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Neoadjuvant Stereotactic Radiosurgery: a Further Evolution in the Management of Brain Metastases

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Abstract

Purpose of Review Recent randomized evidence has supported the use of resection followed by stereotactic radiosurgery (SRS) as standard of care for patients with a limited number of brain metastases. However, there are known toxicities, including a relatively high incidence of leptomeningeal disease. Neoadjuvant SRS has been proposed to minimize these potential sequalae. This review summarizes the current data and principles for neoadjuvant SRS.

Recent Findings Recently published studies have demonstrated neoadjuvant SRS to be feasible and to achieve similar oncological outcomes to postoperative SRS. A decreased incidence of leptomeningeal disease and radionecrosis has been observed. Additionally, neoadjuvant SRS can improve accuracy of target volume delineation and decrease the volume of irradiated normal tissue.

Summary Neoadjuvant SRS has emerged as a promising sequencing management approach. Its main advantages appear to be in reduction of toxicity. Ongoing trials will further explore this treatment method and establish which patients will benefit most from this technique.

Keywords Brain metastases · Stereotactic radiosurgery · Preoperative · Postoperative · Leptomeningeal disease · Radionecrosis · Neoadjuvant

Introduction

Brain metastases are a common occurrence for cancer patients with incidences of approximately 30–45% in patients with melanoma, breast, and lung cancer [1–3]. Treatment can include local modalities (including resection and/or stereotactic radiosurgery [SRS]), whole brain radiotherapy (WBRT), and systemic therapies. SRS is a widely accepted local treatment modality which allows the precise delivery of high and ablative doses of radiation to brain metastatic lesions with minimal irradiation of surrounding tissues [4]. Multiple randomized trials have evaluated whether WBRT can be omitted in patients receiving SRS [5–8]. Whilst the addition of WBRT decreases local and distant intracranial failure rates, it has not been shown to result in an overall survival benefit. Importantly, less acute toxicities and neurocognitive decline is observed in patients receiving SRS alone [9].

Resection followed by SRS has recently been analyzed in two randomized control trials [9, 10]. Mahajan et al. compared gross total resection alone with the same followed by SRS [10]. One-year local control improved from 43 to 72% with SRS but there was no improvement in distant brain control or OS. A trial reported by Brown et al. demonstrated that patients undergoing postoperative SRS had worse intracranial control but similar OS to postoperative WBRT [9]. However, patients undergoing

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postoperative WBRT had significantly worse cognitive deterioration with 85% of patients being affected at 6 months compared to 52% in the SRS cohort.

The recommendation for resection of limited brain metastases and preference for the addition of SRS instead of WBRT is reflected in current guidelines [11]. However, an increase in leptomeningeal disease (LMD) has been observed for patients undergoing resection and postoperative SRS compared to SRS alone [12]. The rate of LMD can be as high as 35% in patients undergoing resection followed by SRS and can occur in a median of less than 4 months [13•, 14, 15].

Recently, immunotherapy and targeted therapies have demonstrated increased CNS penetrance and improved efficacy extracranially [16–18]. Due to patients living longer with decreased extracranial disease burden, the need for effective local therapies with minimal toxicities is required. SRS before resection has been proposed as an alternative to postoperative SRS [19]. Neoadjuvant radiotherapy has advantages in treating primary malignancies such as soft tissue sarcoma, rectal adenocarcinoma, and esophageal cancer in order to downstage the tumor, facilitate radiotherapy planning and delivery, and reduce toxicity [20–22]. In this review, we detail the rationale and expanding current evidence for the regimen of neoadjuvant radiosurgery (NaSRS) for brain metastases.

Current Evidence

NaSRS is not a new treatment approach, with reports in the literature of its use in Japan as early as the late 1990s [23] (Table 1). Groups from North Carolina and Georgia have published the strongest body of evidence for NaSRS [19, 24–27, 28••]. After first presenting their data in 2010, they have published multiple papers of their growing experience of treating patients with NaSRS since 2005. The most recent update was a case series of 117 patients treated from 2005 to 2016 [28••]. Patients underwent NaSRS at a median period of 2 days before resection. The median tumor volume was 8.3 cm^3 (IQR 4.6–13.3) and the median dose was 15 Gy (IQR 14–17). The 1-year local control rate was 80.1%. The 1-year distant intracranial control rate was 54.7%. One-year overall survival (OS) was 60.6% with a median OS of 17.2 months (95% CI 12.3–22.1). One-year LMD and radiation necrosis (RN) rates were 4.3% and 5.1% respectively. Grade 3 toxicity was observed in 2.6%.

