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Preoperative Radiosurgery in Management of Brain Metastases

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Authors' contributions

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

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ABSTRACT

Brain metastases (BMs), the most frequent intracranial tumors, are diagnosed in approximately 30% of all adult patients over the span of planned treatment against a broad spectrum of solid cancers. The prognosis of patients presenting with BM is bleak with an expected median OS of only 4-7 months. However, some particular patients' groups may enjoy longer survival durations with effective systemic and local therapies. At present, the feasible alternatives for active management of BMs typically include the whole-brain radiotherapy (WBRT), surgery, definitive SRS, postoperative SRS, systemic chemotherapy, targeted therapies, and their combination variants. Considering the local treatment, the severe neurotoxic effects of WBRT, and the

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increased risk for radionecrosis and leptomeningeal dissemination after postoperative SRS and together with the ineligibility of certain patients during the postoperative period prompted the energetic quest of alternative treatment strategies for such patients. In this respect, the novel preoperative SRS (PO-SRS) was proposed to provide at least equivalent local control rates with lesser radionecrosis and leptomeningeal dissemination risk. Respecting the scarcity of related literature, the present review aimed to meticulously detail theplausible rationale and accessible evidence for the novel PO-SRS in the management of patients presenting with BMs.

Keywords: Brain metastasis; postoperative stereotactic radiosurgery; local control; survival; complications.

1. INTRODUCTION

Brain metastases (BMs) are relatively almost 10-fold more frequently diagnosed than all other primary brain tumors [1]. For notable instance, the incidence of BM is 20-fold higher than the most common adult brain tumor, namely the glioblastomamultiforme [2]. Regrettably, the incidence of BM typically tends to further increase in the near future due to the implementation of more frequent patient surveillance with dedicated imaging leading to more remarkable rates of detection and allowance of more extended times for BM occurrence in the presence of more effective locoregional and systemic treatments, which significantly enhanced overall survival (OS) times than ever before, particularly the targeted chemotherapies [3]. However, likewise the conventional systemic chemotherapeutics, strikingly contrasting with their excellence in locoregional and systemic tumor control, the potential disadvantage of such targeted agents in common is their inefficiency in penetration of the blood-brain-barrier (BBB) which adds to the increased BM rates.

The risk for development of BM during the disease course varies widely depending on the index primaries, but lung carcinoma, breast carcinoma, and malignant melanoma originated BMs accounts for almost 80% of all BMs [4]. Although the ultimate risk of BM occurrence is 10% to 40% in an average cancer patient, this risk routinely exceeds 50% in autopsy series [4]. The prognosis of patients presenting with BM is dismal with an expected median OS of 4-7 months [5] but some particular patients' groups may survive considerably longer than the expected short survival times: anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer patients may live a median of 49.5 months after the BM development with the use of radiotherapy (RT) in the form of stereotactic radiosurgery (SRS) or whole-brain RT (WBRT) and tyrosine kinase inhibitor therapy [6]. Such evidence suggests that the interventions aiming to control the intracranial disease are critical in certain patients' groups to prolong survival times. Asserting the prime importance of BM control, it has also been exhibited that the death of patients with uncontrolled BM was commonly attributable to neurological dysfunctions rather than the extracranial disease progression, which remains the leading cause of mortality in the well-controlled BM counterparts [7]. So also, the life quality of some patients may be meaningfully improved with effective local interventions by mitigating the neurocognitive complications of BM, even if they do not prolong the remaining survival spans [8].

Currently, the viable options for active management of BMs include the WBRT, surgery (if feasible), definitive SRS, postoperative SRS, systemic chemotherapy, targeted therapies, and their various combinations. However, legitimate concerns about the apparent lack of efficient BBB penetration of most of the systemic agents, the severe neurotoxic effects of WBRT, and the increased risk for radionecrosis (RN) and leptomeningeal dissemination (LMD) after postoperative SRS and together with ineligibility of some patients during the postoperative period led to the eager search of alternative treatment maneuvers for these patients' gathering. In this setting, one such novel maneuver in common is the preoperative SRS (PO-SRS) which is proposed to induce at least equivalent local control rates with lesser RN and LMD risk. The present review aims to meticulously detail theplausible rationale and accessible evidence for the PO-SRS in the management of patients presenting with BMs.

