *BRAF*^{V600} mutations and *ALK* rearrangements) or combined administration of systemic therapies (such as ICIs[110,111] and trastuzumab-emtansine (T-DM1)[112–114]) have been associated with an increased risk of AREs after SRS for brain metastases[27,77,93,115–118] (Table 1). Pathological evaluation of tissue samples remains the gold standard for distinguishing true recurrence of brain metastases from AREs; typical findings indicating AREs include endothelial cell damage with evidence of vessel hyalinization and thrombosis, fibrinoid necrosis and evidence of haemorrhage. Areas of fibrinoid necrosis typically include foamy macrophages and are surrounded by gliosis[119,120]. Beyond the obvious requirement for invasive brain biopsy sampling, tissue histopathological evaluations are not always definitive, and mixed areas of necrosis and viable tumour are not uncommon. Distinct genomic signatures corresponding to the type of therapeutic failure, including either local failure, LMD or AREs, have been reported on translational investigations nested in a prospective trial of SRS for brain metastases[107] — these biological differences remain to be clinically translated for diagnostic or therapeutic purposes. Nevertheless, non-invasive diagnostic modalities facilitating the decision on whether intervention is required for recurrent disease or for symptomatic AREs have long been an unmet need in neuro-oncology[115,121].

Differentiating radionecrosis from tumour recurrence on standard (structural) brain MRI remains challenging[119,122]. Several imaging sequences that are included in standard MRI protocols have been proposed for this purpose, all with limited validation of clinical utility. A low apparent diffusion coefficient, which is suggestive of highly cellular lesions (that limit the diffusion of water), can indicate tumour recurrence[119]. Matching lesion contours between T1 post-contrast and T2 sequences has also been proposed as an indicator of tumour recurrence[119], given that AREs are often associated with a greater degree of blood–brain barrier disruption and oedema than tumours[123]. Alternatively, simple short-interval follow-up scans can be implemented with the philosophy that tumours typically have a greater rate of continued growth[119]. Trials evaluating advanced imaging modalities for evaluating AREs, including PET–CT and PET–MRI, are also ongoing (NCT04410367 and NCT04410133).

Advanced radiomics-based methods to distinguish tumour recurrence from AREs have also been reported over the past decade[124–126], and have been comprehensively reviewed elsewhere[127]. MR perfusion imaging enables the evaluation of relative cerebral blood volume (rCBV), blood flow and tissue permeability, thus theoretically making it possible to distinguish recurrent tumours with high levels of neovascularization — and concordantly a higher rCBV — from devascularized necrotic tissue. Most studies testing this imaging modality in the evaluation of AREs have been retrospective with small cohort sizes, using varying rCBV thresholds and combinations with other imaging sequences, and the overall diagnostic accuracy has been modest[128–131]. The overall performance of MR perfusion studies for this indication is limited by multiple challenges including the frequent lack of baseline MR perfusion imaging, which precludes matched reference images for the assessment of dynamic changes, contamination by blood products within the tumour resection cavity, and close proximity of lesions to large blood vessels, air sinuses and/or bone. Magnetic resonance spectroscopy (MRS) enables evaluation of the metabolic composition of tissue and is another imaging modality that has been evaluated for differentiating between recurrent tumours and radionecrosis[119,127,132,133]. For tumour recurrence, an increase in the choline:creatinine or choline:*N*-acetyl aspartate ratio is expected, whereas an increase in the lipid:choline or lactate:creatine ratio, or a decrease in the choline:creatine ratio is expected for AREs[127,132,133]. Unfortunately, in addition to a minimum lesion size requirement, MRS has thus far been limited by the same overall diagnostic accuracy issues and technical challenges as MRI perfusion for this indication[127,132,133], although trials of MRS for patients undergoing SRS are ongoing (NCT03324360).

PET is another imaging tool that has been evaluated for differentiating between AREs and tumour progression[115,119]. Standard