The same group have compared NaSRS retrospectively to adjuvant SRS [24]. There was no significant difference in tumor volume, number of lesions treated or location. However, considerably more NaSRS patients were ECOG 0 prior to treatment (62% vs. 28%) and had a breast primary (27% vs. 11%). The median dose was 14.5 Gy for NaSRS and 18 Gy for adjuvant SRS. No difference was observed for local or distant control. However, improvements in OS, LMD, and RN were observed for the NaSRS cohort. The NaSRS cohort had a significantly longer median OS, 17.1 vs 13.5 months ($p = 0.04$), which is likely due to the proportion of ECOG 0 patients. The 1-year LMD rate was 3.2% in the NaSRS group vs 8.3% in the adjuvant group ($p = 0.01$). The difference in 1-year RN was even larger with an incidence of 1.5% in the NaSRS cohort compared to 14.6% in the adjuvant cohort ($p = 0.01$).

Subsequently, preoperative SRS was compared to postoperative WBRT [25]. No significant difference was observed for 1-year OS and 2-year local control, distant control or LMD. No patients in the WBRT cohort developed RN whilst nearly 10% of NaSRS patients did. However, there was heterogeneity between the two cohorts. Compared to the WBRT cohort, patients undergoing NaSRS had smaller lesions (median volume, 8.3 for NaSRS vs. 14 cm^3 for WBRT), less multiple lesions (> 1 lesion, 35% vs. 61%) and improved performance status at baseline (ECOG 0, 63% vs. 28%).

>Prabhu et al. compared NaSRS ($n = 63$) and adjuvant SRS ($n = 94$) and SRS alone ($n = 60$) [26]. One-year local control was significantly decreased for SRS alone with rates of 77.5% for NaSRS, 80.9% for adjuvant SRS and 63.3% for SRS alone. The combination of SRS and resection was also significantly superior for OS (1-year OS rate 58.3% vs 58.3% and 42.5%). For RN, significantly higher rates were observed in the adjuvant SRS cohort (1-year rate 22.6%) compared to the NaSRS and SRS alone cohorts (12.3% and 5.0%). At the 2-year interval, there was a trend toward increased LMD for adjuvant SRS (16.1%) compared to NaSRS (5.9%) and SRS alone (5.0%) ($p = -0.12$).

In 2018, a group from University of Texas Southwestern published their retrospective experience of NaSRS in a cohort of 12 patients with a single brain metastasis [29]. The median time period between NaSRS and resection was 1 day. The median maximum tumor diameter was 3.66 cm (range 2.19–4.85 cm) and tumor volume was 14.69 cm^3 (3.38–34.85 cm^3) The median dose was 16Gy (range 12–21 Gy). Whilst local control was achieved in 81.8% at 6 months, this decreased to 49.1% at 12 months. Distant intracranial control was 72.7% at 6 months and decreased to 14.5% at 12 months. Compared to the North Carolina/Georgia groups, these rates of intracranial control were lower which may be explained by patient characteristics, tumor characteristics and/or statistical methods (Kaplan-Meier vs. cumulative incidence methodology). The dose of radiation may also have contributed with some patients receiving as low as 12 Gy. Additionally, this is a smaller cohort, more patients underwent a piece-meal resection, more metastases were located in the posterior fossa, metastases were larger and there was a different proportion of primary malignancies. Twelve-month OS was 74.1% and LMD occurred in 10% with no RN observed.

A Russian group led by Vetlova et al. published a series of 19 patients with 22 brain metastases in 2017 [30]. Resection