2. RATIONALE AND EVIDENCE FOR PO-SRS

For decades, WBRT stayed as the broadly recognized historical standard of consideration for the management of BMs with an expected OS

of 2 to 11 months relying upon the prognostic stratification [9-11]. In 1990, with the ultimate aim to meaningfully improve these outcomes, Patchel et al. published the results of their benchmark trial investigating the role of neurosurgical BM resection added to the standard WBRT and demonstrated that the surgical removal of the BM prior to WBRT significantly lengthened the OS durations from 15 to 40 weeks (P<0.01) in patients presenting with a single BM [12]. Although the follow-up study of the same group failed to confirm these findings (P=0.39), yet, the surgery plus WBRT arm was superior then the WBRT alone arm regarding the significantly lower rates of the local and distant brain failures and neurological death [13].

With an end goal to positively enhance the adverse outcomes, the Radiation Therapy Oncology Group (RTOG) researchers conducted a milestone phase III trial (RTOG 95-08) to compare the WBRT alone against the WBRT plus SRS in patients presenting with 1 to 3 BMs [14]. Although the authors could not demonstrate a notable OS advantage with the addition of SRS to WBRT, yet, the patients with a single BM appeared to exhibit notably improved median OS durations (6.5 vs. 4.9 mo; P=0.04) with SRS boost after WBRT compared to their WBRT alone counterparts. Nonetheless, perceiving the negative neurocognitive impacts of WBRT in the absence of OS benefit with its addition to neurosurgical tumor removal, several researchers investigated SRS alone against SRS plus WBRT for up to 3-4 BMs [15-18]. The published results of these studies demonstrated that albeit the intracranial and local tumor control rates were inferior in the SRS alone group, the omission of WBRT exerted no detrimental effect on the OS outcomes. Because of the intentional omission of WBRT did not detriment the survival outcomes, and as SRS alone achieved nearly a 30% reduction in the neurocognitive decline rates [16,17] with accompanying improvement in the quality of life (QOL) outcomes [18], SRS alone became the choice of initial treatment for patients up to 4 BMs.

Surgery alone or combined with WBRT or postoperative SRS is another substantial treatment alternative for select BMs. Although the surgery and SRS are recognized to be comparative treatments, to our best knowledge, there has never been a large-scale randomized controlled phase 3 trial reported to directly compare these two alternatives. The usual indications for surgery in medically fit patients presenting with a limited number of BMs incorporate; 1) requirement for decompression of significant mass effect, 2) presence of BMs >2 cm, 3) need for decompression surgery for mitigation of steroid-refractory neurological symptoms or antiepileptic refractory seizures, and 4) requirement for tissue diagnosis. Particularly, surgical resection of large and symptomatic BMs may promptly resolve the tumor mass effect and associated edema with resultant alleviation of symptoms and improvement of QOL measures in the most affected cases. Furthermore, in select patients group presenting with large BMs, the combination of surgery with SRS may improve local control (LC) and OS rates in a significant manner compared to SRS alone [19-21]. For BMs, surgical resection as a single definitive treatment modality isn't competent to accomplish palatable LC rates with an estimated 1 to 2-yr local recurrence (LR) rate of 47% to 59% [22]. Therefore, RT either in the form of WBRT/postoperative SRS or PO-SRS is required to enhance the inadmissible LC rates. In this setting, regarding the WBRT-related severe neurocognitive complications, postoperative SRS or PO-SRS seem to be suitable adjuvant or neoadjuvant RT options.

