Stereotactic radiosurgery for brain metastases: current status and future directions

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Abstract The purpose of this review is to provide a comprehensive summary of the management of brain metastases, and the role of stereotactic radiosurgery (SRS), based on the reported randomized controlled trials. An overview of SRS technology is also provided with a focus on the technologic innovations leading to frameless SRS. SRS as it applies to the post-operative patient is also discussed as this treatment will likely be a standard of care option for patients in the future, and currently being evaluated in randomized studies.

Keywords Brain metastases · Radiosurgery · Cavity radiosurgery · Frameless radiosurgery

Introduction

Brain metastases are not only the most common intracranial malignancy, but the incidence has been rising steadily

[1]. For many years, whole brain radiation therapy (WBRT), or supportive care alone, remained the cornerstone of treatment as the prognosis of these patients was generally assumed dismal [2]. However, with increased recognition of prognostic factors specific to patients with brain metastases, and improvements in systemic therapies, subsets of patients that will live years beyond their diagnosis were identified, and alternate more aggressive strategies were in need [3–5].

As radiation and neurosurgical technology evolved, the idea of using radiation as a focal therapy in the brain was pioneered by visionaries like Lars Leksell, and stereotactic radiosurgery (SRS) was born in the 1950s [6]. SRS was initially developed to treat functional neurologic disorders by ablating tissue deep within the brain that could not otherwise be accessed surgically. The treatment then evolved as a focal treatment for brain tumors, and as an adjunct to WBRT for brain metastases to improve local

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Fig. 1 The Leksell Gamma Knife Perfexion

control. Currently, SRS alone is considered, not only an alternative to WBRT, but the treatment of choice for selected patients with brain metastases. The goal of this review is to provide a summary of (1) the recent technological advances in SRS delivery, (2) the latest evidence explaining the role of SRS in the treatment of brain metastases as up-front therapy, and (3) a discussion on the application of SRS in the post-operative patient.

SRS technology

Gamma Knife technology

The latest Gamma Knife model (Fig. 1) has been named the Leksell Gamma Knife (LGK) Perfexion (Elekta, Norcross, GA) [7]. The unit represents a major engineering advance as compared to prior models. The key advantages are as follows: a greater treatment volume space allowing for treatment of lesions otherwise out-of-reach with prior models, multiple rings of collimating holes drilled directly into the one tungsten piece creating three beam sizes of 16, 8, and 4 mm in diameter at the isocenter, an 8-sliding sector design that is computer controlled, each sector is able to slide along the outside surface of the tungsten collimator and align with the different rings of predrilled holes allowing for 192 16-mm diameter beams, 192 8-mm diameter beams, and 192 4-mm diameter beams possible, and blocking achieved by blocking individual sectors and no longer is manual plugging of individual collimating holes required. Ultimately, the new design allows for significant gains in the flexibility of treatment planning, by the ability to create shots that can be a composite of any of the four beam diameters (including zero) within any of the 8 sectors. The clinical gains lie in the rapidity of treatment planning and delivery, in particular, for those cases requiring multiple shot diameters and plugging [8, 9].

Cyberknife technology

The CyberKnife (Accuray, Sunnyvale, CA, USA) consists of a compact linear accelerator (linac) mounted onto a highly flexible robotic arm (Fig. 2) that moves the linac in all six degrees-of-freedom (6 DOF) [7]. The system is inherently coupled to a stereoscopic image guidance system allowing for treatment delivery precision in the order of 1 mm and 1 degree [10]. This was the pioneering technology that propagated frameless SRS, as patients are treated with single fraction SRS in a non-invasive thermoplastic (TP) mask. With the advent of frameless SRS, so did the movement of hypofractionated SRS. By delivering few high dose per fraction treatments, a high total dose can still be achieved while minimizing the risk of necrosis due to the protective effects of fractionation on the normal tissue. This overcomes the total dose reduction required as tumor diameter increases, required for single fraction SRS, to respect the risk of necrosis. A recent retrospective study reported superior rates of local control with hypofractionated SRS as compared to single fraction SRS [11]; however, a randomized controlled trial is required before definitive conclusions can be reached.