Table 1 Summary of current evidence of NaSRS

Paper	Study design	Years	Patients	Timing of surgery	1-year outcomes					
					Local control	Distant control	Overall survival	LMD	RN	Grade 3 toxicity
Prabhu et al. 2018 [27]	Retrospective cohort	2005–2016	117	2 days (median)	80.1%	54.7%	60.6% (median 17.2 months)	4.3%	5.1%	2.6%
A. Patel et al. 2018 [28••]	Retrospective cohort	2011–2015	12	1 day (median)	49.1% (6-month, 81.8%)	14.5% (6-month, 72.7%)	74.1% (6-month, 83.3%)	10%	0%	–
Vetlova et al. 2017 [29]	Retrospective cohort	2015–NR	11	< 48 h	91% (O)	73% (O)	91% (O)	9% (O)	0%	–
K. Patel et al. 2016 [23]	Retrospective cohort	2005–2013	66	< 48 h	84.1%	68.0%	**17.1 months (median)**	**3.2%**	**1.5%**	–
	NaSRS vs. adjuvant SRS	*Adjuvant SRS*	*114*		*87.4%*	*60.9%*	***13.5 months (median)***	***8.3%***	***14.6%***	–
K. Patel et al. 2017 [24]	Retrospective cohort	2005–2013	66	< 48 h	75.5% (2-year)	46.8% (2-year)	59%	3.5% (O)	9.9% (O)	–
	NaSRS vs. adjuvant WBRT	*Adjuvant WBRT*	*36*		*74.9% (2 years)*	*55.0% (2 years)*	*55%*	*3.5% (O)*	*5.6% (O)*	–
Prabhu et al. 2017 [25]	Retrospective cohort	2005–2013	63	< 48 h	**77.5%**	NR	58.3%	5.9%	**5.0%**	–
	NaSRS vs. adjuvant SRS vs. SRS alone	*Adjuvant SRS*	*94*		***80.9%***	*NR*	*58.3%*	*5.7%*	***22.6%***	–
		SRS alone	*66*		***63.3%***	*NR*	*42.5%*	*1.9%*	***12.3%***	–
Yamamoto et al. 2011 [22]	Retrospective cohort	1998–2008	16	NR	75.0% (O)	68.8% (O)	10.5 months (median)	**6.2% (O)**	NR	–
	NaSRS vs. adjuvant SRS	*Adjuvant SRS*	*16*		*93.8% (O)*	*56.3% (O)*	*8.9 months (median)*	***43.8% (O)***	*NR*	–
Clark et al. RAD 1002 2016 [31]	Phase 1 prospective	2011–2012	12	< 30 days	NR	NR	91.7% (90 days)	NR	NR	16.6% (< 90 days SRS)
Bredel et al. RAD 1002 2016 [32]	Phase 1 prospective	2011–2015	20	< 30 days	NR	NR	NR	NR	NR	20.0% (< 90 days SRS)

Italics, comparative treatments. Bold, statistically significant. *NR*, not reported; *O*, overall, not 1-year outcomes. *No comparison was performed within 48 h of SRS. Only 11 of the 19 patients were those with de novo brain metastases as some underwent salvage SRS for a local recurrence after prior SRS or resection. The median dose was 18 Gy (range 14.8–24.36 Gy). At a median follow-up of 6.3 months (range 1.3–17.9), local control was 91%, distant control was 73% and OS was 91%. LMD occurred in one patient (9%).

Multiple other series have been presented over the last decade. In 2011, Yamamoto presented an abstract comparing 16 patients undergoing NaSRS to 139 patients adjuvant SRS [31]. In a propensity-matched analysis, there was no significant difference between the techniques regarding local control, distant control, and overall survival. However, significantly decreased rates of LMD (6.2% vs 43.8%) were observed in the NaSRS cohort.

Acute toxicity rates for 20 patients from a phase I trial, RAD 1002, have been presented as abstracts in 2013 and 2016 [32, 33]. Patients underwent resection within 30 days after SRS. Within 30 days of resection, no grade 4 or above toxicity had been observed. Four patients (20%) experienced grade 3 toxicity, requiring intervention for a wound complication, pseudomeningocele or hemorrhage. The 90-day overall survival was 92%. The 1-year rate of LMD was 5%.

Three series have performed dosimetric analysis comparisons between postoperative SRS and hypothetical NaSRS planning volumes [34–36, 37•]. In a study published in 2019, El Shafie et al. examined treatment plans for 24 patients who had received postoperative SRS [37•]. For NaSRS plans, a significantly reduced irradiated volume of healthy brain was observed. Using an endpoint of dose greater than 28 Gy, the volume of healthy brain irradiated was 6.79 cc for NaSRS compared to 10.79 cc for postoperative SRS ($p = 0.005$). A study by Aliabadi et al. compared plans in 13 patients [34, 35]. Tumors were separated into those smaller and greater than a preoperative size of 15 cc. For tumors with an original volume < 15 cc, a significantly decreased mean volume was irradiated in the NaSRS cohort (9.5 vs 16.8 cc, $p < 0.01$). No significant difference was observed for those with larger size metastases. Twenty patients were included in a study by Rogers et al. [36]. The irradiated volume (planning target volume, PTV) for the postoperative plans was larger than that of the NaSRS plans in 70%. The mean increase in PTV was 160% (range 18–530%). Similar to Aliabadi et al., the benefit of NaSRS was more apparent for smaller volumes. For tumors < 2cm^3, the PTV volume increased by a mean of > 200% in the postoperative plans.