Traditionally based on the favorable results of the Patchell's randomized trial, WBRT has been considered as the adjuvant standard of care for surgically resected BMs [12]. Concerning the severe neurocognitive toxicity of WBRT, postoperative SRS was proposed as a viable alternative for adjuvant WBRT with a 70% to 100% overall crude LC rates [23-42]. In a recently published NCCTG randomized, controlled, phase 3 trial (N107C/CEC·3) 194 patients from 48 centers were enrolled and randomly assigned to SRS (N=98) or WBRT (N=96). At a median follow up of 11·1 months, although there was no significant difference between the median OS times between the two groups (12.2 months for SRS vs. 11.6 months for WBRT; P=0.70), the neurocognitive-deterioration-free survival was longer in the SRS (3·7 vs. 3.0 months; p<0·0001) than in the WBRT arm. Similarly, the 6-month neurocognitive dysfunction rate was also higher in the SRS group (85% vs. 52%; P<0·0003) [41].

The important discoveries of the postoperative cavity SRS studies were the excessive rates of local recurrences (≤44%), radiation necrosis (≤49.4% in 24 months), LMD (≤31%, mostly in 1-year of treatment), the considerable potential for

higher neurotoxic events due to the necessity for planning target volume (PTV) margins, and target volume definition difficulties caused by the postoperative cavity dynamics [3,43-46]. Therefore, taken together, these significant restrictions of the postoperative SRS soundly expanded the enthusiasm for PO-SRS as a theoretically valid alternative, likewise the many other tumor primaries, like rectal cancers.

3. PREOPERATIVE SRS

Preoperative RT with concurrent chemotherapy represents the current standard of care for various tumor types including the sarcomas, rectal, esophageal, and pancreatic cancers [47-50]. Likewise, mainly because of the aforementioned drawbacks of postoperative SRS, the PO-SRS has emerged as a novel treatment modality to maximize the LC rates while minimizing the RN and LMD of postoperative SRS, and the neurocognitive detriment of standard WBRT.

Though the first use of PO-SRS goes back to the Japanese studies performed in1990s, yet the strongest evidence comes from the North Carolina and Georgia groups [21,51-54]. After the publication of the initial study including 47 patients treated PO-SRS from the Levine Cancer Institute and Carolinas Medical Center which revealed 85.6% LC at 1-year (51), the same group reported 1-year LC of 80.1% in an updated series of 117 patients treated with a median PO-SRS dose of 15 Gy administered at a median period of 2 days before the surgical resection (54). The dose used in this study was approximately 20% reduced dose that was used in the RTOG protocol 90-05 [55]. The 1-year respective RN and LMD rates were 5.1% and 4.3% with an overall grade 3 toxicity rate of 2.6%. In a follow-up multi-institutional study, the same group retrospectively compared PO-SRS with postoperative WBRT [53]. The authors reported that there was no difference in OS or 2-yr cavity recurrences between the PO-SRS (24.5%) and adjuvant WBRT (25.1%) groups (P=0.81). Suggesting that preoperative SRS is capable of sterilizing tumor cells that could be spilled to the cerebrospinal fluid at the time of neurosurgery, the authors demonstrated that there was no difference in LMD rates between the two groups at the 2-year time point (3.5% for PO-SRS vs. 9.0% for adjuvant WBRT; P=0.66). However, the PO-SRS was inferior to adjuvant WBRT in terms of overall RN development [9.9% (5.6% symptomatic) vs. 0%; p<0.05].

