

## Clinical Investigation

# Phase 3 Trials of Stereotactic Radiosurgery With or Without Whole-Brain Radiation Therapy for 1 to 4 Brain Metastases: Individual Patient Data Meta-Analysis



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### Summary

We report an individual patient data meta-analysis evaluating stereotactic radiation surgery (SRS) alone versus SRS plus whole brain radiation therapy in patients presenting with 1 to 4 brain metastases. A survival

**Purpose:** To perform an individual patient data (IPD) meta-analysis of randomized controlled trials evaluating stereotactic radiosurgery (SRS) with or without whole-brain radiation therapy (WBRT) for patients presenting with 1 to 4 brain metastases.

**Method and Materials:** Three trials were identified through a literature search, and IPD were obtained. Outcomes of interest were survival, local failure, and distant brain failure. The treatment effect was estimated after adjustments for age, recursive partitioning analysis (RPA) score, number of brain metastases, and treatment arm.

**Results:** A total of 364 of the pooled 389 patients met eligibility criteria, of whom 51% were treated with SRS alone and 49% were treated with SRS plus WBRT. For

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**Note**—An online CME test for this article can be taken at <http://astro.org/MOC>.

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advantage was observed for patients  $\leq 50$  years of age treated with SRS alone. Also in this cohort, no apparent increase was observed in the risk of new brain metastases. SRS alone is supported in patients presenting with up to 4 brain metastases.

survival, age was a significant effect modifier ( $P = .04$ ) favoring SRS alone in patients  $\leq 50$  years of age, and no significant differences were observed in older patients. Hazard ratios (HRs) for patients 35, 40, 45, and 50 years of age were 0.46 (95% confidence interval [CI] = 0.24-0.90), 0.52 (95% CI = 0.29-0.92), 0.58 (95% CI = 0.35-0.95), and 0.64 (95% CI = 0.42-0.99), respectively. Patients with a single metastasis had significantly better survival than those who had 2 to 4 metastases. For distant brain failure, age was a significant effect modifier ( $P = .043$ ), with similar rates in the 2 arms for patients  $\leq 50$  of age; otherwise, the risk was reduced with WBRT for patients  $> 50$  years of age. Patients with a single metastasis also had a significantly lower risk of distant brain failure than patients who had 2 to 4 metastases. Local control significantly favored additional WBRT in all age groups.

**Conclusions:** For patients  $\leq 50$  years of age, SRS alone favored survival, in addition, the initial omission of WBRT did not impact distant brain relapse rates. SRS alone may be the preferred treatment for this age group. © 2015 Elsevier Inc.

## Introduction

Management of patients presenting with a limited number of brain metastases has evolved from whole-brain radiation (WBRT) alone to more aggressive management incorporating stereotactic radiosurgery (SRS) (1, 2). SRS refers to a single dose of radiation delivered with high precision focally to a brain metastasis with the intent of maximizing local control while sparing normal brain tissue. Thus far, there have been 3 completed published randomized controlled trials (RCTs) comparing SRS alone to SRS plus WBRT in patients presenting with 1 to 4 brain metastases (3-5). Although the inclusion criteria were relatively uniform among the trials, the primary endpoints were inconsistent and not designed for survival (1). Endpoints included brain tumor recurrence (3), maintenance of a World Health Organization (WHO) performance status (PS) of at least 2 (5), and neurocognitive functioning as measured using the Hopkins Verbal Learning Test (4). Although each of the RCTs reported consistent and significant gains in both local control and distant brain control with additional WBRT, the impact on survival was conflicting (1).

Without any clear understanding of the treatment effect on survival, current clinical decision making with respect to offering patients SRS alone or SRS plus WBRT is largely based on physician and patient preferences. The purpose of this study was to pool individual patient data (IPD) from 3 RCTs (3-5) and conduct an IPD meta-analysis to evaluate efficacy of SRS, with or without WBRT, for patients presenting with 1 to 4 brain metastases with respect to survival, local failure, and distant brain failure.