Rationale for Neoadjuvant SRS

Leptomeningeal Disease

One of the major rationales for NaSRS is to decrease the risk of leptomeningeal dissemination. LMD is a devastating process often with a poor prognosis due to limited treatment options [38]. Surgical resection of brain metastases carries a risk of increased LMD [39]. Radiographic LMD relapse in the surgery and postoperative SRS setting was recently shown to be clinically significant in terms of neurologic symptoms, receipt of salvage therapy, and survival in a multi-institutional

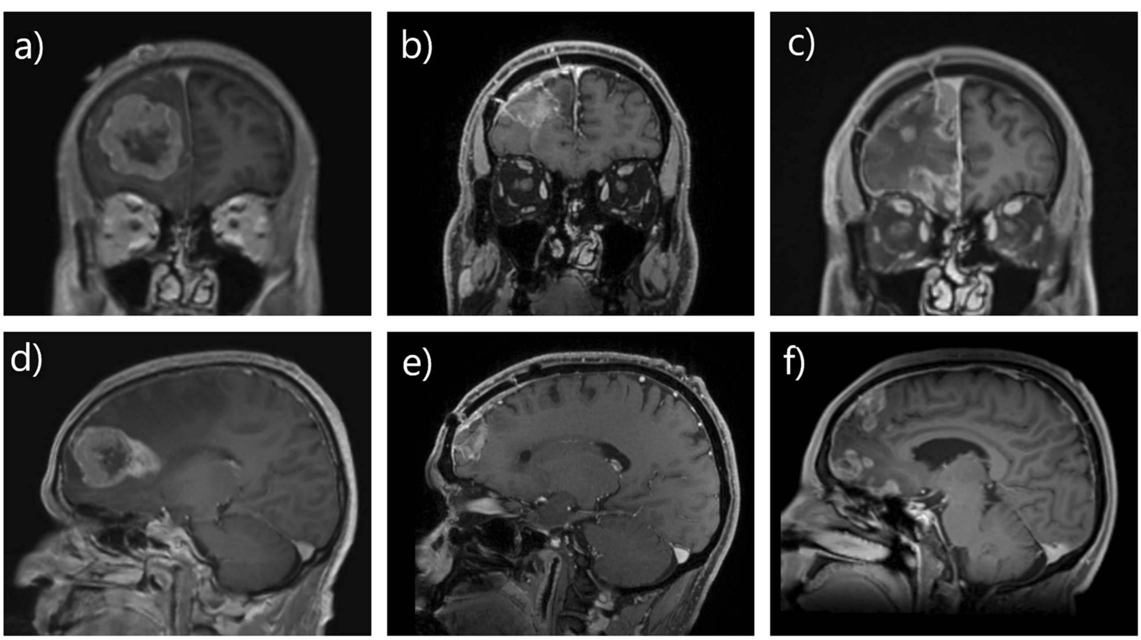

Fig. 1 Coronal and sagittal MRI sequences of a patient who rapidly developed LMD after resection and adjuvant SRS. Preoperative (**a** and **d**), postoperative before SRS (**b** and **e**), widespread LMD in less than 6 months after SRS (**c** and **f**)

retrospective study [40, 41]. Tumor spillage occurs as anatomic borders are disrupted after surgical resection and causes tumor cells to disperse along meningeal surfaces (Fig. 1). The use of NaSRS has been proposed to sterilize malignant cells and prevent viable tumor spillage during resection. Whilst it can be distant, the site of LMD is most likely to be within 5 cm to the resected tumor site [41]. The theory is that irradiated tumor cells have a decreased ability to proliferate and even if there is spread to adjacent sites via spillage into CSF at the time of surgery, these cells have less chance of causing LMD. A number of factors have been found to be more likely associated with LMD including breast primary, piecemeal resection, tumor volume, posterior fossa location, and contact with the CSF pathway [39, 42–45]. Patients with these features would likely gain the most benefit from NaSRS.