The PO-SRS has also been compared with postoperative SRS. In a 2011 abstract presentation, Yamamoto et al. compared 16 PO-SRS patients with their 139 postoperative SRS counterparts with using the propensity-matched analysis method [56]. The authors could not show any significant differences between the two groups in terms of LC, distant control, and OS outcomes, but, of note, the authors reported significantly reduced rates of LMD (6.2% vs. 43.8%; P<0.05) in the PO-SRS cohort. In a study reported by Prabhu et al. [21] the investigators compared the outcomes of PO-SRS (N= 63) and postoperative SRS (N= 94) and SRS alone (N= 60). The results revealed that the 1-year LC was significantly inferior in the SRS alone group (63.3%) compared to PO-SRS (77.5%) and postoperative SRS (80.9%) groups, respectively (P<0.05). However, the 1-year RN rates were significantly higher in the postoperative SRS group (22.6%) than the PO-SRS (12.3%) and SRS alone (5.0%) groups (P<0.05). Likewise, the 2-year LMD incidence was numerically higher in the postoperative SRS group (16.1%) than either of postoperative SRS (5.9%) and SRS alone (5.0%) groups, respectively (P= 0.12). In the largest series to date, Patel et al. retrospectively comparatively analyzed the outcomes of 66 PO-SRS patients with 114 patients who received postoperative SRS (52). Though the LC rates were not different, PO-SRS group had significantly reduced 2-year rates of LMD (3.2 vs. 16.2%; p<0.05) and symptomatic RN (4.9 vs. 16.4%; p<0.05).

Based on the above mentioned clinical evidence, the PO-SRS is superior over the postoperative SRS regarding the RN and LMD rates with at least comparable LC, distant control, and survival rates (Table 1). Though, the results of the prospective phase 3 randomized trials comparing the relative efficacy and safety profiles of those SRS techniques are required to achieve more conclusive remarks.

4. RELATIVE ADVANTAGES AND DISADVANTAGES OF PO-SRS

Despite both of the PO-SRS and postoperative SRS are the two viable treatment alternatives for local management of BMs, yet either modality typically has its pros and cons contrasted with one another. The preferences and weaknesses of PO-SRS are outlined in Table 2.

To begin with, the local control rates of postoperative SRS are usually reported to be

Table 1. Major studies evaluating the preoperative stereotactic radiosurgery

Author	Study design	Patients (n)	Interval to surgery	1-year LC (%)	RN (%)	LMD (%)
Yamamoto et al. [64]	Retrospective PO-SRS vs. postoperative SRS	32	NR	75.0	NR	6.2
Clark et al. [65]	Prospective (Phase 1)	12	<30 days	NR	NR	NR
Bredel et al. [66]	Prospective (Phase 1)	20	<30 days	NR	NR	NR
Patel et al. [52]	Retrospective PO-SRS vs. postoperative SRS	180	<2 days	84.1	1.5	3.2
Vetlova et al. [67]	Retrospective	11	<2 days	91.0	0	9.0
Patel et al. [53]	Retrospective PO-SRS vs. adjuvant WBRT	102	<2 days	75.5 (2-years)	9.9	3.5
Prabhu et al. [21]	Retrospective PO-SRS vs. postoperative SRS vs. SRS alone	223	<2 days	77.5%	5.0	5.9
Prabhu et al. [54]	Retrospective	117	Median 48 h	80.1	4.3	5.1

Abbreviations: LC: Local control; RN: Radiation necrosis; LMD: Leptomeningeal dissemination; PO-SRS: Preoperative stereotactic radiosurgery; NR: Not reported; WBRT: Whole brain radiation therapy

inferior to its PO-SRS counterpart particularly for large lesions (> 3 cm) with a 1-year local failure rate of 44% [43]. Albeit an en bloc resection, rather than a piecemeal tumor resection, may lessen the potential hazard to some degree when plausible, yet tumor spillage is a common problem experienced by up to 50% of the patients undergoing surgery against BM [43]. In such a manner, PO-SRS might sterilize spilled tumor cells and sensibly diminish the potential risk of recurrences beyond the tumor cavity. The higher chance for dose escalation with PO-SRS in non-eloquent tumors pursued by a more generous tumor resection may likewise improve the tumor control rates with no catastrophic augmentation in severe toxicity rates. Such an effective strategy may more markedly reduce the LMD rates with resultant individual decrements in salvage WBRT needs and neurologic death rates.

