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Original Report

Early clinical outcomes for 3 radiation techniques for brain metastases: focal versus whole-brain

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Abstract

Purpose: To present our novel technique for brain metastases (low-dose whole brain radiation therapy [WBRT] with simultaneous integrated boost (SIB) and focal, frameless stereotactic intensity modulated radiotherapy [IMRT]) in the context of patterns of failure, dosimetry, acute toxicity, and overall survival for 3 different radiation techniques.

Methods and Materials: We retrospectively reviewed 92 patients undergoing radiation for brain metastases via the following: (1) "prophylactic" WBRT to a low dose (median 30 Gy) with an SIB to the gross tumor volume plus 2-3 mm margin (median dose 45 Gy) in 10-15 fractions; (2) focal, frameless image-guided stereotactic IMRT (S-IMRT) in 5 fractions to tumor only (median 30 Gy); or (3) conventional (c)WBRT using 2 lateral opposed beams in 10-15 fractions (30-37.5 Gy). The primary endpoints were local (LBC), distant (DBC), and total brain control (TBC) for each of the 3 types of brain radiation. Survival, toxicity, and dosimetry were reported as secondary endpoints.

Results: LBC was achieved in 72%, 78%, and 56% for SIB, S-IMRT, and cWBRT, respectively. DBC (ie, no new brain metastases) was observed in 92%, 67%, and 81% for SIB, S-IMRT, and cWBRT, respectively. TBC (LBC + DBC) was 72%, 67%, and 56% for SIB, S-IMRT, and cWBRT, respectively. No statistical difference in overall survival was observed ($P = .067$), and only 1 patient experienced biopsy proven radionecrosis.

Conclusions: TBC after low-dose WBRT with SIB was acceptable and at least comparable to S-IMRT and cWBRT. SIB seems to be a safe and effective treatment strategy for patients with brain metastases and may efficiently combine the benefits of cWBRT and stereotactic radiosurgery.

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Conflicts of interest: None.

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Introduction

Brain metastases are an unfortunate, yet common problem in oncology, with an estimated annual incidence of 11.1 per 100,000 in the overall population.[1] The mainstays of treatment have been corticosteroids, conventional whole brain radiation therapy (cWBRT), and surgery. Recently, stereotactic radiosurgery (SRS) has been widely and effectively used to either supplement or replace surgery and cWBRT.[2] SRS, and more recently fractionated, focal stereotactic intensity modulated radiotherapy (S-IMRT) over 2-5 fractions, has increased the treating physician's armamentarium[3-5]; however, choosing the optimal treatment recommendation for patients has become challenging. Currently, patients are counseled based on the number of metastases at presentation, the recursive partitioning analysis (RPA) classification for brain metastasis, and the graded prognostic assessment (GPA).[6,7] More recently, a disease specific GPA was reported that better classifies patients according to factors that influence median survival.[8] Moreover, patients with 4 or more metastases, melanoma primary, or uncontrolled systemic disease are known to be at a greater risk of distant brain failure following focal SRS alone.[9] All of these factors must be considered when choosing the appropriate technique for delivering brain irradiation.

The addition of cWBRT to focal SRS or stereotactic IMRT for solitary or a limited number of metastases is an area of ongoing debate. Despite the higher rate of distant brain failure, many argue that SRS alone provides sufficient local control of known brain metastases, while avoiding unwanted neurocognitive side effects of cWBRT.[10] Conversely, others argue that the neurocognitive side effects of developing additional metastases and subsequent salvage treatment overshadow the risk of upfront cWBRT.[11,12] Recently, 2 randomized trials compared SRS alone to sequential SRS plus cWBRT; and, as expected, cWBRT lowered the incidence of brain tumor recurrence. Aoyama et al reported total intracranial recurrence rates of 76% and 47% for SRS alone and the combination of SRS plus cWBRT, respectively; while Chang et al reported corresponding rates of 73% and 27%, respectively.[13,14] Nevertheless, the impact on neurocognitive function was less clear. The Japanese group claims that distant brain failure negatively impacted performance on mental status testing more than the addition of cWBRT,[15] while the M.D. Anderson group provides contrary evidence that cWBRT increased neurocognitive dysfunction when compared to SRS alone.[14] The omission of cWBRT in select patients (RPA class 1 and 1-3 metastases) is being debated, but cWBRT remains the primary treatment of choice for patients with 4 or more brain metastases.

Recent advances in imaging and radiation delivery have greatly improved the accuracy and flexibility of modern radiation therapy. Higher doses of radiation, increased sparing of normal tissue, and noninvasive (frameless) techniques are now possible through the use of image-guided radiation therapy (IGRT) and IMRT. We developed a novel, single isocenter technique that combines the benefit of sequential cWBRT and SRS into 1 treatment course by utilizing both IGRT and IMRT to deliver a "prophylactic" (low) dose of radiation to the whole brain while simultaneously delivering a "boost" (high) dose (simultaneous integrated boost [SIB]) to the gross tumor. This technique is noninvasive, convenient, and potentially cost-effective compared to the traditional combination of cWBRT and frame-based SRS. Initial clinical experience and acute toxicity using such techniques was previously presented in abstract form,[16] and since then subsequent studies have been published establishing the dosimetric advantages and clinical feasibility of WBRT with SIB using image-guided (IG)-IMRT for patients with brain metastases.[17,18] These reports have been very limited in patient number and follow-up, thus the role of SIB in the treatment of brain metastases remains unclear.