## Methods and Materials

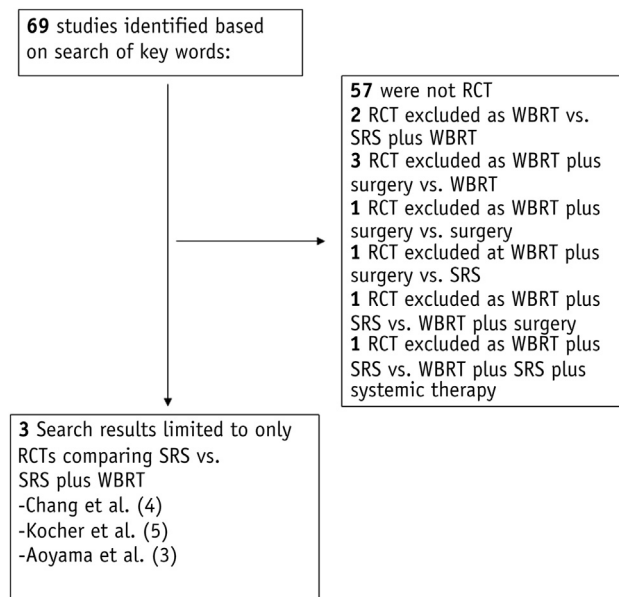
### Randomized Trial Selection Process

A search of publications was performed for English-language articles published from January 1980 through

January 2014 in the PubMed electronic database, using the search terms brain metastases, brain tumors, randomized controlled trials, whole-brain radiation therapy, stereotactic radiation surgery, surgery, and radiation surgery. We also examined the reference sections of published meta-analyses and reviews to identify relevant RCTs (1, 6). Only those RCTs where comparisons consisted of an SRS-alone arm to a SRS plus WBRT arm were selected for review. The selected RCTs had to have met complete accrual criteria in accordance with the original study's primary endpoint, or had to have criteria for a modified endpoint at interim analysis, or terminated early due to early stopping rules by the data safety monitoring board due to a priori criteria such that the study endpoint would otherwise be reached. This resulted in a final selection of 3 RCTs (3-5), and the IPD were obtained from each trial based on the published results from the corresponding authors. Figure 1 summarizes the literature search approach.

### Participants

The first of the 3 RCTs was reported by Aoyama et al (JROSG99-1) in 2006 (3). In that study, 132 patients with 1 to 4 brain metastases were randomized to receive SRS or SRS plus WBRT. Although that trial was initially powered for survival, accrual was terminated at the interim analysis when it was realized that the sample size for survival would be unachievable; however, the sample was sufficient to determine a difference in brain tumor recurrence rates. The Chang et al MD Anderson Cancer Center trial ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier NCT00548756) was subsequently reported in 2009 (4). In that study, 58 patients with 1 to 3 brain metastases were randomized to receive SRS or SRS plus WBRT. That trial was powered to determine a difference in the neurocognitive outcome of total recall. The trial was terminated before the planned sample size, as early stopping rules confirmed superiority in the SRS-alone cohort compared to those treated with SRS plus WBRT. The Kocher et al European Organization for Research and Treatment of Cancer (EORTC) trial 22952-



**Fig. 1.** Flowchart of trials included in the meta-analysis. SRS = stereotactic radiosurgery; RCT = randomized controlled trial; WBRT = whole-brain radiation therapy.

26001 was more complex and consisted of 359 patients with 1 to 3 brain metastases from which a total of 199 patients were treated with SRS as opposed to 160 patients who were treated with surgery. Patients were then randomized to receive WBRT or observation (5). Only the 199 patients initially treated with SRS were included in this IPD meta-analysis. That trial was powered to determine a difference in the proportion of patients alive at 6 months with a WHO PS of 0 to 2. Overall, the EORTC study was completed according to its intended statistical design (5).