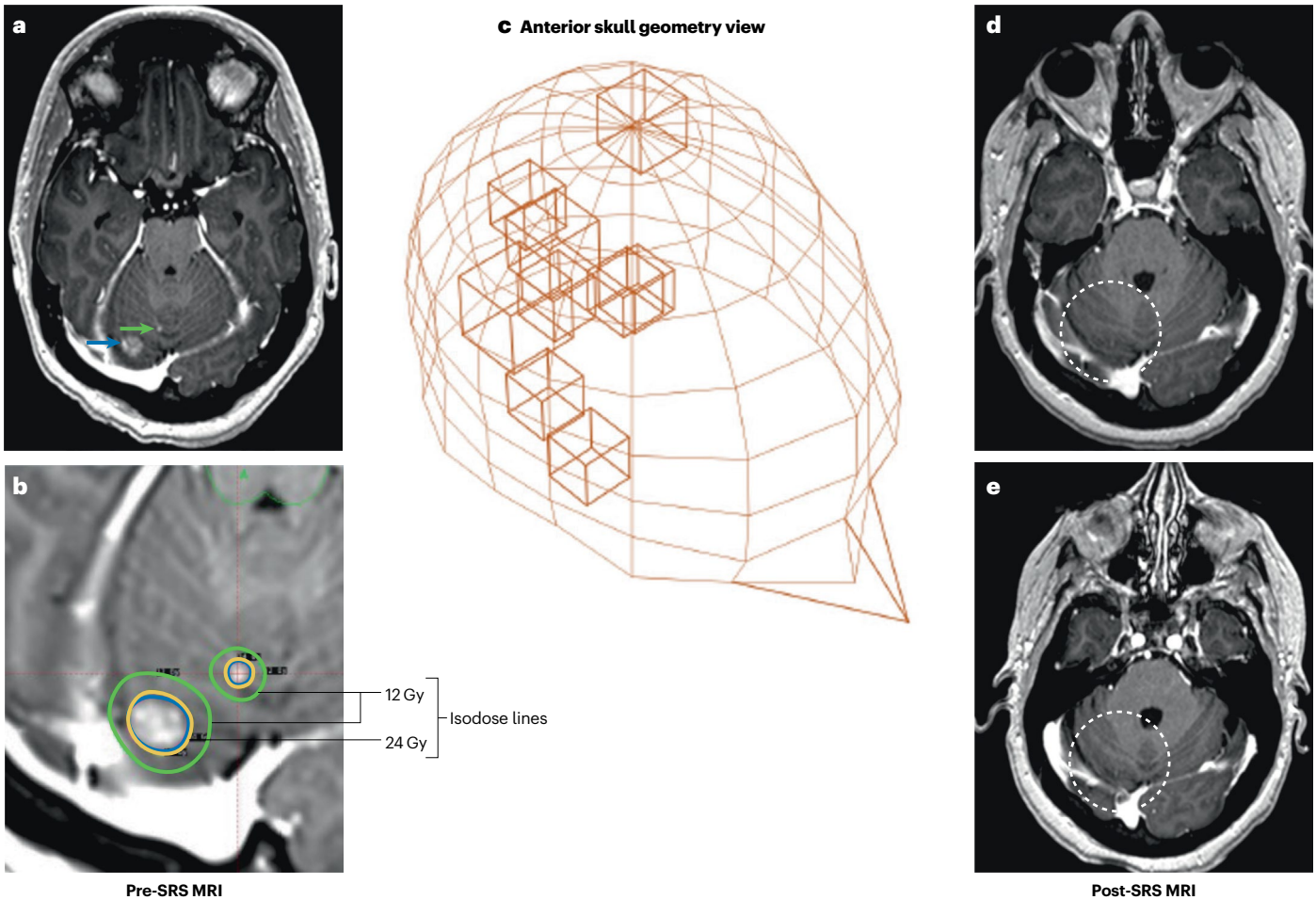

Fig. 3 | SRS and integrated multidisciplinary care for a patient with brain metastases. Provided here is a representative case of a patient with stage IV breast cancer (oestrogen receptor-positive, progesterone receptor-positive and HER2-negative) who developed nine brain metastases (that is, intracranial progression only) after systemic treatment with docetaxel plus capecitabine. To optimize patient outcomes, a multidisciplinary approach was agreed upon with stereotactic radiosurgery (SRS) delivered by radiation oncology and neurosurgery teams. **a**, Axial T1 post-contrast brain MRI scan showing two of the metastases (arrows) in the right cerebellar region. **b**, Zoomed-in view of an axial T1 post-contrast brain MRI scan demonstrating the SRS treatment plan and isodose distribution to the two of the cerebellar brain metastases. The yellow isodose line indicates the prescribed radiation dose (24 Gy) and the green isodose line (12 Gy) is depicted to illustrate the rapid dose fall-off with SRS. **c**, Anterior right skull geometry view demonstrating the locations of the nine brain metastases in this patient. **d**, Representative T1 axial post-contrast brain MRI performed 8 weeks after SRS demonstrating a complete response with resolution of the previously visualized enhancing brain metastases (region of interest highlighted with a dashed circle). The patient was able to remain on systemic treatment with docetaxel plus capecitabine, given the isolated central nervous system progression and that the brain metastases responded favourably to SRS. **e**, Representative T1 axial post-contrast brain MRI scan performed 5 months after SRS, demonstrating sustained complete intracranial response, with the patient being maintained on the same systemic regimen by the breast medical oncology team.

^{18}F-fluorodeoxyglucose-PET relies on the increased metabolic activity of cancer cells compared with necrotic tissue to make a diagnosis; however, sensitivity and specificity have generally been low, with the usually poor resolution of ^{18}F-fluorodeoxyglucose-PET and background brain metabolic activity being likely contributors[134,135]. Amino acid-based PET tracers, such as ^{11}C-methyl-L-methionine (^{11}C-methionine)[136,137], L-3,4-dihydroxy-6-^{18}F-fluorophenylalanine (F-DOPA)[138,139] and *O*-(2-^{18}F-fluoroethyl)-L-tyrosine (F-FET)[140], are more selectively taken up by cancer cells and might, therefore, enhance diagnostic accuracy[115], as comprehensively reviewed for brain metastases by the RANO PET group[141]. A key challenge with many of these tracers is the institutional need for on-site cyclotrons for their generation. Clinical trials evaluating approaches to differentiate tumours from AREs using tracers that are more readily available but classically implemented for PET imaging of tumours outside of the CNS, such as ^{18}F-fluciclovine (used for prostate cancers), are currently ongoing and/or unpublished. These trials include FACILITATE (NCT06048094), REVELATE (NCT04410133) and PURSUE, NCT04410367). Initial results from PURSUE, in which 23 reference lesions in 23 patients were evaluated (10 of 23 as pathologically confirmed recurrence), suggest that a threshold of 'marked' ^{18}F-fluciclovine uptake (that is, levels higher than uptake in the parotid gland) translated into 92–100% sensitivity and 40–80% specificity

across three independent blinded readers[142]. The maximum lesion standardized uptake value of ^{18}F-fluciclovine was found to be a quantitative metric (area under the curve of 0.87), with a maximum lesion standardized uptake value threshold of 4.8, having 80% sensitivity and 85% specificity[142].

Radiation causes damage to vascular tissues surrounding the irradiated lesion, leading to an oxygen diffusion disorder between blood vessels and other surrounding tissues, causing local hypoxia[143]. In turn, hypoxia increases the expression of hypoxia-inducible factor-1α and stimulates reactive astrocytes to secrete the pro-angiogenic factor vascular endothelial growth factor (VEGF)[143]. High levels of VEGF result in the formation of abnormal new blood vessels, leading to a disordered and fragile vascular structure with high permeability[143]. This aberrant vasculature increases fluid leakage into surrounding tissues and thereby promotes the development of brain oedema, which causes localized high intracranial pressure, leading to localized ischaemia and hypoxia, creating a feed-forward cycle that can ultimately manifest as clinical symptoms of AREs.