Herein, we present our early results for 3 different brain radiation techniques: SIB, S-IMRT, and cWBRT. We report the rates of total brain control (TBC), patterns of failure [local brain control (LBC) versus distant brain control (DBC)], toxicity, dosimetry, and median survivals with SIB, S-IMRT, and cWBRT. We hypothesized that the DBC would be lowest in the S-IMRT only group and equivalent in the other 2 groups. We expected higher rates of LBC in both the S-IMRT and SIB groups, when compared to cWBRT. Ultimately, we hypothesized that SIB would result in minimal toxicity with the highest TBC among the 3 treatment groups and would demonstrate similar brain control and survival to the historical results of sequentially combined cWBRT and SRS.

Methods and materials

With approval from our institutional review board, all patients completing treatment for intraparenchymal brain metastases from July 2007 through January 2010 at our institution were retrospectively reviewed. Patients with radiosensitive primary tumors (small cell lung cancer, lymphoma, leukemia, or multiple myeloma), radiological evidence of leptomeningeal metastases, or that received sequential cWBRT and SRS were excluded. Patients received 1 of the following 3 types of brain radiation treatments: (1) WBRT with SIB (n = 40); (2) focal S-IMRT (ie, fractionated SRS) to the metastasis only (n = 20); or (3) cWBRT (n = 32). All treatments were delivered within 15-30 minute time slots. While treatment choice varied among physicians, S-IMRT was often used for patients with 1-3 metastases to avoid potential neurocognitive effects of WBRT, while patients with multiple metastases or poor prognosis were often palliated with cWBRT alone. SIB was generally utilized in patients at increased risk of distant brain failure (uncontrolled extracranial disease, >3

metastases, or melanoma primary) at the discretion of the radiation oncologist.

Treatment technique

For both SIB and S-IMRT treatment groups, computed tomographic treatment planning images were fused with pretreatment magnetic resonance images for inverse treatment planning on Pinnacle[3] v8.0m (Malpitas, CA) based on optimized sparing of organs at risk (OARs: eyes, lens, middle ear, cochlea, oral cavity, parotids, brainstem, scalp, etc) (Fig 1A-C). If targets were close to OARs, such as optic nerve, optic chiasm, or brainstem, the high dose planning target volume (PTV) was allowed to be under dosed to respect normal tissue tolerance of OARs. A single isocenter technique was used for both SIB and S-IMRT patients and was placed in the middle of the cranium (or a centralized location between metastasis). Intensity modulation was performed using the direct machine parameter optimization method available in the Pinnacle[3] system. In this method, the