Linac SRS

Linac-based SRS was initially developed using circular collimators attached to an existing linac head (Fig. 3), and based on multiple arcs of radiation converging onto the target of interest (Fig. 4). It required either a dedicated linac system (for example, the Novalis BrainLAB, Westchester, IL) or a traditional linac retrofitted to meet stereotactic standards of delivery precision (Fig. 4) [7]. These treatments were frame-based and required a dedicated stereotactic

Fig. 2 The Cyberknife VSI model

Fig. 3 A traditional linac fitted with a circular collimator for arc-based SRS delivery. The patient is immobilized using an invasive head frame and the target localization box in place that serves to verify the isocenter location prior to delivery

treatment planning system that integrated the co-ordinates from the stereotactic frame to the treatment planning CT/

Fig. 4 A 3D representation of linac-based arc delivery illustrating the arc-based arrangement of the beams focused on the target, and a coronal MRI illustrating the target and conformity of the dose distribution (green isodose line around the enhancing mass)

MRI. However, recent technologic advances have allowed SRS to be incorporated into mainstream modern linacs and treatment planning systems, allowing for SRS to be available beyond specialized academic centers and into the community at large [12].

The key current technologic advances in SRS delivery include the development of image-guided radiotherapy (IGRT) [13], high definition micro multi-leaf collimators (MLC) [14, 15], intensity modulated radiotherapy (IMRT), and non-invasive head frames allowing for immobilization that approximates what has become the standard based on the invasive head frame [16].

IGRT is by far the most significant advance allowing for the precision required for frameless SRS. IGRT systems can be grouped according to those based on stereoscopic X-rays, cone-beam CT (CBCT), or both [16, 17]. Stereoscopic X-ray systems typically use a pair of orthogonally placed X-ray tubes that allow for X-ray images to be taken every 30–45 s, that are then co-registered to the digitally reconstructed radiographs (DRR) based on the treatment planning CT. The image fusion relies on an automated process with verification fundamentally based on two-dimensional (2D) skeletal anatomy. This system is well-established and fundamental to Cyberknife and Novalis target tacking technology. However, as CT technology evolved, and it became possible to mount a CT unit onto a linac [or integrate it into the linac itself per TomoTherapy (TomoTherapy Inc., Wisconsin, USA)], CBCT-based IGRT was born. The advantage of kilovoltage CBCT is the acquisition of three-dimensional (3D) imaging allowing for the most accurate match to the corresponding 3D treatment planning CT. Excellent initial setup accuracy using 3D–3D match with both frame based [18] and frameless systems [19, 20] has been observed. The greatest limitation of a CBCT-only system is the inability to obtain intra-fractional images without stopping treatment [20]. To overcome this limitation and ensure the patient's position is correct in near-real time, one of the more significant developments alongside frameless SRS has been the use of in-room infra-red (IR) guided camera systems [21]. In general, a TP mask with an integrated bite block provides the head immobilization while IR reflective fiducial markers placed on the bite plate provides the stereotactic coordinate system registered to treatment isocenter (as defined by the treatment planning CT scan). In room IR cameras provide the real-time positioning feedback during treatment such that if a significant deviation is observed then treatment can be stopped, and the patient repositioned [22].

The transition from circular collimators to MLC based delivery allowed improved targeting and highly efficient treatments of more complex lesions by delivering IMRT based SRS, also known as intensity modulated radiosurgery (IMRS) [14, 15]. Initial IMRS plans typically treated each isocenter sequentially, whereas newer single isocenter

IMRS plans treat multiple lesions simultaneously [23]. This is a major advantage with respect to delivery efficiency. For example, the study by Nath et al. reported a beam on time of 5.4 min for the treatment of multiple brain metastases, the median number of targets was 5, using IR-guided IMRS (overall treatment time was 21 min) [23]. This technique requires significant experience as rotational effects have greater effects on target coverage when the isocenter is not in the center of the target, and why delivery precision is paramount. In an effort to further the efficiency of treatment delivery, volumetric modulated arc therapy (VMAT) is becoming widely practice such that an entire treatment can be delivered in a single 360° gantry rotation [24]. Fifty percent reductions in average delivery times have been reported [24]. The next generation of technology aimed to further delivery efficiency is flattening filter-free photon delivery. It reduces beam on time via doubling or even tripling the beam output of a traditional linac [25]. This ultra-high dose rate may also have unique radiobiologic effects of the target and tumor tissue and requires careful evaluation.