Glucocorticoids are typically the first-line treatment for symptomatic AREs; however, some patients might have AREs that are refractory to these agents or might be unable to taper-off of glucocorticoids without recurrence of ARE symptoms. Long-term steroid use has considerable systemic adverse effects. Additionally, in patients who are receiving ICIs (for extracranial and/or intracranial disease) and develop symptomatic ARE, the use of steroids is known to reduce ICI efficacy[144,145]. The anti-VEGF-antibody bevacizumab can be useful in patients with steroid-refractory ARE[121], but concerns regarding haemorrhagic adverse effects, the need for repeated cycles of intravenous infusion and impaired wound healing within 4 weeks after treatment limit widespread use of this agent[119,121]. *Boswellia serrata* extract, an anti-inflammatory compound often available over the counter has been investigated in a non-randomized trial involving 50 patients with grade 1–3 radionecrosis following SRS for brain metastases[146]. In this trial, the complete response rate was 15% and an additional 40% of patients had a partial response[146]. Only three patients had toxicities, all grade 1–2 (ref. 146). Surgery, accompanied by tissue analysis for confirmation, remains a treatment option for radionecrosis that does not respond to medical therapy. Meanwhile, laser interstitial thermal therapy (LITT) has shown promise for the management of AREs post-SRS of brain metastases[147–151]. LITT is a minimally invasive approach in which a probe (laser catheter) is inserted through the skull into the brain parenchyma under intraoperative image guidance (such as MRI guidance[147,152] or stereotactic guidance[153]), with subsequent controlled heating of the probe tip causing tissue ablation. However, characteristic oedema can develop post-procedure, owing to thermal effects and ablated tissue left in situ, with corresponding temporary clinical deterioration[154]. Nevertheless, LITT has been found to be useful for both symptom management and local control[151,155], with data from the prospective multicentre LAANTERN registry demonstrating a post-procedure 1-year cumulative incidence of brain metastases recurrence of 19% in 90 patients with biopsy-proven ARE[151]. By permitting steroids (for ARE) to be stopped rapidly, LITT facilitates resumption of discontinued ICIs and/or can minimize the affect of steroids on the efficacy on ongoing ICI treatment (for patients who were on ICIs before ARE)[154]. Finally, given that tissue sampling can be done intraprocedurally, LITT offers an opportunity for histopathological confirmation of radionecrosis versus tumour recurrence (with direct tumour ablation if found to be present)[154]. This biopsy sampling also enables updated molecular profiling of the residual or recurrent tumour if present[121].

The ongoing REMASTer RCT is enrolling patients with radiographic changes post-SRS across two cohorts: a tumour recurrence cohort (A), with randomization to either LITT followed by surveillance or LITT followed by hypofractionated radiotherapy; and a ARE cohort (B), randomized to LITT with supportive medical therapies or supportive medical therapies (including steroids) alone (NCT05124912).

Emerging role of neoadjuvant SRS

Over the past decade, momentum favouring preoperative or 'neoadjuvant' SRS for the treatment of brain metastases in selected patients[156], specifically those who do not urgently require surgery for symptom management or histopathological analysis, has increased. Here, we discuss the underlying concepts, practical challenges and emerging clinical evidence for this strategy.

Mitigating iatrogenic seeding of brain parenchyma and leptomeninges

Despite the local control achieved with adjuvant SRS or FSRS (for large resection cavities), recurrence of brain metastases within or near the resection cavity is common (with local failures rates of approximately 10–40%)[156–158]. After resection and adjuvant SRS or FSRS, the development of LMD, typically with a nodular phenotype[159], is well-recognized to be associated with neurological death[160,161].

This local recurrence is potentially theorised to occur secondary to either the standard paradigm of peritumoral invasion[162], the iatrogenic seeding of non-irradiated cancer cells along the surgical tract[163], and/or spillage of cancer cells into the meningeal and cerebrospinal fluid spaces during surgery, the latter theory being supported by data demonstrating increased rates of LMD following postoperative SRS[164]. In a retrospective observational study including 180 patients undergoing resection of brain metastases, the LMD development rate at 2 years was 16.6% among 114 patients who underwent neoadjuvant SRS ($n = 114$) versus 3.2% in 66 patients who received adjuvant SRS[165]. In a single-centre observational study of 235 patients, postoperative FSRS to resection cavities (137 lesions in total) was associated with a significantly higher risk of LMD than FSRS of intact, unresected brain metastases (total of 183 lesions; OR 2.30, 95% CI 1.24–4.29; $P = 0.008$). The rates of LMD at 1 and 2 years were 20% and 24%, respectively, in patients with FSRS of resection cavities compared with 6% and 10%, respectively, in those with FSRS of intact metastases[166]. These unadjusted comparisons need to be interpreted cautiously given the potential for some level of confounding by indication. Meanwhile, LMD development is an end point in several ongoing trials of neoadjuvant versus adjuvant SRS (Supplementary Table 1).

The PROPS-BM cohort study ($n = 404$ patients) reported that with neoadjuvant 15 Gy SRS or three-fraction 24 Gy FSRS, 2-year rates of local recurrence, LMD and any-grade ARE were 13.7%, 5.8% and 7.4%, respectively[167]. Another multi-institutional study involving 242 patients receiving neoadjuvant SRS demonstrated LMD rates of 6.1% and 7.6% at 1 and 2 years, respectively[168]. Locoregional immunological profiling nested in a randomized phase II trial of neoadjuvant SRS, which compared low-dose versus high-dose peri-operative dexamethasone (no significant difference found across any comparative outcome), has provided a translational framework for maximizing intracranial $CD8^+$ T cell responses in future trials of neoadjuvant SRS[169].

Avoiding the challenge of postoperative target volume planning

Tissue-based target volumes, in the general context of radiotherapy, include the gross tumour volume, the clinical target volume (CTV)

and the planning target volume (PTV), as reviewed elsewhere[170]. For patients planned to undergo adjuvant SRS, current guidelines recommend including the surgical cavity in the treatment plan[156,171]; however, the surgical tract and the leptomeninges are not always included as part of the postoperative SRS PTV, leaving these areas potentially containing cancer cells untreated. Other challenges include difficulties in contouring the irregular margins of tumour resection cavities, particularly the meningeal margin. Irregular margins can arise owing to incompletely collapsed resection cavities, subtotal resections, adjacent areas of tissue infarction and/or postoperative scar formation[32,33,165,172].