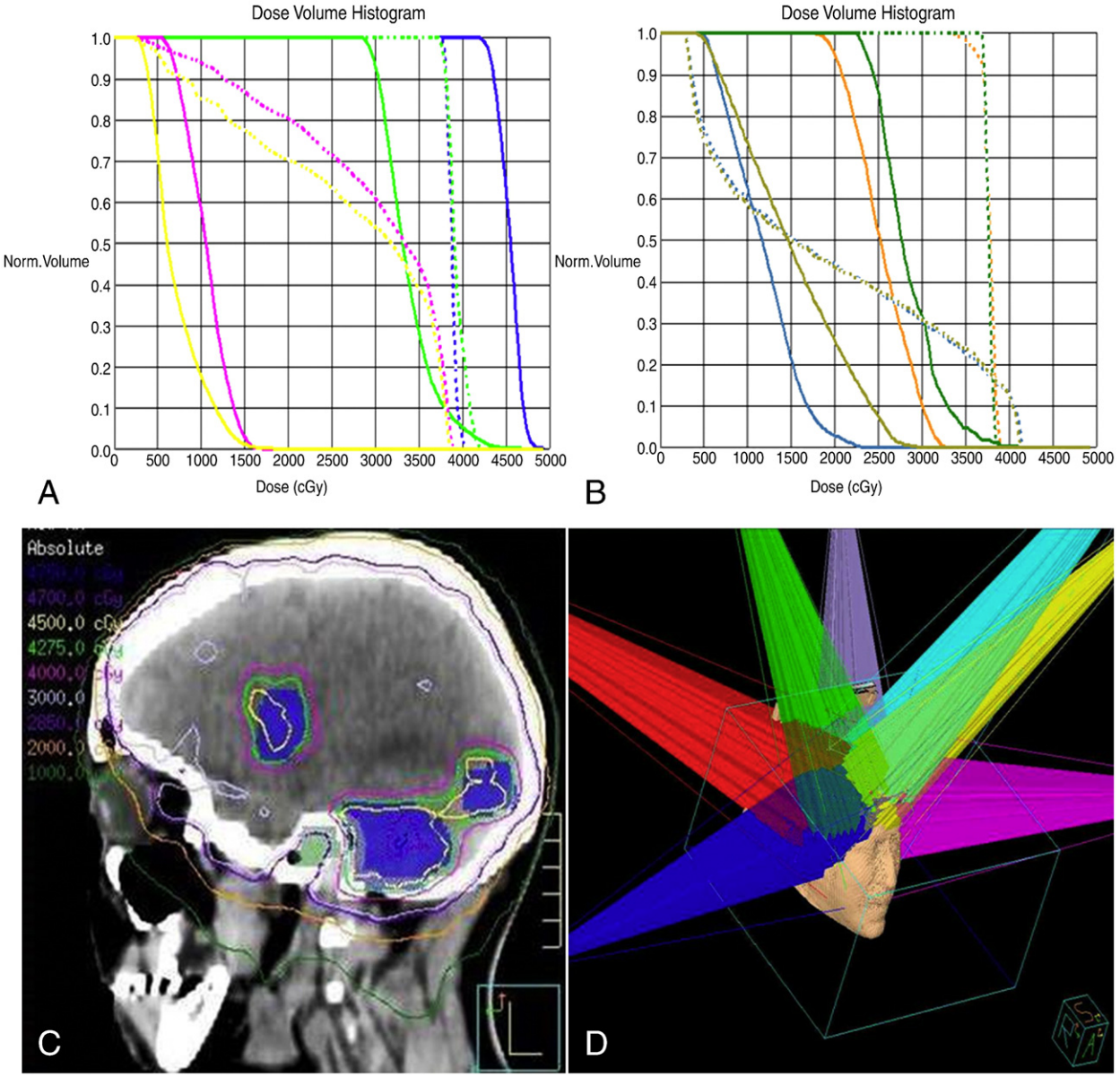

Figure 1 Sample treatment planning for simultaneous integrated boost (SIB) with the prophylactic whole-brain technique. To highlight the extent of organ sparing we demonstrate dose volume histograms comparing the plan for a sample patient using both SIB and conventional whole brain radiation therapy. (A) Planning target volume (PTV) boost (blue), PTV whole-brain (green), right-left parotid (magenta-yellow). (B) Right-left cochlea (green-orange), right-left eye (blue-gold). (C) Computed tomographic planning images showing absolute dose prescription isodose lines with dose to boost PTV of 45 Gy (gross tumor volume of gross metastases plus 2-3 mm margin) and lower "prophylactic" dose to whole-brain of 30 Gy all in 15 fractions with optimized sparing of organs at risk: cochlea, parotid, scalp, lens, etc. (D) Single isocenter, 5-10 non-coplanar beam arrangement for SIB technique.

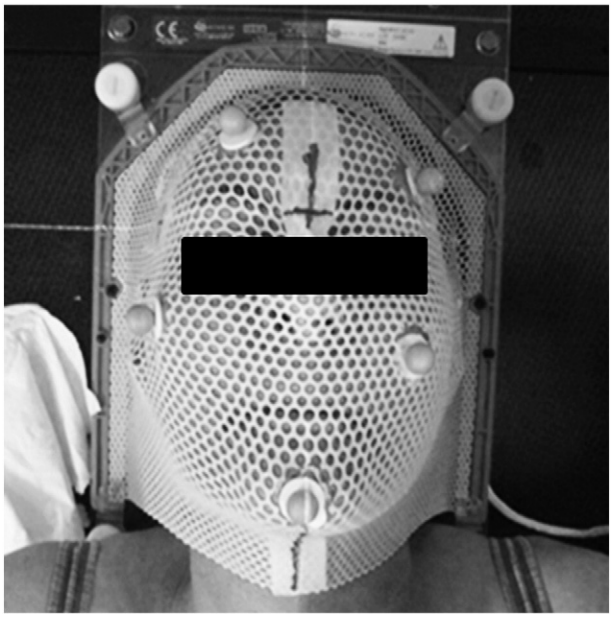

Figure 2 Fiducial reflector technique. Placement example of 5 fiducial reflectors (body markers) directly on the patient's face through cutouts in the Aquaplast mask for optimal intrafraction monitoring via BrainLAB's Exactrac system. Notice the marker placement allows a clear view of each reflector by the infrared reflector at the foot of the table.

leaf sequences and deliverable fluences were computed for every iteration during optimization, thereby incorporating all the restrictions of the multileaf collimators (MLCs) during the process. The leaf positions and the weight of each segment were parts of the optimization process. The optimization followed a gradient-based, sequential quadratic programming algorithm. To keep the number of segments as low as possible and minimize the treatment delivery time; the number of segments per beam, minimum segment area, and monitor units (MU) per segment were chosen to be $\leq$10, $\leq$2.5 cm^2, and $\leq$3.5 MU, respectively. The dose calculations were performed using the adaptive convolution-superposition option with heterogeneities for all of our plans. Interfraction and intrafraction motion were monitored and corrected with BrainLAB's Exactrac IGRT system (Chicago, IL) with patient positioning maintained by a custom fit Aquaplast mask (Avondale, PA) and stereoscopic infrared camera tracking via 5 fiducial reflectors placed directly on the patient's face through small cutouts in the patient's mask (Fig 2). Radiation was delivered via a MLC-based, noncoplanar, 5-10 beam arrangement to maximize skin (scalp) sparing using 6 MV photon beams from Siemen's Primus or Oncor linear accelerators with 1 cm MLCs (Fig 1D). The collimator was adjusted to allow "best fit" of MLCs to the targets.