The study populations within each RCT were relatively consistent such that each tumor was eligible for SRS, (as confirmed by baseline magnetic resonance imaging) patient  $\geq 18$  years of age, and radiosensitive tumors (i.e. hematologic, small-cell, germ cell) were excluded. With respect to performance status, the inclusion criteria for each trial stipulated a Karnofsky performance status (KPS)  $\geq 70$ , and/or a WHO PS of 0 to 2, and/or a recursive partitioning analysis (RPA) class of 1 or 2 (RPA class 1 refers to controlled primary disease,  $< 65$  years of age, KPS of  $\geq 70$ , and no extracranial metastases; RPA class 2 refers to a KPS of  $\geq 70$  and any combination of controlled primary disease, age, and extracranial metastases; and RPA class 3 refers to KPS of  $< 70$ ) (7). Upon review of the IPD, we identified 25 patients with a KPS of  $< 70$  (RPA class 3). We chose to exclude those patients as it has been consistently observed that PS is among the most powerful predictors of survival (7). As a result, the pooled analysis consisted of 364 of the eligible 389 patients. Of note, 2 of the 3 RCTs allowed up to 3 metastases (4, 5), with only the Aoyama trial (3) allowing up to 4 metastases. We did not exclude patients with 4 metastases as this factor is less likely to impact survival, and a recent phase 2 study confirmed no survival

disadvantage in patients presenting with 2 to 4 versus 5 to 10 metastases (8).

## Statistics

A 1-stage time-to-event IPD meta-analysis approach was performed, fitting a hierarchical Cox regression model (9). The 1-stage meta-analytic method has the advantage that potential confounders and prognostic factors can be adjusted, compared to the more traditional 2-stage approach. In addition, interaction terms can be explored if there are imbalances between treatment arms within a study, or if differences across studies might be a concern or cause of heterogeneity (10-12). In a 2-stage analysis, adjustments might not be effective especially in small, individual studies of IPD data, or even possible (differences across studies would not be taken in to account) if the summary data are extracted from published reports (10-12). We used the mixed-effects Cox regression modeling approach, using mixed-effects Cox models R software, with the assumptions of random study effects (random intercept per study) and random treatment effects (across studies) for each outcome of survival, local failure and distant brain failure. Besides the treatment variable (SRS alone vs SRS plus WBRT), we a priori included 3 covariates: age, RPA class 1 versus 2, and number of brain metastases (1 vs  $\geq 2$ ) in the multivariate model. These covariates are known important prognostic factors, and were collected at baseline in all 3 RCTs. The interaction term of any of these covariates with treatment was also included in the model if such an interaction term remained significant with a  $P$  value of  $\leq .05$  in the multivariate adjusted analysis. The methods within each trial were followed with respect to defining local failure, distant brain failure and neurologic death; event status and time to event was based on initial failure date.

## Results

The baseline statistics in the 3 selected RCTs, with a total of 364 eligible patients, as well as the distribution of local failure, distant brain failure, all-cause mortality, and neurologic death are summarized in Table 1. Of the 364 patients, 186 (51%) were treated with SRS alone and 178 (49%) with SRS plus WBRT. In the SRS-alone and SRS plus WBRT cohorts, the median (lower, upper quartile) time to death was 10 months (4.5, 18) and 8.2 months (4, 13), respectively, and the mean ( $\pm$ SD) time to death was 15 months ( $\pm 16$  months) and 14 months ( $\pm 14$  months), respectively. In the respective cohorts, the median (lower, upper quartile) time to local failure was 6.6 (3.4, 14) months and 7.4 (3.8, 16) months, respectively, and the mean ( $\pm$ SD) time to local failure was 11 ( $\pm 14$ ) versus 13 ( $\pm 13$ ) months, respectively. The median (lower, upper quartile) time to distant failure was 4.7 months (2.8, 11) and 6.5 months (3.8, 16), and the mean