Intact, unresected lesions can be more accurately contoured during SRS dosimetry planning, largely because the planned CTV is the same as gross tumour volume, without the need to include additional or disrupted margins (with typically a 1–2 mm PTV expansion[173,174]). Thus, incidental radiation to the adjacent non-malignant brain parenchyma can be minimized, while also maximizing direct radiation exposure of malignant tissues. In a comparative dosimetry study of simulated preoperative versus delivered postoperative SRS, preoperative SRS was estimated to reduce V12Gy substantially (mean volumetric decrease of 31.8% compared with postoperative SRS plan, $P = 0.0008$)[175], despite the PTV being similar on paired analyses. Preoperative dosimetry plans were also more conformal ($P < 0.001$) and had steeper dose drop-offs at lesion margins when compared with postoperative plans ($P = 0.0018$)[175]. These findings might explain the lower incidence of AREs associated with neoadjuvant versus adjuvant SRS[78,165]. In a single-arm phase II trial evaluating neoadjuvant SRS for one to four symptomatic brain lesions, the 6-month local control rate was 100% in 32 patients who completed follow-up, with 1-year rates of LMD, AREs and distant failure of 4.8%, 7.7% and 40.8%, respectively[176].

In addition to the importance of quality of MRI simulation for SRS, as has been comprehensively discussed by a German multisociety taskforce[177], the timing of planning MRI is also meaningful[178]. A prolonged time from surgery to SRS (>4 weeks) can lead to inferior local control[179], although cavity dynamics must also be considered in the timing of adjuvant SRS given that its shape, volume and precise location can change over time[180]. Recommendations are that SRS should be performed within 1–2 weeks following surgery[156,180].

Another consideration specific to FSRS is the concept of interfraction cavity dynamics[49,181–183]. As part of the ongoing international MOMENTUM registry evaluating outcomes of radiotherapy using the Unity MRI–LINAC system (NCT04075305), an analysis of 15 patients undergoing adjuvant five-fraction FSRS for resected brain metastases found a significant reduction in the cavity treatment volume at fraction three compared with baseline (median relative reduction of −11.4% on gadolinium-enhanced T1c and −8.4% on T2/FLAIR sequences, $P = 0.009$ and 0.032, respectively), supporting the case for adaptive treatment planning[183]. Adaptive approaches are a fundamental aspect of the emerging paradigm of 'personalized radiotherapy'[19,184].

Ongoing trials and unanswered questions

Several ongoing trials are evaluating the role of neoadjuvant SRS through randomized comparison with adjuvant SRS[185], including NCT03741673, NCT03750227, NCT05871307 (RADCAV, which has a third arm testing intraoperative SRS), NCT05438212 (NRG-BN012) and NCT04474925, or in a single-arm setting (NCT03368625) (Fig. 2 and Supplementary Table 1). Given that the neoadjuvant SRS dose could potentially be lower, for example, in the setting of dose de-escalation protocols, a conundrum exists as to how postoperative residual disease should be managed in patients with subtotally resected lesions that have already been treated with preoperative SRS. At present, no formal dosimetry recommendations are available for neoadjuvant SRS, and results are awaited from ongoing and/or unpublished trials (such as NCT01252797).

Another concern relates to the absence of pathological confirmation of brain metastases with the neoadjuvant SRS approach, which might affect insurance authorization and patient counselling. Countering this latter concern, none of the contemporary clinical trials testing SRS have required biopsy-based confirmation of brain metastases for enrolment or inclusion, demonstrating the acceptably low risk of false-positive diagnoses made with imaging alone. Other issues include the logistical challenges of neoadjuvant SRS, particularly surrounding the integration of this approach into standard clinical workflows and related reimbursement issues.

Combining SRS with ICIs

Over the past two decades, ICIs have become a critical pillar of SOC therapy, either alone or in combination with chemotherapy, for most metastatic solid tumours[186], with major successes in controlling intracranial disease in patients with melanoma[187–189] and NSCLC[190].

Potential synergy with immunotherapy in preclinical studies

Radiotherapy is recognized to not only directly induce damage in cancer cells, but also to promote a local immune response[191]. Ionizing radiation induces DNA double-stranded breaks, leading to apoptosis and necrosis, the release of tumour-associated antigens and thus increased dendritic cell, $CD4^+$ and $CD8^+$ T cell activation, as well as upregulation of MHC expression, thereby further enhancing antigen presentation[191] (Fig. 4). Many other mechanisms also promote lymphocyte infiltration into the tumour microenvironment[191,192] (Fig. 4).

Typically, the antitumour immune response generated by radiotherapy alone is not sufficient for durable intracranial control, given that approximately 30–50% of patients develop new, distant intracranial lesions post-radiotherapy in the long term[193]. This disease recurrence is attributed, in part, to the persistent immunosuppressive environment of occult brain metastases, characterized by suboptimal dendritic cell function and a low abundance and/or functional impairment of $CD8^+$ T cells[193–195]. Radiotherapy, while inducing DNA damage, also induces upregulation of DNA exonuclease TREX1 in cancer cells, which breaks down cytosolic damaged DNA and thus dampens immunogenic cGAS–STING signalling[196]. SRS for brain metastases has been found to be associated with the replacement of tumour-infiltrating T cell clones by circulating clones that do not support antitumour immunity[197]. Therefore, removing potential brakes on immune activation, using ICIs, presents a rational combinatorial approach[194].