The dose schedules and corresponding biologically effective dose (BED) calculations are outlined in Table 1. The SIB group received a higher dose (median 45 Gy) to the gross metastases (boost PTV was defined as gross tumor on contrast-enhanced T1 weighted magnetic resonance imaging (MRI) plus 2-3 mm margin) and a lower dose (median 30 Gy) as "prophylaxis" to the normal surrounding brain via 10-15 fractions over 2-3 weeks. Focal S-IMRT consisted of a median dose of 30 Gy in 5 fractions over 1-2 weeks (PTV was also defined as gross tumor on T1 MRI plus 2-3 mm margin). The cWBRT consisted predominantly of 30 Gy in 10 fractions or 37.5 Gy in 15 fractions over 2-3 weeks using conventional opposed lateral beams to deliver 6 MV photons.

Table 1 Fractionation schemas

No. (%)	Tumor PTV Dose (Gy)	Whole Brain Dose (Gy)	Fractions	BED 3 (Gy)	BED 10 (Gy)
SIB					
14 (36%)	40	25-32	10	93.3/45.8-66.1	56/31.3-42.2
1 (2%)	45	25	10	112.5/45.8	65.3/31.3
23 (58%)	45	30-37.5	15	90/50-68.6	58.5/36-46.9
1 (2%)	46.5	32.25	15	94.6/55.4	60.9/39.2
1 (2%)	48	33.75	15	99.2/59	63.4/41.3
S-IMRT					
2 (10%)	20	—	5	46.7	28
16 (80%)	30	—	5	90	48
1 (5%)	32.5	—	5	102.9	53.6
1 (5%)	40	—	10	93.3	56
cWBRT					
1 (3%)	—	20	5	46.7	28
1 (3%)	—	28.5	10	55.6	36.6
19 (60%)	—	30	10	60	39
11 (34%)	—	37.5	15	68.6	46.9

Corresponding biologically effective dose calculations (BED = nd × [1+ d/(α/β)], where n = number of fractions and d=dose per fraction). BED10 = biologically effective dose for an assumed α/β of 10 for acute responding tissue. BED3 = biologically effective dose for an assumed α/β of 3 for late responding tissues.

cWBRT, conventional whole brain radiation therapy; PTV, planning target volume; SIB, simultaneous integrated boost; S-IMRT, stereotactic intensity modulated radiotherapy.

Table 2 Patient characteristics

Characteristics	SIB (n=40)	S-IMRT (n=20)	cWBRT (n=32)
Sex			
Male	20 (50%)	11 (55%)	10 (31%)
Female	20 (50%)	9 (45%)	22 (69%)
Age, median (range)	61 (39-78)	63 (46-87)	59 (41-86)
Race, No. (%) White	39 (98%)	20 (100%)	32 (100%)
KPS, median (range)	60 (40-90)	40 (20-80)	50 (20-80)
Primary tumor types			
NSCLC	26 (65%)	8 (40%)	18 (56%)
Breast	3 (7%)	—	12 (38%)
Melanoma	5 (13%)	5 (25%)	—
GU	3 (7%)	3 (15%)	1 (3%)
GI	1 (3%)	3 (15%)	—
Other/unknown	2 (5%)	1 (5%)	1 (3%)
No. of brain metastases			
1-3	21 (53%)	20 (100%)	10 (31%)
4-6	12 (30%)	—	4 (13%)
>6	7 (17%)	—	18 (56%)
Stable extracranial disease	6 (15%)	7 (35%)	9 (28%)
RPA class			
I	3 (7%)	1 (5%)	3 (9%)
II	9 (23%)	4 (20%)	3 (9%)
III	21 (53%)	10 (50%)	23 (73%)
Unknown	7 (17%)	5 (25%)	3 (9%)
Craniotomy prior to RT	6 (15%)	3 (15%)	4 (13%)
Required salvage RT	1 (3%)	2 (10%)	5 (16%)

cWBRT, conventional whole brain radiation therapy; GI, gastrointestinal; GU, genitourinary; KPS, Karnofsky Performance Scale; NSCLC, non-small cell lung cancer; RPA, Recursive Partitioning Analysis; RT, radiotherapy; SIB, simultaneous integrated boost; S-IMRT, stereotactic intensity modulated radiotherapy.

Follow-up and monitoring

Patients were typically seen at 1 month post-treatment for follow up with subsequent visits at the discretion of the treating oncology team. Treatment response was measured via post-treatment MRI based on World Health Organization criteria.[19] LBC was defined only for the 50 patients with MRI follow-up as CR (complete response), PR (partial response), or SR (stable response) at the site of the treated metastases for the duration of radiographic follow-up. Some cases that were scored as local failures may have actually been pseudoprogression on MRI, thus our local brain failure represents the worst case scenario. Distant brain failure was defined as the development of new brain metastases not present on pretreatment MRI. Some patients required salvage reirradiation, but were censored at failure and thus scored only based on their initial radiation treatment.