Contouring

NaSRS may improve the accuracy of target definition for contouring. Target volume delineation of intact metastases is relatively straightforward with adequate imaging, requiring identification of the contrast-enhancing and/or space occupying lesion. This has a high level of reproducibility compared to cavity delineation in adjuvant SRS. The contouring of surgical cavities is generally more challenging due to postoperative changes which result in the ambiguous definition of the target volume (Fig. 2). There tends to be greater variability amongst clinicians in defining the postoperative clinical target volume (CTV) [46]. Recent consensus guidelines from ten worldwide experts for contouring of surgical cavities for postoperative SRS displayed disparate inter-rater agreement [46]. This inconsistency was particularly evident for brain metastases in an infra-tentorial location, and in contact with the venous sinus. As demonstrated by Vellayappan et al., significantly less inter-observer variability and improved plan conformity is evident for NaSRS compared to that of postoperative SRS [47]. Due to difficulty in contouring the postoperative cavity, a margin of 1–2 mm is generally added to reduce the risk of geographic miss in the postoperative setting [48].

Radionecrosis

The irradiated volume of brain tissue could be decreased with NaSRS (Fig. 2). Exposing large volumes of normal brain to moderate isodoses in radiosurgery can lead to toxicity [49]. Dosimetric studies have demonstrated the reduction in the volume of irradiated normal brain tissue for hypothetical NaSRS plans when compared to postoperative SRS for the same lesions [37•]. In contouring guidelines, additional tissue is recommended to be included in the GTV and CTV along with the complete contrast-enhancing cavity [46]. This includes the surgical tract as well as a 5–10-mm extra margin along the bone flap if the tumor was in contact with the dura preoperatively. If the tumor was not in contact with the dura or if it was in contact with a venous sinus then a 1–5-mm margin was recommended to be added to the cavity. In comparison, only the metastasis is included in the target volume for NaSRS lesions with no need for normal tissue to be included. Due to the decreased volume irradiated, dose de-escalation may even be possible with NaSRS. Compared to their standard SRS protocol, Asher et al. reduced the NaSRS dose by approximately 10–20% with comparable local control [19]. The combination of this dose reduction and decrease in normal tissue irradiated could lead to lower rates of RN.

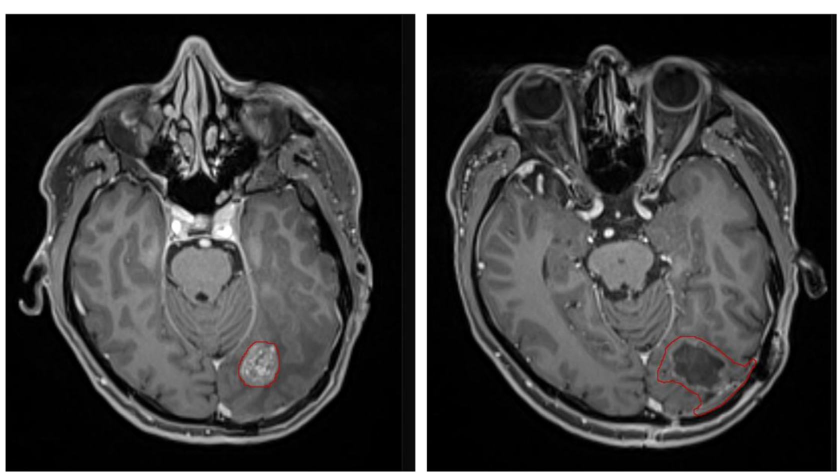

Fig. 2 Comparison of target volumes between NaSRS and adjuvant SRS for the same patient

Post-Treatment Complications

Whilst surgical resection of brain metastases is generally safe, up to 20% of patients will suffer from 30-day morbidity [50]. This could potentially delay or even result in patients not being able to receive adjuvant SRS. This was observed in a phase II trial where 20% of patients did not proceed to planned SRS after resection [51]. For NaSRS, there should be minimal barriers to patients proceeding to resection. SRS-induced acute toxicity is rare with < 3% requiring hospitalization in the 2 weeks after [52]. Additionally, a delay in patients receiving adjuvant SRS could result in systemic therapy being withheld for a longer period of time.

Logistics and Requirements of Postoperative SRS

NaSRS may be easier to implement with less time burden to the patient as well as be less resource intensive. Patients would be able to undergo both NaSRS and resection in a decreased total treatment time overall or even a single hospitalization. Most NaSRS series have dictated short timelines of approximately 48 h between SRS and resection. However, there have been no comparison to other periods and a longer timeframe may be acceptable. For adjuvant SRS, there is conflicting evidence regarding the optimal interval between resection and SRS [53, 54]. Additionally, postoperative SRS requires a follow-up MRI to assess the response of the tumor to resection and to guide contouring for radiotherapy. Postoperative tumor cavity dynamics are unpredictable and can change significantly in the weeks after resection [55]. Therefore, a repeat MRI as close as possible to postoperative SRS is required [56].