**Table 1** Descriptive statistics for 364 patients and those stratified by SRS versus SRS plus WBRT age groups

Factor	Total no. of patients (n = 364)	SRS alone (n = 186)	SRS plus WBRT (n = 178)	SRS alone age >50 yr (n = 155)	SRS plus WBRT age >50 yr (n = 141)	SRS alone age ≤50 yr (n = 31)	SRS plus WBRT age ≤50 yr (n = 37)
No. of females/males (%/%)	128/236 (35/65)	65/121 (35/65)	63/115 (35/65)	47/108 (30/70)	47/94 (33/67)	18/13 (58/42)	16/21 (43/57)
Median age, yr (range)	62 (33-86)	62 (33-86)	61 (35-78)	64 (51-86)	65 (51-78)	45 (33-50)	45 (35-50)
Age ≤50 yr (%)	68 (19%)	31 (17%)	37 (21%)				
RPA1/RPA2 (%/%)	149/215 (41/59)	73/113 (39/61)	76/102 (43/57)	56/99 (36/64)	50/91 (35/65)	17/14 (55/45)	26/11 (70/30)
No. of brain metastases (%)							
1	217 (60%)	111 (60%)	106 (60%)	92 (59%)	80 (57%)	19 (61%)	26 (70%)
2	88 (24%)	44 (24%)	44 (25%)	36 (23%)	36 (26%)	8 (26%)	8 (22%)
3	47 (13%)	24 (13%)	23 (13%)	21 (14%)	21 (15%)	3 (10%)	2 (5%)
4	12 (3%)	7 (4%)	5 (3%)	6 (4%)	4 (3%)	1 (3%)	1 (3%)
Extracranial metastases	202 (56%)	100 (54%)	102 (58%)	82 (52%)	77 (55%)	18 (58%)	25 (68%)
Cancer type							
Lung	214 (59%)	109 (59%)	105 (59%)	100 (65%)	84 (60%)	9 (29%)	21 (57%)
Breast	43 (12%)	22 (12%)	21 (12%)	12 (8%)	11 (8%)	10 (32%)	10 (27%)
Kidney	24 (6%)	11 (6%)	13 (7%)	6 (4%)	13 (9%)	5 (16%)	0 (0%)
Other	83 (23%)	44 (23%)	39 (22%)	37 (24%)	33 (23%)	7 (23%)	6 (16%)
Local failures (%)	72 (20%)	51 (27%)	21 (12%)	41 (26%)	17 (12%)	10 (32%)	4 (11%)
Salvage treatment after local failures (%)	45 (63%)	37 (73%)	8 (38%)	29 (71%)	7 (41%)	8 (80%)	1 (25%)
Distant brain failures (%)	156 (43%)	98 (53%)	58 (34%)	78 (50%)	39 (28%)	20 (65%)	19 (51%)
Salvage treatment after distant failures (%)	100 (64%)	72 (73%)	28 (48%)	56 (72%)	19 (49%)	16 (80%)	9 (47%)
Total deaths (%)	314 (86%)	157 (84%)	157 (88%)	135 (87%)	126 (89%)	22 (71%)	31 (84%)
Neurologic deaths (%)	99 (27%)	55 (30%)	44 (25%)	43 (28%)	36 (26%)	12 (39%)	8 (22%)

Abbreviation: RPA = recursive partitioning analysis.

(±SD) time to distant brain failure was 9.6 months (±13 months) versus 12 months (±12 months), respectively.

Patient age as a continuous variable was found to be a significant treatment effect modifier on survival ( $P = .04$  for the interaction term); which means that the treatment effect on survival differs for patients with different ages. From the fitted regression model with the interaction term, estimates of the adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CI) of treatment effects on survival (SRS vs SRS plus WBRT) were calculated and shown at 35 to 80 years of age in 5-year intervals (Table 2, Fig. 2). As shown in Table 2 and Figure 2, patients ≤50 years of age initially treated with SRS alone had a significantly lower hazard of mortality than patients with similar ages treated with SRS plus WBRT. However, there were no significant differences in mortality between the 2 treatment groups for patients >50 years of age (Table 2 and Fig. 2). For patients ≤50 years of age, the median survival was 13.6 months in the SRS-alone cohort as opposed to 8.2 months in the SRS plus WBRT cohort. The median survival was 10.1 months

and 8.6 months for patients >50 years of age treated with SRS alone and SRS plus WBRT, respectively. Based on our finding of treatment benefit of SRS alone on survival for patients ≤50 years of age, we also summarized the baseline characteristics of 296 patients >50 years of age and 68 patients ≤50 years of age in Table 1. Of note with respect to histology, other than a greater proportion of renal cell carcinoma patients in the cohort of SRS-alone patients ≤50 years of age, compared to the cohort of SRS plus WBRT patients ≤50 years of age, there were no significant differences between groups ( $P > .05$ ). In keeping with survival analyses and our other a priori-selected covariates, we also observed a statistically significant lower hazard of mortality among patients with 1 metastasis as compared to those with ≥2 metastases (HR = 0.72, 95% CI = 0.57-0.90), and among patients with RPA class of 1 as compared to class 2 (HR = 0.75, 95% CI = 0.56-0.99).