The cumulative 2-year incidence of RN may be as high as 49.4% for BMs >1 cm, of which up to 20% may remain symptomatic requiring various additional treatments including a repeat surgery for removal of the symptomatic lesion [57]. The RN incidence is directly associated with the tumor size and prescription SRS dose and limits the possible escalation of the typical doses beyond the conventional dose ranges. In this setting, compared to postoperative SRS, the PO-SRS could reduce rates of as much of the normal tissue receiving near target SRS dose is surgically removed after PO-SRS [58]. Conversely potentially increasing the considerable risk for RN, in postoperative SRS, the planning target volume (PTV) usually covers the surgical cavity with a 2 mm safety margin of theoretically normal healthy brain parenchyma at all directions [59].

Previously it has been shown that the LMD risk was significantly associated with various key factors including the index breast primary, posterior fossa BM location, piecemeal tumor resection, meningeal tumor contact, large tumor size, and postoperative SRS [60]. Accessible evidence respectfully suggests that the PO-SRS and WBRT have a similar LMD incidence risk that is comparably lower than the excessive risk with postoperative SRS [53]. For instance, recently Patel et al. have reported that the 2-year risk of LMD was significantly higher in the postoperative SRS than the PO-SRS (16.6% vs. 3.2%, P=0.01) in a series of 180 patients [52]. As mentioned before, this result might be associated with the lesser chance of spilled tumor cells to proliferate if they were previously irradiated, which is the case for PO-SRS.

Although a recently developed guideline has been published for accurate delineation of postsurgical BM cavity for SRS, yet the contouring process of this technique is still challenging with regards to the ambiguity of target volume definition because of unpredictable postoperative changes in the tumor cavity which leads to notably large inconsistencies between clinicians' clinical target volume (CTV) definition [59,60]. This key issue has been investigated by Vellayappan et al. which demonstrated that the inter-observer variability was appreciably reduced and plan conformity was improved by PO-SRS compared to postoperative SRS [61]. For this apparent reason, to decrease the risk of geographic misses, a generous PTV margin of 2 mm is typically added to the CTV, meaning that the rim of 2 mm of healthy brain parenchyma will unnecessarily receive the prescribed excessive doses likewise the tumor cavity. Because the contouring of intact tumor volume is more straightforward and no PTV margin is needed, it is reasonable to assume that PO-SRS is more accurate and safe regarding the target volume definition and severe toxicity risks, respectively.

The basic radiobiological principles dictate the reduced efficacy of RT in hypoxic environments like the postsurgical tumor cavities, namely due to the loss in oxygen enhancement ratio. Considering this established rule, it is rational to expect that the tumor cells may be less radiosensitive in the post-surgical tumor cavity compared to the well-oxygenated intact tumors, particularly when fractionated SRS is intended, which may lead to dose reductions for PO-SRS with no tumor control probability loss with accompanying reductions in severe complication rates.

Compared to postoperative SRS, the PO-SRS is not only a less resource-intensive procedure, but it is also clinically more feasible due to being easier to implement with less time burden. In most patients, the PO-SRS is usually followed by the surgery as it is possible to perform both procedures in a single short-term single hospitalization. In contrast, the optimal interval between the surgery and postoperative SRS is still conflicting [62,63]. Furthermore, it might also be strenous and uncomfortable to perform postoperative SRS in a timely manner in cases experiencing delayed wound healing or

postoperative complications, particularly if fractionated postoperative SRS is intended. In cases with severe operative complications, the global medical condition may even mandate the cancellation of the SRS.

Despite the clear advantages, the PO-SRS has also some substantial disadvantages. One major criticism against the PO-SRS is the apparent absence of pathological confirmation before the SRS procedure, and therefore, the risk of being subject to unnecessary or inappropriate RT, like the benignant lesions or primary intracranial malignancies. Though up to 11% suspected BMs were shown to be non-metastatic during the biopsy or surgery by Patchell et al. in 1990, yet it is imperative to point out that the discriminative power of the imaging techniques has undergone a significant evolution after this publication and the discriminative accuracy of current imaging tools is now far beyond the historical ones. Endorsing this statement, Prabhu et al. demonstrated that the risk for a non-metastatic lesion after PO-SRS was only 0.8% in a 2018 study consisting 118 patients who underwent PO-SRS and surgery for BMs [54]. Therefore, the PO-SRS seems to be safe in terms of pathological concerns as the risk for the inappropriate use of PO-SRS is negligibly small, even if not zero.