As MLC technology advanced with very small leaf widths, the use of cones is limited to only very small lesions in the brain. Typically, cones are still required for those lesions measuring less than 0.5–1 cm where accurate small-field dosimetry creates a challenge to the use of MLC. One of the limitations to traditional linac systems, as compared to the Cyberknife, lied in the inability to correct the patient's position in all 6 DOF. Technologic developments in treatment couches have resulted in full 6-DOF motion couches; this has been shown to improve the overall accuracy of delivery [26], and another key technology to frameless SRS. It is important to note that despite 6-DOF couches and IGRT, without intra-fraction imaging a simple thermoplastic mask does not meet the strict standards for single fraction SRS as reported by Lightstone et al. [27].

Clinical outcomes focused on randomized controlled trials

The role of surgery and local control

Surgical trials were the first to establish the benefit of aggressive local therapy to improve local control (LC) for patients with brain metastases. The practice changing Patchell study randomized patients to WBRT alone or to surgery plus post-operative WBRT, and concluded superior local control with surgery [28]. In addition, a survival advantage was observed in the surgery plus WBRT arm. This study, and one other randomized controlled trial (RCT) evaluating the same question, justified surgery for single brain metastases in an otherwise fit patient (excellent performance

status, young and controlled extra-cranial disease) [29] followed by WBRT.

However, when both arms were treated with surgery and patients then randomized to post-operative WBRT or no WBRT, we observed in a second Patchell RCT a reduction in both local and distant recurrences in the post-operative WBRT arm (10 % vs. 46 %, $p<0.001$; 14 % vs. 37 %, $p<0.01$, respectively) [30]. We also observed a reduction in the neurologic death rate (44 % vs. 14 %, $p=0.003$) as a result of post-operative WBRT; however, no difference in overall survival or length of functional independence time. It should be noted that the trial was not powered for survival. Overall, one can conclude that when local control is optimized then patients do not benefit with respect to survival from additional WBRT; however, when treated inadequately with WBRT alone then a survival advantage may be observed. Therefore, local control can improve survival in selected patients.

A recent RCT conducted by the European Organization for Research and Treatment of Cancer (EORTC) investigated surgery alone in one of the 4 treatment arms [31]. The Kocher study concluded a 59 % rate of recurrence in the surgery alone arm as compared to 27 % in those treated with adjuvant post-operative WBRT at 2 years. No survival difference was observed as there was no WBRT alone arm. These data represent modern evidence which again concludes that surgery alone is inferior treatment with respect to local control as compared to combined modality therapy. However, one could argue that for patients with a short life expectancy (<3 months), and have undergone a gross total resection, that withholding WBRT is not unreasonable.

The idea of withholding WBRT is based on the notion that it is over-treatment for a patient with a limited number of brain metastases, and to spare the patient the adverse neurocognitive effects of WBRT. In particular as survival is not impacted and these patients are often early in trajectory of their disease, many advocate to treat with focal therapy and reserve the WBRT for later. How do you focally treat the post-operative patient? The answer lies in the more recent development of surgical “cavity” SRS. This treatment is becoming more apparent in the literature and currently being tested in a RCT (Intergroup N107C, NCT01372774). Cavity SRS will be reviewed in more detail in later sections.

The role SRS as an alternative to surgery

With respect to SRS as an alternative to surgery, there has not been a completed RCT to provide conclusive evidence that SRS can replace surgery with respect to efficacy. One RCT was attempted by Muacevic et al., and the study failed to meet the accrual target [32]. The study was reported with

31 patients randomized to SRS alone and 33 patients to microsurgery followed by WBRT. No difference in freedom to local recurrence was noted between the two arms ($p=0.06$), although again this study was closed prematurely and as a result under-powered. Furthermore, we do not have a RCT comparing surgery alone to SRS alone; however, the local recurrence rates in surgery alone arms, based on the reported RCTs discussed above, is poor enough such that we can assume inferiority. With the advent of surgical cavity SRS, one RCT that could potentially change practice is to randomize patients to SRS alone vs. surgery plus cavity SRS. Unfortunately there are major challenges in randomizing patients to a surgical arm as patients often have pre-defined views as to how they want their brain metastases treated and most do not want to undergo a craniotomy unless they have to. Conversely, it would be unethical to randomize a patient requiring surgery to a SRS treatment. Therefore, in modern practice, the role of surgery is for large tumors >3 cm and in those causing significant mass effect and/or edema; otherwise, SRS is the preferred treatment modality.