Tumor Radiobiology

Due to the oxygen enhancement ratio, the efficacy of radiotherapy is decreased in hypoxic environments [57]. This scenario would be expected in the tumor bed and surgical tract after resection. Therefore, in the non-hypoxic pre-resection microenvironment, tumor cells may be more radiosensitive. Hence, NaSRS would be more effective and potentially require a reduced dose for the same probability of tumor control.

Potential Pitfalls

Histopathological Considerations

Historically, 11% of patients with a radiographically suspected single brain metastasis was found to not have metastatic lesions after biopsy or resection in a 1990 trial [58]. Therefore, if this occurred in patients planned for NaSRS, patients could be subject to unnecessary radiotherapy. However, contemporary imaging is much more advanced. There is a higher accuracy in regard to detecting brain metastases and differentiating between brain metastases and other intracranial pathologies [59, 60]. This has been demonstrated in recent studies, where Prabhu et al. reported only a single patient out of 118 (0.8%) having unexpected non-metastatic disease after treatment with NaSRS and resection [28••].

Alterations in Management Plans

Treatment plans are always dynamic and patients initially planned for resection followed by SRS may have SRS withheld for a number of reasons. Intra-operatively, there may be difference in tumors macroscopically. Known lesions may have progressed or new lesions could have been found since the most recent MRI. Some patients may be more suitable for surveillance with salvage SRS or other treatment options including WBRT, further resection or supportive care. Peri-operative complications, before or after SRS, may significantly impact overall outcomes and quality of life. However, the rate of not completing planned surgery after NaSRS is low due to the relatively short period of time between the 2 treatments. In the recent study by Prabhu et al., only 2 of 120 patients (1.7%) treated with NaSRS did not proceed to planned surgery, both due to unrelated intercurrent illnesses [28••]. This reinforces the importance to select patients who are appropriate for NaSRS and resection with multi-disciplinary input. Strict protocols would need to be followed including the interval from NaSRS to resection and appropriate imaging follow-up.

Wound Complications

It is not clear whether NaSRS would increase the risk of wound or other postoperative complications compared to adjuvant SRS. There is no conclusive association for radiotherapy with wound healing or surgical site infection in CNS malignancies [61–63]. As per current guidelines for postoperative SRS, the surgical tract is recommended to be irradiated. This area of the brain can either be avoided or the dose minimized in comparison in the setting of NaSRS which could potentially lessen the dose to normal tissue. In neoadjuvant radiotherapy for other malignancies, increased wound complications have been observed in sarcoma but not in rectal cancer [21, 64].

Current Trials

Many trials exploring NaSRS for brain metastases are currently underway. Cohorts generally include patients with four or less brain metastases with maximum dimensions of 40–60 mm. Two are phase I dose escalation/de-escalation studies [65, 66]. In the RAD1002 trial, brain metastases from 2 to

4 cm received 15 Gy initially and tumors 4–6 cm received 12 Gy [65]. A phase I/II trial from the Case Comprehensive Cancer Center is estimated to complete recruitment shortly [67]. Resection is performed 2 weeks or less after SRS with a primary outcome of maximum tolerated dose and local control. Phase II trials from Indiana and Toronto have recently commenced which focus on local control and radiation toxicity respectively [68, 69].

Conclusion

After early evidence, neoadjuvant radiosurgery is a feasible treatment option for patients with limited brain metastases. Similar outcomes to adjuvant SRS regarding overall survival, local control and distant control have been observed. The major potential advantage for NaSRS appears to be decreasing the risk of leptomeningeal disease and symptomatic radiation necrosis. NaSRS may be most appropriate for a subset of patients including those at a higher risk of LMD and for those who do not require acute neurosurgical management. Multi-disciplinary input from radiation oncologists, neurosurgeons, medical oncologists and radiologists is vital for NaSRS to occur successfully. Further questions regarding the optimal timing of SRS before resection, the role of dose de-escalation, concurrent use of systemic therapies and neuro-cognitive outcomes need to be explored.

Compliance with Ethical Standards

Conflict of Interest Cristian Udovicich, Claire Phillips, David Kok, Damien Tange, Nikki M. Plumridge, Roshan S. Prabhu, and Neda Haghighi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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