Several preclinical studies have demonstrated improved locoregional tumour control when radiotherapy is combined with ICIs[191,198,199]. Radiation-induced neoantigen release, in combination with ICIs, reinvigorates tumour-reactive $CD8^+$ T cells in the tumour microenvironment[200] (Fig. 4). Additionally, anti-PD-(L)1 antibodies can activate T cells that are yet to be exposed to tumour antigens and rejuvenate exhausted T cells, whereas radiotherapy stimulates naive T cell differentiation and proliferation, and potentially T cell recruitment, in response to released neoantigens[201]. In a mouse model of poorly immunogenic breast cancer, systemic antitumour effects were observed with an anti-CTLA4 antibody when combined with irradiation of the primary tumour, driven by cytotoxic T cell activation and tumour infiltration[198]. Additionally, adjuvant ICIs slowed the growth of

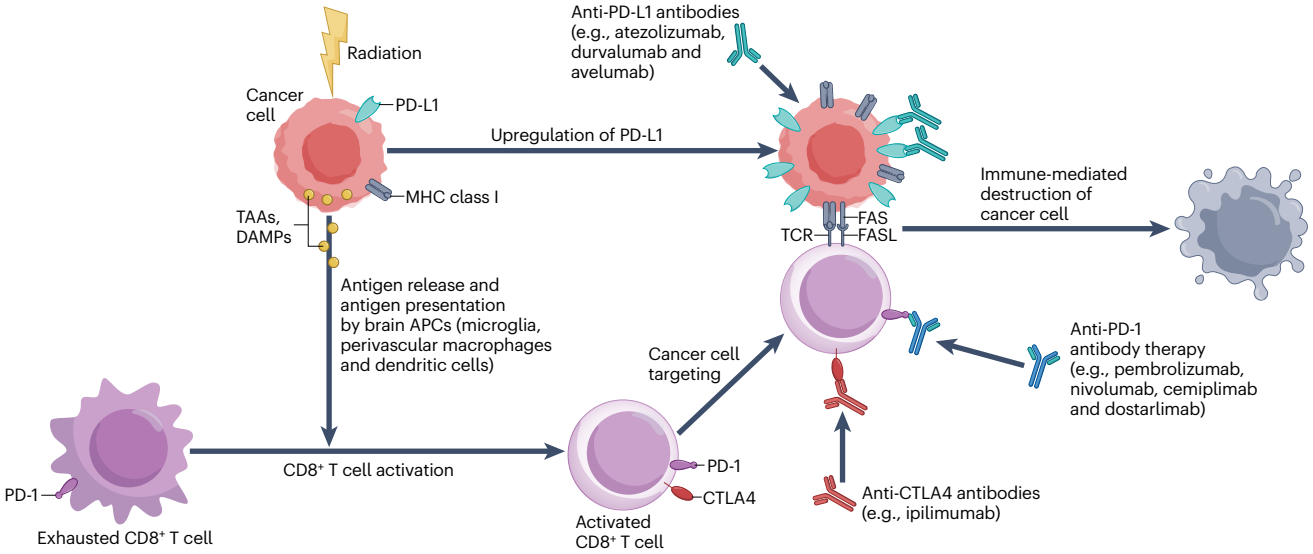

Fig. 4 | Key immunological effects of radiation and potential synergy with immune-checkpoint inhibitors. Radiation leads to the release of tumour-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs) from the irradiated cancer cells, which lead to enhanced antigen presentation. Ultimately, enhanced antigen presentation can result in (re)activation of exhausted tumour-reactive T cells, resulting in immune-mediated destruction of cancer cells. Additionally, upregulation of PD-L1 often occurs in irradiated cancer cells, which can induce inhibitory PD-L1–PD-1 signalling in tumour-reactive T cells. Thus, combining anti-PD-(L)1 antibodies or other immune-checkpoint inhibitors (such as anti-CTLA4 antibodies) with SRS can enhance local and distant tumour control. APC, antigen-presenting cell; FASL, FAS ligand; MHC, major histocompatibility complex; TCR, T cell receptor.

unirradiated tumours and increased the number of tumour-infiltrating lymphocytes[198]. Fractionated radiotherapy plus anti-PD-(L)1 antibodies, compared with fractionated radiotherapy alone, leads to effective CD8⁺ T cell responses that enhance local control, survival and resistance to tumour rechallenge in syngeneic mouse models[202].

Preclinical investigations of radiation in combination with ICIs in models of brain metastases, although comparatively fewer, have suggested similar synergy as observed with primary tumours. Radiotherapy has been shown to sensitize 'immunologically cold' brain metastases to ICIs in mouse models of breast cancer[203]. Preclinical studies in models of melanoma brain metastases also indicate that radiotherapy and ICI might also synergize in upregulating the expression of genes involved in cancer cell apoptosis and enhance the inflammatory response associated with antitumour B cell activation[204]. Taken together, these findings suggest that combining ICIs with SRS could potentially enhance the antitumour immune response (for improved local control) and could be used to not only eradicate distant occult lesions (for improved distant control), but also to potentially prevent the emergence of new brain metastases (with the potential to improve OS)[193].

Evidence from retrospective studies of SRS plus ICIs

These preclinical findings have been recapitulated in retrospective studies involving patients receiving ICIs combined with SRS of brain metastases[14,205–210]. These studies have reported a variety of benefits when SRS is delivered concurrently with ICIs (variably defined as ICI therapy initiated within 1–4 weeks of SRS or to up to five biological half-lives before or after SRS)[111,211] and an increased rapidity of response compared with a more prolonged treatment gap between ICIs and SRS[212]. Clinical evidence especially supports the combination of ICIs with FSRS[111,212], in line with preclinical findings that fractionated radiation plus ICIs leads to greater immune activation than single-fraction radiation[199], which also aligns with the mechanistic understanding of repeated immune activation with radiation. In patients with NSCLC and resected brain metastases, the combination of ICIs plus postoperative FSRS was associated with improved distal intracranial control compared with versus FSRS alone[213].

Controversy still exists regarding the optimal sequencing of ICIs and SRS. Some evidence favours the use of ICIs before SRS, as a means to prime the immune system and thus bolster the antitumour effects of SRS[193]. However, data from one of the aforementioned retrospective studies indicate that ICI-naive patients receiving SRS followed by ICIs have better overall tumour-size reductions than those receiving ICIs first followed by SRS (−63% versus −45%; $P < 0.001$)[211]. In particular, this large-scale analysis found that patients naive to ICIs undergoing SRS followed immediately (within one biological half-life) by ICIs had the best response rates and with a 12-month ARE rate of only 3.2%[211]. Notably, steroids had a negative effect on tumour response and OS[211].