The role of SRS as boost therapy to WBRT alone

As SRS emerged into mainstream radiation oncology practice, the first question to be answered was if SRS as a boost following WBRT confers any advantage as compared to WBRT alone. At that point in time (1980s), WBRT was largely considered the standard of care. Two RCTs have been reported on this question. Radiation Therapy Oncology Group (RTOG) 95-08 was the major RCT with 333 patients, and patients with 1 to 3 newly diagnosed BM [maximum diameter 4 cm, good performance status, and Recursive Partitioning Analysis [RPA] class 1 or 2 [33]], were randomized to receive WBRT with or without SRS [33]. Results demonstrated a modest but statistically significant improved survival for patients with single metastases treated with WBRT and SRS (median survival of 6.5 vs. 4.9 months, $p=0.0393$). However, on multivariate analysis, the significance of the treatment arm was borderline ($p=0.0533$). Importantly, the trial was powered for this endpoint. No survival benefit was found for patients with multiple BM; however, SRS was shown to improve local control, improve the KPS and decrease steroid dependency. This trial was practice changing and provided evidence to support in patients with a single brain metastases and otherwise fit, that combined modality therapy increased local control and survival as compared to WBRT alone. Furthermore, the study provides evidence that there is a dose response relationship in brain metastases as those metastases treated with combined modality therapy had better local control. The results are conceptually similar to what we observed in the surgical studies of WBRT

alone vs. WBRT plus surgery, with respect to the benefits of more aggressive local control translating into better patient outcomes.

A second and much smaller RCT was reported by Kondziolka et al. [34]. The study was much smaller with a total of 27 patients and included patients with 2 to 4 metastases. The study was stopped prematurely as the primary endpoint of a difference in local control was met. LC rates were 92 % in the WBRT plus SRS group and 0 % for the WBRT only group, and the median time to local progression was 36 vs. 6 months ($p=0.0005$), respectively. Survival was not significantly different and 11 vs. 7.5 months in the WBRT plus SRS arm vs. the WBRT alone arm, respectively. Interpretations of this study are limited given the extremely high local failure rate in the WBRT arm which does not reflect common clinical observations; and therefore, illustrative of bias when sample sizes are inadequate.

A recent meta analysis by Tsao, Xu and Sahgal pooled the reported data from these two RCTs, and concluded no difference in OS with a hazard ratio (HR) of 1.63 (95 % CI 0.72–3.69, $p=0.24$) while LC significantly favoring WBRT plus SRS with a HR of 2.88 (95 % CI 1.63–5.08, $p=0.003$) [35].

The role of SRS alone as compared to WBRT plus SRS boost

With the establishment of SRS improving LC, the next question was whether or not WBRT was in fact necessary, and could be reserved as a salvage therapy. Three major RCT have been reported on this subject, and each with different primary endpoints.

Aoyama et al. reported the first RCT (JROSG 99-1) comparing definitive SRS alone to WBRT plus SRS as a boost [36]. A total of 132 patients with 1 to 4 BM [maximum diameter of 3 cm and a Karnofsky Performance Status (KPS) of 70 or higher] were randomized. The initial trial was designed to be powered for survival; however, due to limited accrual, the trial was stopped once sufficient power for a difference in brain tumor recurrence was reached. From this study, greater local failure and distant brain recurrence rates were observed in those randomized to SRS alone. At 1 year, the rate of new brain metastases appearing was 41.5 % and 63.7 %, and the 1-year local control rate was 88.7 % and 72.5 %, in the WBRT plus SRS and SRS alone arm, respectively. Salvage therapy was used more frequently in the SRS only arm (29 patients vs. 10 patients, chi-squared $p<0.001$). Neurocognitive testing was based on the mini-mental status exam (MMSE), and no significant difference was observed between the two arms.

Chang et al. reported the second major RCT evaluating SRS with and without WBRT [37]. Uniquely, this study was

powered based on detecting a significant difference in neurocognitive outcomes between the two arms. The primary endpoint was based on the Hopkins Verbal Learning Test (HVLT) scores as a measure of neurocognitive function. A total of 58 patients (1–3 metastases and good overall performance status with an RPA class 1 or 2 and KPS $\geq$ 70) were randomized to undergo SRS alone or combined WBRT with SRS boost. The trial was halted early as patients who received both SRS and WBRT were more likely to suffer a drop in HVLT total recall scores at 4 months (52 % mean posterior probability of decline vs. 24 %). This observation persisted at the 6 month time point as well. With respect to local control, WBRT reduced the incidence of new brain metastases and improved local control of the site treated. Therefore, failure did not negate the neurocognitive benefit to SRS alone. This is evidence that the treatment of WBRT itself is what causes impaired neurocognition and not relapse. A RCT of prophylactic WBRT in patients with lung cancer also studied neurocognition using the HVLT, and provided further evidence of the adverse impact of WBRT, and not relapse, on memory [38].