Patient age as a continuous variable was also found to be a significant treatment effect modifier on distant brain failure ( $P = .04$  for the interaction term); which means that



**Table 2** Hazard ratio estimates for SRS alone versus SRS plus WBRT at different ages for overall survival and distant brain failure

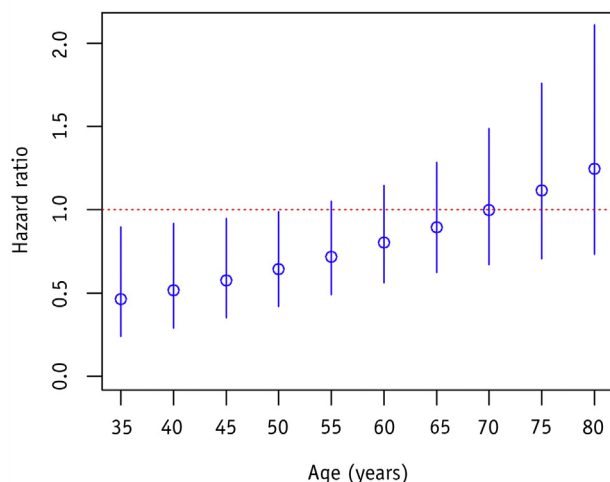
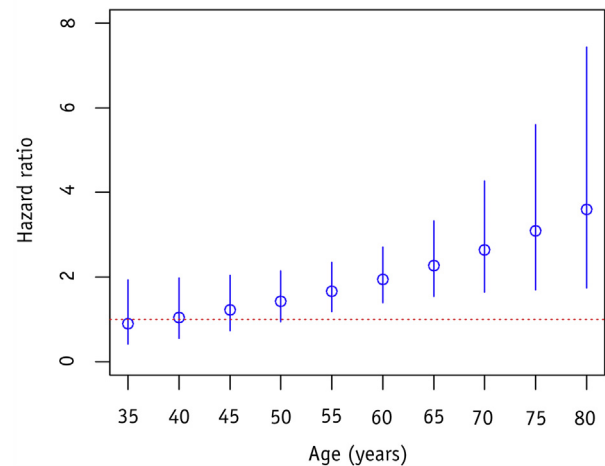
Age*	HR (95% CI) for†	
	Overall survival	Distant brain failure
35	<b>0.46 (0.24-0.9)</b>	0.90 (0.42-1.94)
40	<b>0.52 (0.29-0.92)</b>	1.05 (0.56-1.98)
45	<b>0.58 (0.35-0.95)</b>	1.23 (0.73-2.05)
50	<b>0.64 (0.42-0.99)</b>	1.43 (0.95-2.15)
55	0.72 (0.49-1.05)	<b>1.67 (1.19-2.35)</b>
60	0.80 (0.56-1.14)	<b>1.95 (1.40-2.71)</b>
65	0.90 (0.62-1.29)	<b>2.27 (1.55-3.33)</b>
70	1.0 (0.67-1.49)	<b>2.65 (1.64-4.27)</b>
75	1.12 (0.71-1.76)	<b>3.09 (1.70-5.61)</b>
80	1.24 (0.73-2.11)	<b>3.60 (1.75-7.44)</b>

Abbreviations: CI = confidence interval; HR = hazard ratio.

\* Because treatment effect depends on the patient's age (as it was a significant effect modifier), estimates of effects (HRs and corresponding 95% CIs) are presented at patients' ages from 35 to 80 years at intervals of 5 years.