Importantly, treatment-related imaging changes (TRICs) following concurrent treatment with ICIs and FSRS need to be better understood. In patients receiving SRS, a significantly increased risk of AREs has been reported with combined use of ICIs with SRS (HR 2.56, 95% CI 1.35–4.86; $P = 0.004$), with the association being strongest for melanoma brain metastases (HR 4.02, 95% CI 1.17–13.82; $P = 0.03$)[110]. However, TRICs can encompass not only imaging-defined radionecrosis (that is, AREs), but also treatment-related beneficial effects, which provide an early signal of antitumour immune activation and clinical efficacy. An international multicentre retrospective study involving 697 patients with a total of 4,536 brain metastases revealed that TRICs following SRS and ICIs were associated with improved OS (median 29.0 versus 23.1 months in patients without such changes; multivariate HR 0.66, 95% CI 0.45–0.96;

$P = 0.03$)[214]. Therefore, the management of imaging changes in the early period should be nuanced and close observation is warranted[215]; in the absence of true tumour progression or symptomatic cerebral radionecrosis, TRICs could herald an enhanced immune response within the tumour.

Trials combining SRS and ICIs

The combination of ICIs and SRS seems to confer superior intracranial control compared with SRS alone, translating to improvements in OS in large retrospective series[14,207–210]. However, prospective registry studies and, ideally, RCTs are needed to address certain questions. For example, the optimal timing or sequence of these therapies remains quite unclear. A single-arm phase II trial demonstrated a 1-year CNS progression-free survival of 45.2% in patients with brain metastases from NSCLC or RCC treated with the anti-PD-1 antibody nivolumab followed within 14 days by SRS, with no apparent increased risk of AREs[216].

Although some completed early phase trials evaluating safety of combining radiation with ICIs did have separate arms for SRS and WBRT (such as NCT01703507 and NCT02696993)[217], head-to-head randomized comparisons of safety and long-term intracranial control following SRS versus WBRT when combined with ICIs also remain to be reported. Trials evaluating different ICIs, including dual ICI therapy, combined with SRS (including NCT02696993, NCT05522660, NCT04889066, NCT04711824 and the ABC-X trial (NCT03340129) that builds upon the ABC RCT[187,188]) are either currently ongoing or remain to be published. The ongoing phase III HYPOGRYPHE trial (NCT05703269) is evaluating ICIs combined with either SRS plus or three-to-five-fraction FSRS, with primary end point of grade ≥2 ARE. Other radiation dosing strategies associated with a potentially reduced the risk of AREs, such as personalized ultrafractionated stereotactic ablative surgery[218] and reduced-dose SRS, are being investigated in combination with immunotherapies in early phase trials (Fig. 2 and Supplementary Table 2).

Integration of SRS and modern targeted therapies

Modern targeted therapies such as brain-penetrant tyrosine-kinase inhibitors (TKIs) and antibody–drug conjugates (ADCs)[59] have generated major enthusiasm as additional tools in the armamentarium for the management of patients with advanced or metastatic cancers[219–221]. Notable CNS-active targeted therapies include, but are not limited to, osimertinib for *EGFR*-mutant NSCLC[222,223]; alectinib, brigatinib and lorlatinib for *ALK*-rearranged NSCLC[224–227]; crizotinib and entrectinib for *ROS1*-rearranged NSCLC[228,229]; selpercatinib for *RET*-altered NSCLC[230,231]; dabrafenib and trametinib for *BRAF*^{V600}-mutant melanoma[232]; cabozantinib for RCC[233,234]; combination of tucatinib, trastuzumab and capecetabine for HER2$^+$ breast cancer[235,236]; and the ADC trastuzumab–deruxtecan (T-DXd) for HER2$^+$ or HER2-low breast cancer[237–241]. The reported intracranial activity of some of these novel therapies, as well as their ongoing investigations in conjunction with SRS, are reviewed in the Supplementary Information.

Clinical decision-making

Given the emerging evidence supporting the efficacy of CNS-active systemic therapies against both extracranial and intracranial disease, professional society guidelines, particularly those with a medical oncology focus[4,16], have conditionally recommended standalone systemic therapies for (an increasing range of) subgroups of patients with brain metastatic disease harbouring targetable driver mutations, with cranially directed therapy (WBRT, SRS or surgery) potentially omitted or deferred[6,242]. The paradigm of 'CNS downstaging' is also being discussed[243], whereby patients with stable but extensive CNS involvement (otherwise requiring WBRT) receive systemic therapy alone, leading to a reduction in their CNS disease burden and thus conversion of some patients into candidates for SRS alone. However, considerations such as the toxicities of highly active systemic therapies and the potential for proliferation of drug-resistant subpopulations in the brain — given that the blood–brain barrier can create a sanctuary for treatment-resistant subclones — all necessitate a cautious and data-driven approach[244–246].

In the front-line setting, the evidence is probably not strong enough yet to support omission of local therapy for all brain metastases in patients with oncogene-driven solid tumours for which CNS-active systemic therapies can be utilized, except for those with stable, asymptomatic, small brain metastases originating from melanoma, HER2$^+$/low breast cancer, and *EGFR*-mutant, *ALK-rearranged* or *RET*-altered NSCLC (Fig. 1 and Supplementary Information). However, this space is a rapidly evolving with considerable practice heterogeneity. Notably, trials of CNS-active systemic therapies are increasingly allowing enrolment of patients with larger, albeit stable, brain metastases, with the COMBI-MB trial, for example, permitting lesions up to 4 cm in diameter[232].

Conceptually, if systemic agents and SRS are combined, the systemic therapy acts against the CNS micrometastatic deposits and small metastases, whereas SRS acts on the overt, targetable lesions. Although data from the BRATR RCT comparing targeted therapies plus SRS (for up to three lesions) versus targeted therapies alone for patients with brain metastases from *EGFR*-mutant, *ALK*-rearranged or *ROS1*-altered NSCLC (NCT04193007) remain unpublished, emerging retrospective reports have indicated a benefit from combining these treatments. In the multicentre, retrospective TURBO-NSCLC study evaluating the utility of novel TKIs (osimertinib or lorlatinib), either with upfront SRS ($n = 117$) or without SRS ($n = 200$), in patients with TKI-naive *EGFR*-mutant or *ALK*-rearranged brain metastatic NSCLC, the combinatorial approach significantly improved local CNS control (HR 0.30, 95% CI 0.16–0.55; $P < 0.001$) and time to CNS progression (HR 0.63, 95% CI 0.42–0.96; $P = 0.033$), albeit with similar OS (median 40 months with TKI plus SRS, versus 41 months with TKI alone; $P = 0.50$)[247]. The benefits of SRS were particularly pronounced in patients with brain metastases of >1 cm in diameter[247]. The advantage of combining upfront SRS with osimertinib has been corroborated in another multicentre retrospective study from Japan, with significantly improved CNS progression-free survival (HR 0.36, 95% CI 0.15–0.87) as well as OS (HR 0.37, 95% CI 0.16–0.87) compared with osimertinib alone[248].