With respect to more traditional outcomes, the combined treatment arm in the Chang study showed worse median survival (5.7 vs. 15.2 months, $p=0.003$). Importantly, this trial was not powered for survival and; therefore, some of the imbalances in the treatment arms favoring the SRS alone cohort may explain the unexpected survival advantage. The imbalances favoring the SRS alone arm consisted of a greater number of patients in RPA class 1 group, more patients having higher GPA scores, a lower total intracranial target volume, and fewer patients with solid organ metastases. Certainly, these factors can explain the survival result. However, we also observe that patients treated with SRS alone received systemic therapy over 1 month earlier, and a median of two more cycles, than those in the SRS plus WBRT arm. Therefore, it is also reasonable to argue that these factors contributed to the survival advantage favoring SRS alone. Ultimately, only a larger RCT powered for survival, or pooled analysis resulting in sufficient numbers of patients to give appropriate power, will provide firm conclusions specific to survival.

Kocher et al. reported the EORTC 22952-26001 study [31]. This is the third and latest RCT to be reported, and powered to determine the impact of SRS alone, as compared to WBRT plus SRS, with respect to performance status decline. This study also evaluated surgery alone as compared to surgery plus WBRT as discussed previously. Patients enrolled in this trial had a good performance status (World Health Organization [WHO] Performance Status [PS] score of 0–2), stable systemic disease, and/or asymptomatic synchronous primary tumors. The primary endpoint was time to a WHO PS of greater than 2. They concluded no difference in functional decline between

any of the arms. The median time to a PS of more than 2 was 10 months in the observation arm and 9.5 months in the WBRT arm ($p=0.71$). On multivariate analysis, the only factors impacting on the primary endpoint were the initial WHO PS (0 vs. 2, $p=0.004$), and presence of systemic tumor ($p<0.001$). No difference in overall survival was found with a median survival of 10.9 months in the observation arm and 10.8 months in the WBRT arm ($p=0.89$). Neurologic death was more frequent in the observation arm (44 % vs. 28 %, $p=0.002$ chi squared). Progression was predictably higher in the observation group with a 2-year relapse rate at the initial site of 59 % vs. 27 % ($p<0.001$), and at new sites of 42 % vs. 23 % ($p=0.008$), as compared to with the use of WBRT, respectively. Salvage therapy was used in 51 % of relapses in the observation arm versus 15 % in the WBRT arm. Of the salvage therapies used, WBRT was used more in the observation group (31 % vs. 3 %), and similar use of SRS was observed in both arms (12 % vs. 11 %).

A meta analysis reported by Tsao, Xu and Sahgal, pooled data from JROSG 99-1 and the M.D. Anderson trial and found no difference in OS with a HR of 0.98 (95 % CI 0.71–1.35, $p=0.88$) [35]. Because of how the survival data were reported in the EORTC study, the authors could not extract the data for the SRS alone and WBRT plus SRS groups for a pooled survival analysis. However, when combining the surgical arms of that study and, therefore, the entire survival result, no survival difference was observed (not reported in study and provided by the corresponding author). With respect to local control and distant brain control, the meta analysis based on data from all three RCT's concluded an expected advantage favoring WBRT for both LC and distant brain control with a HR of 2.61 (95 % CI 1.68–4.06, $p<0.0001$) and 2.15 (95 % CI 1.55–2.99, $p<0.00001$), respectively.

Ultimately, based on these three RCT's and the meta analysis by Tsao, Xu, and Sahgal, it can be concluded that both LC and distant brain control are improved with the addition of WBRT and that there is no survival advantage to either SRS alone or WBRT plus SRS boost therapy. Based on the functional endpoints, it can be concluded that WBRT impairs neurocognition at 4 and 6 months post-WBRT and neither treatment impacts adversely the patient's overall performance status. With respect to relapse, the data support that the development of new brain metastases is not detrimental to neurocognition, or performance status, as long as patients are followed closely and treated with prompt salvage therapy. Therefore, SRS alone should be considered a standard of care treatment option for patients presenting with 1 to 4 brain metastases.