† Estimates were obtained from adjusted analysis for important confounders and prognostic factors. Significant estimates (boldface) with  $HR < 1$  and  $HR > 1$  suggest protective and harmful effects, respectively, of SRS alone at the corresponding age on the respective outcome.

the treatment effect on distant brain failure differs for patients with different ages. From the fitted regression model with the interaction term, estimates of the adjusted HRs and corresponding 95% CIs of treatment effects (SRS vs SRS plus WBRT) on distant brain failure were calculated and shown at 35 to 80 years of age in 5-year intervals (Table 2, Fig. 3). The risk of distant brain failure for all patients  $\leq 50$  years of age initially treated with SRS alone was not

**Risk of mortality of SRS vs. SRS plus WBRT at different ages****Fig. 2.** Estimates of treatment effects (SRS vs SRS plus WBRT) and corresponding 95% CIs on survival at 35 to 80 years of age at 5-year intervals. SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.**Risk of distant failure of SRS vs. SRS plus WBRT at different ages****Fig. 3.** Estimates of treatment effects (SRS vs SRS plus WBRT) and corresponding 95% CIs on distant brain control at 35 to 80 years of age at 5-year intervals. SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

significantly different from that for those initially treated with SRS plus WBRT. Beyond age 50, the risk of distant failure was significantly higher for all patients in the SRS-alone cohort than in the SRS plus WBRT cohort. Patients with 1 metastasis had a significantly lower risk of developing distant brain failure than those with  $\geq 2$  metastases ( $HR = 0.63$ , 95% CI = 0.46-0.88). No significant relationship was observed for RPA class 1 versus 2 ( $HR = 0.79$ , 95% CI = 0.56-1.14).

For local brain failure analysis, treatment effect was not modified significantly by any of the covariates. The estimate of HR was 1.01 (95% CI = 0.98-1.03) for every year of increase in patient age, 0.74 (95% CI = 0.46-1.18) for number (1 vs  $\geq 2$ ) of brain metastases, and 1.28 (95% CI = 0.76-2.17) for RPA class 1 versus 2. The analysis model with no interaction term revealed that SRS plus WBRT was associated with a lower hazard of local brain failure than SRS alone ( $HR = 2.56$ , 95% CI = 1.54-4.26).

A total of 63% (45 of 72) of local failures and 64% (100 of 156) of distant failures underwent salvage treatments (Table 1). Although there were more failures and salvage treatments in those treated with SRS alone versus SRS plus WBRT (Table 1), there were no statistically significant differences in the proportions of salvage treatment for local and distant failures according to patient age groups within corresponding treatment arms (for example, in patients  $> 50$  years of age treated with SRS alone, 71% of local failures were salvaged as compared to 80% in patients  $\leq 50$  years of age treated with SRS alone) (Table 1). Moreover, the median survival times for those undergoing any salvage brain therapy was 18.2 months and 16.2 months in patients  $\leq 50$  years of age compared with those  $> 50$  years of age, respectively. Median survivals for

those not undergoing any salvage brain therapy were 7.0 months and 5.9 months in patients  $\leq 50$  years of age compared with those  $>50$  years of age, respectively. With respect to neurologic death (Table 1), there were no statistically significant differences among the cohorts. Of note, the number of neurologic deaths was greater in the SRS-alone cohort for patients  $\leq 50$  years of age versus those in the SRS plus WBRT cohort  $\leq 50$  years of age, at 39% versus 22%, respectively, although the comparison was not statistically significant.

A post hoc sensitivity analysis was performed to determine whether data from any 1 trial confounded the results. When we performed a step-wise exclusion of any of the 3 data sets, the estimates of treatment effects were not significant, but the directions were consistent with that observed when analyzing the entire data. Therefore, no single randomized trial impacted the result.

## Discussion

Considering each of the RCTs included in this IPD meta-analysis comparing SRS alone to SRS plus WBRT (3-5), prior meta-analysis based on aggregate published data (1, 6), and prior studies evaluating the addition of SRS plus WBRT with systemic agents or surgery (13-22), it has been consistently observed that in patients presenting with a limited number of brain metastases, the addition of WBRT increases both local control and distant brain control. In these trials, the limited sample sizes prevented subset analysis and we assumed, with respect to these 2 specific endpoints, that the benefits of WBRT were uniform within the study populations.