Several RCTs combining SRS with CNS-active therapies are ongoing or unpublished including OUTRUN (SRS plus osimertinib versus osimertinib alone for *EGFR*-mutant NSCLC, NCT03497767), DURABLE (SRS plus alectinib versus alectinib alone for *ALK*-rearranged NSCLC, NCT05987644), USZ-STRIKE/ (systemic therapy with SRS versus systemic therapy for melanoma or NSCLC, NCT05522660) and BEPCOME-MB (SRS plus encorafenib, binimetinib and pembrolizumab versus the three-drug combination alone for *BRAF*^{V600}-mutant melanoma, NCT04074096). Another phase III RCT in India is enrolling patients with *EGFR*-mutant or *ALK*-rearranged NSCLC to compare upfront versus delayed cranial radiotherapy, in context of CNS-active therapies (NCT05236946).

Given the high activity of these modern systemic therapies, prudence will be needed when combining them with SRS. For example,

combining the CNS-active ADC T-DM1 (refs. 59,249) with SRS has now been well-recognized to be associated with increased neurotoxicity and symptomatic AREs[112–114,250], potentially driven by upregulation of aquaporin-4 (ref. 114). Another study of SRS combined with any ADC (T-DM1, T-DXd or sacituzumab govitecan) for brain metastases from various solid tumour types (>70% breast cancer) reported a higher risk of symptomatic AREs with concurrent ADC treatment (adjusted HR 4.31, 95% CI 1.95–9.50; $P < 0.001$), controlling for prior radiation and lesion volume[251]. Meanwhile, some studies evaluating T-DXd combined with SRS have reported low rates of symptomatic AREs[252,253]. Similarly, patients with melanoma brain metastases receiving SRS plus BRAF inhibitors have been reported to have a higher incidence of symptomatic AREs (28.2% versus 11.1% with SRS alone at 1 year; $P < 0.001$)[254], although data from some other studies do not support this association[209,255–257]. Mechanistic investigations have implicated BRAF inhibitors as radiosensitizers, with vemurafenib being more potent than dabrafenib[258]. Meanwhile, data from a retrospective study on CNS-active systemic therapies combined with personalized ultrafractionated stereotactic ablative surgery in a total of 109 brain lesions, predominantly in patients with lung or breast cancer, suggest good local control without substantial increase in toxicity[218].

Currently, although upfront systemic treatment options can be considered in lieu of SRS or resection of brain metastases, decisions need to be made on a case-by-case basis by multidisciplinary tumour boards, weighing the pros and cons of deferring local therapy with consideration of the optimal timing of SRS relative to systemic therapies[12] (Figs. 1 and 3). Moreover, optimizing the delivery of salvage SRS[157,259,260] in patients with intracranial radiographic progression following modern CNS-active systemic therapies (with or without prior SRS) is of growing interest. In this setting, non-invasive and accurate differentiation of true tumour progression from AREs and corresponding management also remain challenging[108,109].

Additionally, withholding systemic therapy until brain metastasis-directed local therapy has been completed remains a common practice among many oncology groups. This approach can potentially lead to delays in systemic treatment or worse, the emergence of new brain metastases following local therapy owing to a failure to prevent further metastatic dissemination from extracranial tumours and/or

Glossary

Adverse radiation events (AREs)
are any negative adverse effects or complications arising secondary to radiotherapy, which affect non-tumour tissues and organs near the treatment site, can occur during or following treatment and range in severity. AREs reflecting necrosis or leaky blood vessels resulting in oedema are sometimes referred to as radiation necrosis or radionecrosis or radiation-induced contrast enhancement.

Beam modulation
refers to the technique of varying the intensity and shape of radiation beams as they are delivered to the patient. This enables more precise targeting of the tumour while minimizing exposure and thus damage to surrounding non-tumour tissues.

Biologically effective dose (BED)
is a measure that quantifies the biological effect of a given dose of radiation, taking into account the dose per fraction and the total dose delivered, relative to the tissue-specific sensitivity to radiation.

Clinical target volume (CTV)
as defined broadly, is the volume of tissue that contains the gross tumour volume visible on imaging, along with a potential margin of surrounding tissue potentially invaded by malignant cells. For whole-brain radiotherapy, the CTV is typically the entire brain. With stereotactic radiosurgery for small intact lesions, the CTV is the same as gross tumour volume on imaging as microscopic spread is considered minimal.

Co-planar beams
refer to multiple radiation beams that are directed from different angles but lie within the same plane. This technique is used to ensure uniform dose distribution across the target area while sparing surrounding non-tumour tissues.

Gross tumour volume
is the volume of the tumour that is clearly visible on imaging, typically a fine-cut contrast-enhanced T1-weighted MRI for SRS targeting intact lesions.

Isocentres
are crucial in radiotherapy planning as the focal points of radiation beam intersection, around which the gantry, the treatment couch and the collimators all rotate to ensure accurate tumour targeting.

Isodose
refers to lines on a radiation treatment plan that connect points receiving the same dose of radiation. These lines help visualize the distribution of radiation within the target area and surrounding tissues, facilitating treatment planning.

Planning target volume (PTV)
includes the clinical target volume plus a margin of surrounding tissue (such as an added 1–2 mm for stereotactic radiosurgery or 3–5 mm for whole-brain radiotherapy — referred to as the PTV expansion) to account for variations in lesion size, shape and position, relative to the radiotherapy beam.