Acute toxicity (occurring within 90 days following brain irradiation) was reported in accordance with the Common Toxicity Criteria v3.0. Patients were monitored for restarting dexamethasone after their post-radiation taper as this is sometimes a marker for radiation-induced neurotoxicity. All patients were followed by a multi-disciplinary oncology team and re-biopsy was only performed based on clinical need. Only pathologically confirmed radiation necrosis was counted; however, any white matter changes suggestive of radiation-induced damage on post-treatment MRI were recorded.

Table 3 Dosimetery and organs at risk sparing

	SIB Median (range)	S-IMRT Median (range)
PTV coverage	0.92 (0.74-1.00)	0.90 (0.70-0.97)
PTV homogeneity	1.08 (1.02-1.17)	1.09 (1.04-1.13)
OAR mean dose (cGy)		
Brainstem	3289 (2424-4070)	482 (36-1280)
Cochlea	2616 (1826-3309)	344 (93-945)
Eye	957 (594-1591)	112 (8-300)
Lens	463 (329-849)	78 (5-237)
Optic chiasm	3079 (2177-3714)	300 (35-774)
Optic nerve	2563 (1824-3387)	203 (13-967)
Parotid	771 (587-1265)	—
Scalp	1093 (714-2910	—

PTV coverage defined as PTV minimum dose-prescription dose (where <0.90 represents a minor deviation and <0.80 represents a major deviation), and PTV homogeneity defined as PTV maximum dose-prescription dose (where >2.0 represents a minor deviation and >2.5 represents a major deviation) as previously described in the RTOG radiosurgery quality assurance guidelines.[20]
OAR, organs at risk; PTV, planning target volume; SIB, simultaneous integrated boost; S-IMRT, stereotactic intensity modulated radiotherapy.

Statistical analysis

Statistical analysis was done using SPSS version 18.0 (Chicago, IL). The general linear model was used to determine differences between groups for continuous variables. The χ^2 test (and Fisher exact test where appropriate) were used in the determination of differences between categoric variables. Survival and control from the date of the diagnosis of brain metastasis until the respective event were calculated using the Kaplan-Meier method. Comparisons between groups were completed using the log-rank test. A P value of $< .05$ was considered significant.

Results

The patient characteristics by treatment group can be seen in Table 2. For SIB, the median prescribed dose to tumor planning target volume (PTV) was 45 Gy (range, 40-48 Gy) and median prophylactic dose to whole brain (excluding metastasis) was 30 Gy (range, 25-37.5 Gy) delivered over a median of 13 fractions (range, 10-15). For S-IMRT, the median dose was 30 Gy (range, 20-40 Gy) in a median of 5 (range, 5-10) treatments. For cWBRT, the median dose was 30 Gy (range, 20-37.5 Gy) in a median of 10 (range, 5-15) fractions. Organs at risk (OAR) sparing and dosimetric