With respect to survival, we have previously learned that in patients with an expected long-term survival, such as those presenting with 1 metastasis and an RPA of 1, that strategies to optimize local control (additional surgery or SRS to WBRT) can yield survival benefits when the alternative treatment is WBRT alone (16, 17). However, in the SRS-alone versus SRS plus WBRT trials (where local control is optimized in both arms by SRS), the impact on survival has not been clear. Both the Aoyama et al (3) and Kocher et al (5) trials reported no survival advantage to additional WBRT, whereas the Chang et al (4) trial reported a survival advantage favoring SRS alone. Importantly, none of these trials were intended to address survival as the primary endpoint.

By performing an IPD meta-analysis, we were able to perform subset analyses and report age as a significant treatment effect modifier with respect to both survival and distant brain control. In those patients  $\leq 50$  years of age, a survival advantage was observed with SRS alone compared to their age-matched cohort treated with SRS plus WBRT (Table 2, Fig. 2). For patients older than 50 years of age no survival disadvantage was observed with SRS alone. With respect to distant brain failure, patients  $\leq 50$  years of age treated with SRS alone had no increased risk of developing

new brain metastases compared to their age-matched cohort treated with SRS plus WBRT (Table 2, Fig. 3). Beyond age 50, the risk of new distant brain metastases was significantly greater in patients treated with SRS alone. Age was not a treatment effect modifier for local failure, and additional WBRT reduced the risk of local tumor failure. We also observed that patients presenting with 1 metastasis had a favorable survival and a lower risk of distant brain failure than patients with 2 to 4 metastases, and that patients with an RPA 1 versus 2 had favorable survival. These latter findings are in excellent agreement with those of published reports (7, 8, 17).

Although this IPD meta-analysis could not analyze the toxicity aspects of the treatment arms, there are now randomized studies that clarify the adverse effects of WBRT. It is now clear, based on a randomized study evaluating prophylactic cranial irradiation in patients with non-small-cell lung cancer, that WBRT leads to a decline in memory function despite a reduction in the incidence of new brain metastases (23). Unfortunately, the trial could not accrue sufficiently for the endpoint of survival (23). The association between WBRT and adverse neurocognitive outcomes in patients treated upon the development of brain metastases has also been reported by Chang et al (4). This trial concluded that the addition of WBRT to SRS results in significantly worse memory function than SRS alone despite a reduction in intracranial relapse rates. Clearly these studies show that WBRT is independently compromising neurocognition. With respect to quality of life (QOL), we have recently learned from the EORTC RCT comparing observation versus WBRT, after either SRS or surgery, that the addition of WBRT results in worse QOL outcomes (24). This finding may be critical given the results of a QOL analysis, from a RCT comparing high-dose radiation for lung cancer primary tumors to lower dose radiation (with chemotherapy), reported in abstract form (25). The high-dose radiation arm yielded a clinically meaningful decline in QOL and survival compared to the low-dose arm. The authors postulate that the decline in QOL, as a patient-reported outcome, may explain the negative survival result even though provider related toxicities were not significantly different (25).

Given the recent data confirming harm to cognition and QOL with WBRT (2,23,24), and the potential for a survival detriment when compromising QOL (25), we hypothesize that in patients  $\leq 50$  years of age that exposure to the adverse effects of WBRT without yielding a therapeutic gain with respect to distant brain relapse rates (no significant difference in distant brain failure was observed in these younger patients when treated with SRS alone vs SRS plus WBRT) (Table 2, and Fig. 3) may explain our survival results. Note that when WBRT reduced the rate of new brain metastases, as observed in the older patients (age  $>50$  years, Figure 3, Table 2) treated with SRS plus WBRT vs SRS alone, no survival advantage or disadvantage was observed between the two arms.

We acknowledge that our explanation remains speculative and an area of further investigation; however, there are uncontrolled and limited data emerging that also report the association between treatment with SRS alone and favorable survival rates compared to treatment with WBRT (26, 27). We also acknowledge that the observation of distant brain failure rates being no greater in the younger patients, despite the lack of WBRT, and the implication on survival remain to be explained. Biomarkers, nomograms, and new imaging techniques to identify those patients not at risk of distant brain failure is an active area of investigation, and may assist in the selection of patients best suited for SRS alone.