Simultaneous-integrated boost techniques
involve delivering different doses of radiation to different areas of the tumour simultaneously within a single treatment session. This approach enables higher doses to be targeted at the tumour while sparing surrounding non-tumour tissues, potentially improving treatment efficacy and reducing overall treatment time.

Stereotactic radiosurgery (SRS)
is a highly conformal radiation therapy approach that is predicated on the ability to immobilize the target organ for precise targeting of radiation beams. The skull being a fixed and rigid space is an ideal region for SRS, as there is minimal motion during therapy.

Tumour treating fields (TTFields)
is a novel treatment modality involving non-invasive delivery of low-intensity, intermediate-frequency alternating electrical fields, typically via several electrodes placed on the scalp — ideally near the tumour — for brain metastases, to disrupt the ability of cancer cells to grow and divide.

Box 1 | Unanswered questions related to SRS for patients with brain metastases

- What are the safe and optimal thresholds for the number and size of brain metastases that can be treated (and retreated) with stereotactic radiosurgery (SRS) over the patient's metastatic disease course?
- Does the delivery of SRS with different platforms (Gamma Knife, CyberKnife, Zap-X, LINAC or others) lead to clinically meaningful differences in patient outcomes?
- How should tumour histology inform decision-making related to SRS dosing and fractionation?
- Is there a meaningful therapeutic benefit of fractionated SRS versus SRS for brain metastases that are <2 cm in diameter?
- Should hypofractionation of SRS be used as a strategy for clinically relevant risk reduction for adverse radiation events, especially in patients at high risk?
- What is the optimal sequence, timing and fractionation for achieving maximum synergy from the combination of SRS with immune-checkpoint inhibitors?
- In patients treated with immune-checkpoint inhibitors and SRS, how can beneficial treatment-related imaging changes (that is, therapeutic effects) be differentiated reliably from adverse treatment-related imaging changes (that is, imaging-defined radionecrosis)?
- What is the optimal approach for combining modern central nervous system (CNS)-active systemic targeted therapies with SRS, and which patients, if any, can potentially benefit from CNS downstaging using novel systemic therapies alone?
- Which specific subgroups of patients should receive neoadjuvant SRS, and what dose schedule is optimal?
- What is the optimal treatment approach for postoperative residual disease in patients with subtotally resected lesions who have received neoadjuvant SRS?
- What questions above can be meaningful informed through molecular profiling?
- How to decide, as a multidisciplinary team, when the limits of what can be achieved with SRS have been reached, or with other CNS-directed therapies for that matter, and when the patient would benefit most from best supportive care?
  - The approach to this final question will need to be based on both clinical insight and ethical considerations.

the outgrowth of occult brain metastases. Thus, the results of RCTs combining these modalities (Fig. 1 and Supplementary Table 2), which could have practice-changing consequences, are eagerly awaited.

Future directions

In the absence of data from RCTs, several unanswered questions surrounding the sequencing, combination and schedule of SRS in clinical practice persist (Box 1). The clinical utility of emerging data on genomic predictors of response (or resistance) to radiotherapy[51,52,261] for decision-making with regards to these questions also remains to be established. This uncertainty is compounded by the well-recognized issues of exclusion or restricted enrolment of patients with brain metastases, and the lack of prespecification protocols for CNS-specific outcomes collection in phase III trials evaluating systemic therapies for solid tumours[262]. This uncertainty in the evidence influencing clinical decision-making needs to be clearly discussed with patients.

Finally, consensus on and high-quality evidence pertaining to these unanswered questions (Box 1) will necessitate further multicentre trials and prospective registry studies with prespecified end points, facilitated by academic research consortia, professional societies and multi-institutional collaborations[10,246]. The optimal conduct of and meaningful inference from future investigations will be enabled by incorporating recommendations emerging from prior multisociety summits on brain metastases[10,263].

Conclusions

SRS has been established as a SOC treatment paradigm for metastatic brain disease, with emerging evidence regarding its role in both the postoperative and preoperative setting, as well as its integration with modern systemic therapies. The emergence of ICIs and CNS-active targeted therapies reaffirms the importance of a multidisciplinary approach to the management of brain metastases. However, several persisting challenges and questions remain to be answered, with corresponding clinical trials ongoing, including (1) upper limits for the number and size of brain metastases that can be safely treated with SRS over the entire course of the disease, (2) the importance of tumour histology for SRS dosing and fractionation (Table 1), (3) the optimal sequence and timing of ICIs and targeted therapies relative to SRS, (4) the best approach to selecting patients for neoadjuvant SRS, along with establishing clear dose delivery guidelines, and (5) how to decide as a multidisciplinary team when limits of what can be achieved with SRS – or other CNS-directed therapies for that matter – have been reached and when the patient would benefit most from BSC (Box 1). The approach to this final question will need to be based on both clinical insights and ethical considerations. Although challenges remain in obtaining safe and durable intracranial control of brain metastases, advances in SRS utilization, delivery, combinatorial approaches and post-treatment monitoring will lead to improved patient outcomes.

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A.M., D.B., A.O., H.W. and E.M. researched data for the article. A.M., A.O., P.D.B. and R.K. contributed substantially to discussion of the content. A.M., D.B., A.O., H.W., E.M. and W.H. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests
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Review criteria This review utilizes data from landmark trials reported over the past two decades along with recent published literature (through database searches using appropriate combinations of search terms related to 'brain metastasis', 'brain malignancies', 'SRS', 'stereotactic radiosurgery', 'radiotherapy', 'whole brain radiotherapy', 'WBRT', 'brain radiation', 'Gamma Knife', 'Cyber Knife', 'LINAC') as well as works presented at the 2022, 2023 and 2024 annual meetings of the Society for Neuro-Oncology (SNO), American Society for Radiation Oncology (ASTRO), American Society for Clinical Oncology (ASCO), and the SNO/ASCO Annual Conferences on CNS Clinical Trials and Brain Metastases. References were also curated from major reviews in the field as well as guideline publications from professional societies. Clinical trials pertaining to brain metastases were also reviewed from ClinicalTrials.gov (accessed 20 September 2024). The final reference list was refined by a multidisciplinary panel with expertise in radiation oncology, medical oncology, neuro-oncology, neurosurgery, neuroradiology and clinical trial design.

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