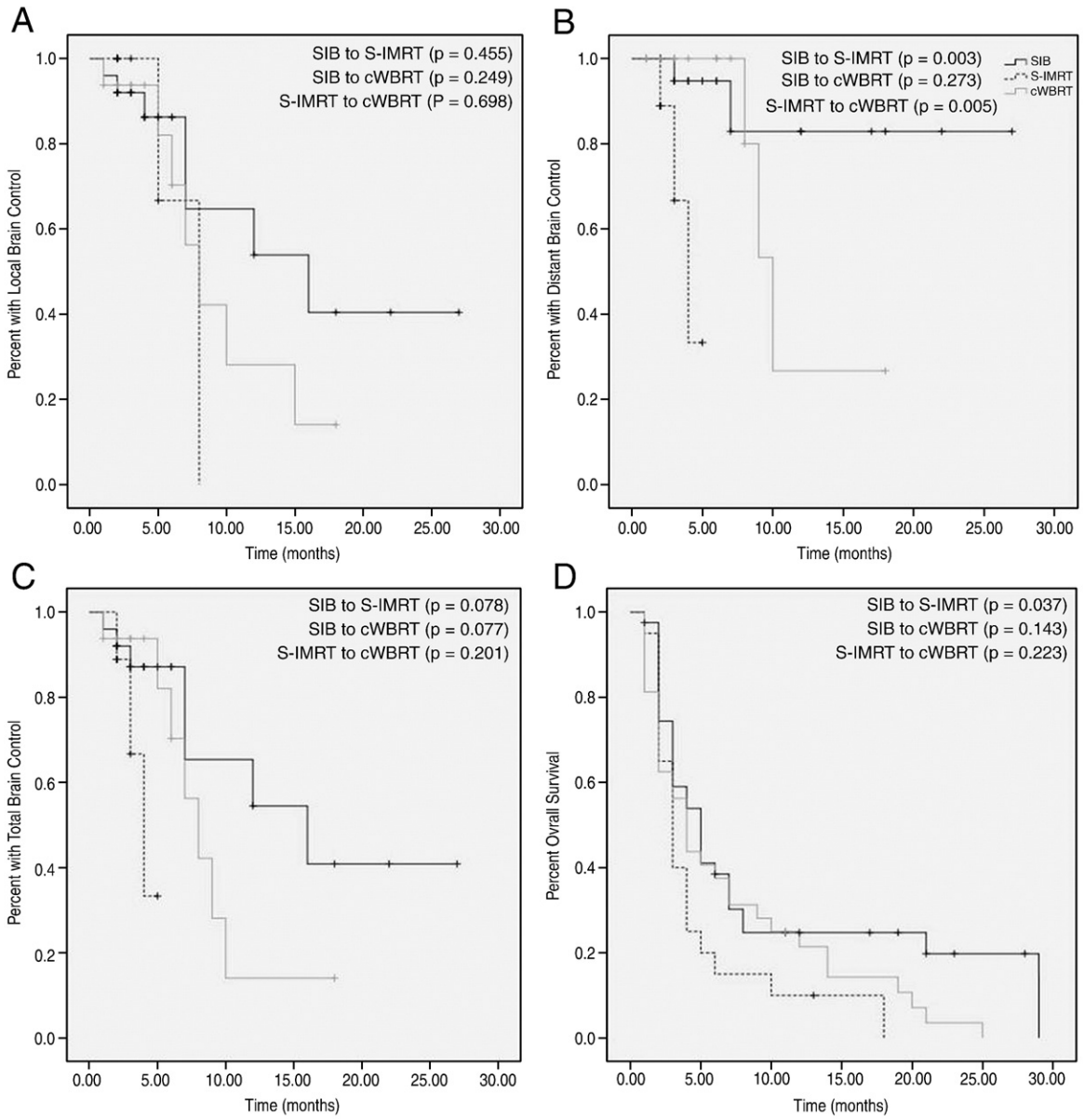

Figure 3 Actuarial tumor control and overall survival. (A) Kaplan-Meier plot of local brain control over time. (B) Kaplan-Meier plot of distant brain control over time. (C) Kaplan-Meier plot of total brain control over time. (D) Kaplan-Meier plot of median survival based on initial brain tumor management. SIB, simultaneous integrated boost with low dose whole brain radiation therapy; cWBRT, conventional whole brain radiation therapy; S-IMRT, stereotactic intensity modulated radiotherapy.

Table 4 Control rates of 2 large randomized controlled trials using sequential cWBRT and SRS compared to the current study

	LBC	DBC	TBC
RTOG 9508 (n=331)			
cWBRT + SRS	82%	n/a	75%
cWBRT alone	71%	n/a	70%
Japanese Radiation Group 99-1 (n=132)			
cWBRT + SRS	89%	58%	53%
SRS alone	73%	36%	34%
Actuarial results of current study (n=92)			
SIB	86%	94%	87%
S-IMRT (fractionated SRS) alone	67%	33%	33%
cWBRT	70%	80%	70%
Crude results of current study (n=92)			
SIB	72%	92%	72%
S-IMRT (fractionated SRS) alone	78%	67%	67%
cWBRT alone	56%	81%	56%

Actuarial rates for tumor control (1 year) from RTOG 9508[20] and Japanese Radiation Group 99-1[13]; in comparison to the actuarial (6 months) and crude rates presented herein.

cWBRT, conventional whole brain radiation therapy; DBC, distant brain control; LBC, local brain control; n/a, not available; RTOG, Radiation Therapy Oncology Group; S-IMRT, stereotactic intensity modulated radiotherapy; SRS, stereotactic radiosurgery; TBC, total brain control.

outcomes (PTV coverage and PTV homogeneity) are recorded in Table 3; calculated as previously described in the RTOG radiosurgery quality assurance guidelines.[20]

Tumor control and survival

Fifty patients (50 of 92, 54%) underwent post-treatment MRI; 63% of SIB, 45% of S-IMRT, and 50% of cWBRT. Median radiographic follow-up was 4 (range, 1-27), 4 (1-27), 2 (2-8), and 5 (1-18) months for overall, SIB, focal S-IMRT, and cWBRT patients with a median number of images of 3 (range, 1-12). Kaplan-Meier results for tumor control are shown in Figure 3, with the respective 6-month actuarial results and crude rates for tumor control documented in Table 4 in comparison to 2 large randomized controlled trials using sequential cWBRT and SRS. There were no isolated local failures in the S-IMRT group; however, there were 5 (20%) isolated local brain failures in the SIB group and 4 (25%) in the cWBRT group. No isolated distant failures were recorded in the SIB or cWBRT groups. Median survival was 4 (range, 4-29), 5 (1-29), 3 (1-18), and 4 (1-25) months for overall, SIB, focal S-IMRT, and cWBRT patients, respectively (see Fig 3).