Potential limitations of this study include an observed imbalance in the primary cancer type in patients  $\leq 50$  years of age treated with SRS versus SRS plus WBRT. There were patients  $\leq 50$  years of age with a renal cell primary treated in the SRS-alone cohort compared to those  $\leq 50$  years of age treated with SRS plus WBRT (Table 1). When we analyzed the effect of this factor by excluding these patients, the same trends were observed as those of our reported results for the entire sample. An analysis was also performed to determine whether our result would hold true when considering only the lung cancer and breast cancer cohorts, given that there were higher numbers of lung cancer patients in the SRS plus WBRT cohort and breast cancer patients in the SRS-alone cohort, even though the differences were nonsignificant ( $P > .05$ ). The analysis yielded the same trends with respect to our reported results for the entire sample. Caution must be observed in histology-specific subset analyses as they are limited in terms of sample size, and considered exploratory with the intent to confirm trends in the outcome direction. Therefore, firm histology-specific conclusions cannot be drawn. Of note, there was a greater proportion of RPA1 to RPA2 patients in younger patients ( $\leq 50$  years) treated with SRS plus WBRT than the SRS-alone cohort (Table 1); however, the difference was not statistically significant.

Ultimately, what is required are histology-specific trials for brain metastases, and these are challenging due to the potential for numerous factors to influence outcomes in the metastatic patient. For example, variability in terms of the sites and numbers of extracranial organs involved, patients being at different points in the trajectory of their disease (ex oligometastatic or a diffuse disease pattern) and the heterogeneity with respect to exposure (or to be exposed) to various systemic therapies with some now having activity in the brain. Of note, a recent large study of 1194 patients treated with SRS alone for 1 to 10 metastases also did not observe significant differences in survival when comparing the primary cancer types of breast versus lung, renal cell versus lung, others versus lung, with the exception of patients with gastrointestinal primaries versus lung primaries (8). In that study, the authors also examined the rate of distant brain failure and overall survival in patients with 2 to 4 versus 5 to 10 metastases treated with SRS alone. They observed no significant differences in either outcome. This is important as our conclusions are made for patients with

up to 4 metastases even though only one of the 3 RCTs in this meta-analysis included patients with 4 metastases. However, we acknowledge that our results may be more applicable to those presenting with up to 3 metastases as only the minority of patients had 4 metastases (Table 1).

With respect to salvage therapy, there were more relapses in the SRS-alone cohorts both locally and distantly, and more salvage treatments (Table 1). We observed that patients who were treated with brain salvage treatments, as opposed to no brain salvage treatments, had longer survival. No statistically significant differences in the proportion of patients receiving salvage therapy with respect to age within corresponding treatment arms (Table 1) were observed, and the same impact on survival in those treated with salvage versus no salvage according to age was observed. Therefore, although we could not obtain the needed information as to what local/distant salvage therapies were delivered, the extra cranial disease status at the time of relapse, PS at the time of brain relapse and details with respect to chemotherapy delivery or molecular status of the primary, we acknowledge that these are RCTs with the expectation that unforeseen factors causing bias downstream from the initial treatment were accounted for by the randomization. Furthermore, most of the prognostic factors that were available from all 3 studies were similarly distributed in the 2 treatment arms as well as sub groups of age; therefore, we expect that any impact due to residual imbalances including that of salvage treatment in the IPD meta-analysis would have minimal impact on the estimates of treatment effects. We also acknowledge that there was a non-significant difference in the number of neurologic deaths in younger patients ( $\leq 50$  years of age) treated with SRS alone versus SRS plus WBRT (Table 1), which may be a drawback to both the increased local/distant failure rates and use of salvage procedures when treating with SRS alone, despite the overall survival results. However, the sample is limited, and there is subjectivity in neurologic death assessments compared to the harder endpoints of local control, distant brain control, and overall survival.

## Conclusions

In conclusion, based on the use of SRS alone as initial therapy for patients with 1 to 4 brain metastases, this IPD meta-analysis suggests (with the above caveats taken into consideration) a survival advantage in patients  $\leq 50$  years of age; in addition, the initial omission of WBRT did not adversely impact distant brain relapse rates in this cohort. SRS alone may be the preferred treatment for this age group.

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