Fig. 5 A 3D representation of linac-based arc delivery illustrating the arc-based arrangement of the beams focused on the target, and a coronal MRI illustrating the target and conformality of the dose distribution (the green isodose line is the prescription 20 Gy isodose and conforms around the enhancing mass)

New directions

Surgical Cavity SRS

Surgery will always have a role in the management of brain metastases; however, as a result of SRS the role of surgery is less pervasive in the patient who presents with a solitary metastases. Certainly, surgery is indicated for patients with symptomatic edema refractory to steroids and requiring rapid relief, when a tissue diagnosis is necessary such that other sites of disease are not amenable to biopsy, for tumors >3 cm, or when significant mass effect/neurologic compromise is present. Despite microsurgical resection, local recurrence rates remain high at 45–59 %, and as discussed the role of WBRT is to reduce the risk of both local recurrence and emergence of new brain metastases. What has come into question is the role of focal radiation to the surgical cavity in an effort to spare patients from post-operative WBRT. The intent is also to dose escalate the cavity as the risk of recurrence is still high at 27 % at 2 years based on the EORTC study with post-operative WBRT. An example of a patient's treatment plan for post-operative cavity SRT, planned for 30 Gy in 5 fractions, is shown in Fig. 5. This is the typical approach at the Sunnybrook Health Sciences Center (University of Toronto, Toronto, Canada) such that the cavity is delineated using the T1 post-gadolinium MRI as the clinical target volume (CTV), and a 2-mm planning target volume (PTV) is then applied. All patients are treated with their head immobilized in a rigid thermoplastic mask, and using the Elekta Synergy unit (Elekta, AB) equipped with a 4 mm MLC (Fig. 6) and a Hexapod robotic couch (Medical Intelligence, Schwabmuenchen, Germany).

A recent review by Roberge et al. evaluated 19 trials consisting of 852 patients treated with resection cavity SRS [39]. Overall crude LC was 79 % and the estimated 1-year actuarial LC was 95 % when weighted by number of patients per trial. The incidence of new distal metastases was 51 %, which is as expected from what we have learned from the RCTs evaluating SRS alone. Late toxicity was reasonable with necrosis rates ranging from 0 to 6 %.

The field of cavity radiation is in its early stages and several questions remain to be answered sufficiently. For example, how to delineate the optimal target volume, is there a need for margin into the brain tissue to encompass

potential microscopic disease (some put ~2 mm beyond the gross cavity), when to deliver treatment post-op, how stable the surgical cavity is during treatment, and the optimal radiotherapy total dose and number of fractions. Although, many use single fraction SRS, due to the irregularity of the volume and often large cavity volume some have been fractionating the radiation using stereotactic techniques. Although the majority of the current clinical data are based on cavity SRS as an alternative to WBRT, Roberge et al. pursued a different strategy [40]. He reported on cavity SRS as a boost to WBRT with the aim to improve upon local control while maintaining the benefits of optimal distant brain control. The SRS dose in his series of 44 patients was 10 Gy/1 fraction, and the WBRT dose 30 Gy in 10 fractions. The actuarial 1 and 2-year LC rate was 91 % with a median follow up of 10.1 months.

Fig. 6 A patient immobilized in a thermoplastic mask on the Elekta Synergy unit equipped with a CBCT unit and the Hexapod robotic couch

Ultimately, what is needed are RCTs evaluating cavity SRS. The NCCTG has an ongoing randomized phase III RCT comparing post-resection SRS vs. WBRT alone (Inter-group N107C, NCT01372774), and we hope will answer the question definitively. In that study, neurocognition and survival are the primary endpoints. The M.D. Anderson Cancer Center is pursuing a slightly different question, and accruing to a phase III RCT comparing post-operative SRS vs. observation for completely resected metastasis (NCT00950001). The primary endpoint is LC. Both studies are important and will guide the future application of cavity SRS.

Conclusions

The treatment of patients with brain metastases has evolved in complexity as patients are living longer. The focus of treatment has shifted from WBRT to focal therapy in an effort to preserve neurocognition without a survival detriment. The next few years will yield very exciting data, and contribute to patient-centered care rather than the one size fits all approach of the past with WBRT alone.

Conflict of interest None of the authors have any conflicts of interest to declare.

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