Toxicity

Treatment-related toxicity for the respective techniques is outlined in Table 5. Empirically, the authors noted less alopecia, conductive hearing loss, otitis media, xerostomia, and taste changes with SIB and S-IMRT versus cWBRT due to the IMRT sparing of OARs. White matter changes on post-treatment MRI were observed in 5 patients (4 receiving SIB and 1 receiving S-IMRT). Thirty-five of the 92 patients were restarted on dexamethasone following their scheduled post-radiation taper: 48%, 40%, and 25% of SIB, focal S-IMRT, and cWBRT patients, respectively. Only 1 patient experienced pathologically confirmed brain necrosis; this patient received cWBRT followed by salvage gamma-knife radiosurgery at an outside facility, and 2 separate courses of salvage S-IMRT. She survived 25 months from the diagnosis of brain metastases secondary to adenocarcinoma of the breast.

Discussion

The use of cWBRT in patients with 1-3 brain metastases has been criticized in recent literature for inadequate LBC and potential for unnecessary neurocognitive toxicity as compared to more focal techniques for brain irradiation, such as SRS or focal S-IMRT. The primary advantage of cWBRT over focal brain radiation is the decrease in overall brain recurrence by preventing the development of new brain metastases. Conventional WBRT provides patients with diffuse metastatic disease a simple, cost-effective method of palliation that prevents recurrence, progression-related toxicity, unnecessary doctor visits, and hospital admissions. For those who prefer whole brain irradiation, our single-isocenter, SIB technique conveniently combines the advantages of "prophylactic" WBRT with the benefit of a stereotactic-like boost into an efficient, noninvasive course of treatment. Nevertheless, many patients choose focal radiation alone and while focal, frameless, fractionated S-IMRT may represent an acceptable alternative to traditional SRS, our results for LBC and survival suggest that more work is needed to optimize a number of parameters (dose, margins, fractionation, patient selection, etc) before S-IMRT can be recognized as a comparable focal treatment to traditional SRS.

Our actuarial results mirror the randomized data for cWBRT and SRS from Radiation Therapy Oncology Group (RTOG) 9508 and Japanese Radiation Group 99-1.[13,21] As expected, our DBC was significantly worse for focal S-IMRT. Our TBC was numerically superior in the SIB group, even though not statistically significant. Similarly, the crude LBC for the SIB and S-IMRT groups was numerically superior to cWBRT, but also did not reach the level of significance. It is interesting to note that there were no isolated local failures observed in the S-IMRT group; however, it is difficult to make a definitive conclusion since patients were censored at first failure, and survival was short due to the poor Karnofsky Performance Scale (KPS) of all treatment groups and features of the metastases treated.

Table 5 Acute or treatment-related toxicities

Adverse Event	SIB	S-IMRT	cWBRT
Fatigue			
Grade 1	64%	38%	60%
Grade 2	23%	6%	27%
Grade 3	0%	0%	3%
Grade 4-5	0%	0%	0%
Skin			
Grade 1	41%	0%	37%
Grade 2-5	0%	0%	0%
Nausea			
Grade 1	18%	0%	23%
Grade 2	5%	0%	13%
Grade 3-5	0%	0%	0%
Vomiting			
Grade 1	0%	6%	7%
Grade 2	0%	0%	3%
Grade 3-5	0%	0%	0%
Headache			
Grade 1	20%	13%	37%
Grade 2	13%	0%	7%
Grade 3-5	0%	0%	0%

cWBRT, conventional whole brain radiation therapy; SIB, simultaneous integrated boost; S-IMRT, stereotactic intensity modulated radiotherapy.

The poor median survivals seen in all 3 treatment groups are comparable to historic results in the literature for RPA class II-III,[6] and likely account for the low rate of radiographic follow-up (54% had post-treatment MRI). While age and KPS are similar (see Table 2), there are obvious differences in the control of extracranial disease, number of metastases, and tumor histology among the treatment groups based on inherent biases in selection criteria for the 3 techniques. Based only on the GPA, one would expect poorer survival for the cWBRT group since the majority had more than 6 lesions.[7] In addition, the recently published diagnosis-specific GPA (DS-GPA) reported that histology is also a predictor of survival and the overrepresentation of breast cancer in the cWBRT group combined with the preponderance of melanoma and gastrointestinal cancers in the other groups may have altered our survival results.[8] Similar results of inferior survival despite superior LBC have been previously reported for patients with single brain metastases treated with S-IMRT alone versus surgical resection plus cWBRT.[22] Herein, survival analysis by treatment groups is difficult due to inherent biases in this retrospective review, a small number of patients, interplay of various systemic factors, poor performance status, and often untreated primary tumors.

While our results for PTV coverage and OAR sparing suggest feasibility of radiation planning and delivery for SIB and S-IMRT, an important challenge is defining which subgroup of patients may benefit from these complex approaches. Subgroup analysis from RTOG 9508 shows that the addition of a sequential SRS boost to cWBRT significantly improves survival in patients with a solitary metastasis (6.5 vs 4.9 months, $P = .0390$), significantly impacts KPS preservation at 6 months (42% vs 25%), and decreases steroid use (54% vs 33%) for all patients.[21] Furthermore it remains unclear if SIB is more appropriate for patients at increased risk for distant brain failure (melanoma primary, uncontrolled systemic disease, or 4 or more metastases).[9] Our results and previous prospective studies document the increased risk (30%-40%) of distant brain failure associated with focal therapy alone and potential neurotoxicity associated with distant brain failure.[11-13] More work is warranted using various fractionation schedules and techniques in a prospective trial to better define subgroups which may benefit in terms of brain control, survival, quality of life, toxicity, and neurocognitive outcomes.