Treatment plan modifications may be needed during the interval between the PO-SRS and planned surgery because of various reasons. However, as recently shown by Prabhu et al. only 2 (1.7%) of 120 patients couldn't undergo the planned surgery, because of intercurrent illnesses [54]. On the other hand, contrasted with the typical 6 to 48 hours interval between the PO-SRS and surgery, the frame-based SRS is frequently performed 2 to 5 weeks of surgery leading to a prolonged time frame provision for development of postoperative complications which may defer or cancel the intended postoperative SRS due to numerous causes including the early tumor progression [3].

Finally, although no solidly proven relationship between the SRS for BMs and wound healing or surgical site infection exist, yet PO-SRS has been unjustly accused for its potential to increase the risk of wound healing problems, infections, and postoperative complications compared to postoperative SRS. However, even if the risk may not be zero, still the risk for any unfortunate complications after PO-SRS should be lesser than the postoperative SRS as the relatively hypoxic surgical tract is covered with a global 2 mm PTV margin of healthybrain parenchyma compared to zero PTV margin and 20% reduced prescription doses used for PO-SRS.

Table 2. Advantages and disadvantages of preoperative stereotactic radiosurgery compared to postoperative radiosurgery

Advantages
• Better or equivalent tumor control rates
• Lesser tumor spillage risk
• Higher tumor cell sterilization probability
• Possible dose reduction with equivalent efficacy
• Possibility for safer dose escalation
• More accurate target volume definition
• No need for planning target volume magrin
• Lesser normal tissue volume in prescribed dose
• Possibility for reduced overall toxicity
• Possibility for anti-tumor immunity activation
• Lesser radiation necrosis risk
• Lesser leptomeningeal dissemination risk
• Shorter hospitalization period
• No risk for treatment cancellation
Disadvantages
• Absence of pathologic confirmation
• Risk for unnecessary or inappropriate irradiation
• Questionable wound healing problems
• Questionable increased risk for wound infection

5. CONCLUSION

The postoperative SRS, to a large extent, has supplanted the adjuvant WBRT in patients undergoing BM resection to reduce the unfavorable neurocognitive consequences of WBRT. However, the relatively elevated rates of RN and LMD of postoperative SRS led to a reasonable search for novel alternative techniques. In this regard, the PO-SRS appears to convincingly decrease the excessive rates of symptomatic RN and LMD of postoperative SRS to more reasonable levels with similar tumor control rates. Furthermore, the need for only a single session short-term hospitalization and only a <48 hours of overall total treatment time properly render the PO-SRS a more convenient treatment option for BMs compared to its postoperative SRS counterpart. However, in absence large-scale randomized studies comparing the comparative efficacy of the timing of the surgery relative to initiation of the PO-SRS, multifractionated PO-SRS should still be favored in patients with larger tumors or those located in eloquent brain parenchyma or vicinity of the critical organs though in the expense of lengthened total treatment durations. Avoidance of normal brain tissue irradiation due to no need for PTV margins (usually 2 mm for postoperative SRS) and potential activation of neoantigen presentation (self-vaccination) with an irradiated intact tumor in the era of immune checkpoint inhibitors and other immunotherapeutics propose the PO-SRS as a safe and anti-tumoral immunity-enhancing SRS technique over the postoperative SRS. However, the results of the published PO-SRS studies should be cautiously interpreted until the successful outcomes of phase 3 randomized controlled trials comparing PO-SRS against postoperative SRS in terms of tumor control efficacy and the true RN and LMD incidences become available. Finally, the postoperative SRS and PO-SRS should be cautiously weighed in patients with chronic illnesses that may lead to longer or complicated wound healing processes, immune suppressive patients with a higher tendency for wound infections, and those patients with radiologically suspect lesions hinting primary brain tumors or unknown primary tumors.

CONSENT AND ETHICAL APPROVAL

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

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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