The techniques presented herein were delivered as intended in 100% of patients irrespective of lesion number, size, or location. These factors certainly influenced physician preference of techniques, but there were no instances when the chosen technique was unable to be delivered. The SIB technique was initially implemented in patients with as many as 14 brain metastases; however, the time required to contour and plan a large number of brain lesions became cumbersome. Also, as the number of lesions increases, the integral dose may likewise increase beyond what is accepted in cWBRT or SRS patients. For tumors in close proximity to critical OARs such as the optic chiasm, the PTV dose was relaxed to respect established normal tissue tolerances. Finally, the risk of radionecrosis with increasing tumor size from SRS may be ameliorated by prolonging the fractionation schema in S-IMRT and SIB. Therefore, our SIB boost dose and S-IMRT dose were not altered based on tumor size.

Acute toxicity was minimal and there were no documented cases of radiation necrosis in the S-IMRT or SIB patients. The low incidence of white matter changes and necrosis suggests that all 3 radiation techniques are tolerable, with incidences consistent with that reported in the literature.[23] The higher use of dexamethasone in the SIB and S-IMRT groups was noted; however, our clinic routinely tapers steroid use within the first 1-2 weeks following treatment, and some patients did not initially use steroids at all. The apparent difference in post-treatment need for dexamethasone may represent residual treatment-induced edema that presented clinically due to rapid tapering, rather than an indicator of clinical progression. Limited long-term follow-up and poor survival may have masked late toxicity since necrosis may not have had time to develop. More work is needed in this area to better define late toxicity and neurocognitive function following these newer techniques.

The tolerability of both regimens may allow further dose escalation without compromise in quality of life. Unlike single fraction SRS for brain metastases, the selection of radiation dose for focal, fractionated S-IMRT has not been

well documented. We chose to deliver 30 Gy in 5 fractions for most patients based on existing data.[24] Our crude LBC of 78% and the absence of isolated local failures using fractionated S-IMRT is comparable to the 80%-90% local control results of SRS in the literature, possibly suggesting sufficient dosing for patients receiving hypofractionated S-IMRT.[25,26] Similarly, SIB patients demonstrated improved crude LBC over cWBRT, but were still numerically (but not statistically) inferior to the S-IMRT patients. The 5 isolated local failures with SIB may indicate that the opportunity for dose escalation remains open.

Comparable dosing guidelines for SIB with 2-3 week radiation regimens are currently lacking in the literature. The boost dose for SIB was conservatively chosen based on BED modeling to approximate 60 Gy in 30 fractions. This widely accepted regimen for primary brain tumors is comparable to 45 Gy in 15 fractions. Some studies have used higher doses based on extrapolated BED calculations from RTOG 0023 data for patients with primary brain tumors.[27] For example, 32.25 Gy was given in 15 fractions to the whole brain with SIB to 63 and 70.8 Gy for brain metastases that were $\geq$2.0 cm and <2.0 cm, respectively.[18,28] Based on the possibility of inferior LBC in our study, we are considering increasing the boost dose for SIB. Our selection of the "low" dose for the whole brain of the SIB plan was chosen based on the current dosing guidelines for prophylactic cranial irradiation for patients with non-small cell lung cancer as seen in the recently reported RTOG 0214 and National Comprehensive Cancer Network recommendations.[29] More work is needed in this area to optimize a variety of treatment parameters such as the optimal target volume, margins, radiation dose, etc.

Recent literature combined with our early results has prompted us to develop treatment guidelines based on the number of brain metastases and prognosis. Our goal is to maximize brain tumor control while minimizing potential neurotoxicity. In general, patients with a good prognosis and 1-3 lesions are usually treated with focal S-IMRT alone, 4-6 lesions and good KPS with SIB, and patients with a worse prognosis or many lesions with cWBRT. An interesting side benefit of SIB has been the lack of permanent and even sometimes temporary, alopecia due to scalp sparing. Our 5-10 beam SIB arrangement allows en-face directed photons to utilize the radiation buildup region to further decrease scalp dose. Others have reported similar results.[30,31] Further research is warranted using this novel technique to spare additional OARs, such as the hippocampus, as seen in other reports.[18,28]

Conclusions

We investigated early clinical outcomes (dosimetry, acute toxicity, tumor control, and survival) using IG-IMRT to deliver WBRT with SIB for brain metastases and a frameless technique of focal hypofractionated S-IMRT compared to cWBRT. The results presented herein suggest the feasibility of radiation therapy planning, delivery, and patient tolerability. S-IMRT and WBRT with SIB may be safely delivered to brain metastases with minimal early toxicity and control that is at least comparable to cWBRT. Our results for WBRT with SIB and S-IMRT are encouraging and warrant further standardized prospective investigation.

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