Editorial

Is "watch and wait" a viable option for surgically resected brain metastases?

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Introduction

A Phase III Japan Clinical Oncology Group (JCOG) trial, by Kayama *et al.*, randomized patients with ≤4 brain metastases (single brain metastasis in 73%), who underwent resection of at least one brain metastasis, to adjuvant whole brain radiotherapy (WBRT) or salvage stereotactic radiosurgery (SRS) (1). Salvage SRS was defined as upfront SRS to any residual brain lesion(s) after surgery, or SRS when surveillance magnetic resonance imaging (MRI) revealed recurrence of ≤8 new brain metastases of size ≤3 cm or volume ≤10 mL. This was a non-inferiority study, powered to detect potential differences in overall survival (OS). For the primary endpoint, there was equal OS of 15.6 months after either adjuvant WBRT or salvage SRS. For intracranial progression free survival (IC-PFS), a secondary endpoint, there was a 6-month benefit in favor of adjuvant WBRT. The authors showed that after 1 year, both the Mini-Mental Status Exam (MMSE) and Karnofsky performance status (PS) were stable for approximately 45% of patients in both arms. However, at as early as 91 days, Common Terminology Criteria for Adverse Events (CTCAE) v3.0 Grade 2–4 cognitive dysfunction developed in 16% of patients after adjuvant WBRT versus 8% after salvage SRS.

Notably, there was significant "crossover" between the arms, with 30% of patients in the WBRT arm requiring focal radiation and 37% of patients in the salvage radiosurgery arm requiring WBRT. As the authors do not report outcomes based upon treatment actually received (i.e., used intention to treat analyses), this crossover may have obscured some of the mental status benefits of avoiding upfront WBRT. The reported cumulative incidence of Grade 2–3 radionecrosis was approximately 2% in both arms despite 30–40% of patients requiring WBRT and focal radiation, however this was not reported past 91 days, and likely represents an underestimation of late radionecrosis.

The "salvage" aspect of the salvage SRS arm is somewhat of a misnomer. The JCOG authors reported that 60% of patients (in both arms) had no post-operative residual disease. As the trial protocol mandates SRS to residual disease within 21 days post-operatively, this implies that the 40% of patients on the salvage SRS arm would have received SRS <21 days post-surgery—essentially adjuvant SRS—to un-resected or partially-resected residual disease. This contrasts the typical definition of "salvage" where there is the expectation that there is no residual disease after the completion of the primary treatment (e.g., surgery).

Taken together, the results from Kayama *et al.* suggest that active MRI monitoring of select patients after surgery for brain metastases (without residual disease) results in a lower rate of intracranial control but non-inferior OS compared to adjuvant WBRT—in the fact, the survival in both arms is 15.6 months. The authors provide compelling evidence that a significant proportion of patients can be spared from WBRT (which was used in 37% of the salvage SRS patients), which is known to be associated with significant cognitive neurotoxicity.

While the JCOG authors discuss their trial as an

adjuvant WBRT *vs.* salvage SRS trial, it can be grouped in the category of trials that have compared postoperative adjuvant radiotherapy *vs.* observation with serial imaging, generally with radiotherapy (often WBRT) used for salvage (*Table S1*). While the investigators discuss their motivation being to detect a possible improved OS with adjuvant WBRT, and hoping to preserve this effect with salvage SRS (subsequently powering their trial for OS), there is no randomized evidence supporting adjuvant radiotherapy leading to increased OS, which we discuss below.

Adjuvant radiotherapy *vs.* observation

Historically, until the 1980s, even a single brain metastasis carried a very grim prognosis. In an era with less effective systemic therapy, less sophisticated supportive care and less advanced imaging modalities to sufficiently detect small asymptomatic metastases, patients with brain metastases would had a dismal prognosis, with high death rates from both intra-cranial and extra-cranial progression. Thus a fairly nihilistic approach of WBRT alone would be offered, with median prognosis of 3–6 months, until the landmark randomized study by Patchell *et al.* (6) showed that the addition of surgery to WBRT for a single metastasis increased median survival from 15 to 40 weeks.

Given the significance and extent of benefit from surgery, a series of trials attempted to answer the logical next question: can the benefit of surgery be sustained by surgery alone?

Another study by Patchell *et al.* (this one being a cooperative group study) (2) attempted to ask: does the addition of WBRT to surgery decrease intracranial recurrence for a single brain metastasis? The results show that while intracranial recurrence (at the initial site or at new sites) and neurologic death decreased, there was no difference in OS or functional independence.

The European Organisation for Research and Treatment of Cancer (EORTC) 22952 trial by Kocher *et al.* (3) added a modern twist to the second Patchell *et al.* study, by allowing SRS or surgery to ask the question: does the addition of WBRT to local therapy (surgery or SRS) improve functional independence (deterioration of WHO PS to >2)? They found that neither functional independence nor OS were significantly impacted by the addition of adjuvant WBRT to local therapy, though WBRT was associated with lower rates of intracranial progression and neurologic death, which is the same conclusion as the second Patchell study.

A trial by Mahajan *et al.* from MD Anderson Cancer Center (4) posed an even more modern question of adjuvant radiation: for 1–3 completely resected brain metastases (62% had a single metastasis), with resection cavities ≤4 cm, does SRS improve time to local recurrence compared to observation? Both arms had 60–63% patients with a single brain metastasis. The findings were that local control was—as expected—improved with SRS in a size dependent fashion (>90% LC for <2.5 cm lesions with surgery) while—yet again—OS was not improved.

To recap, at least 3 randomized trials (2-4) have asked variations of the same question, and the overwhelming consensus is that while there is control benefit to adjuvant radiotherapy (WBRT or SRS), there is no discernible survival benefit. When Kayama *et al.* state that "*…surgery combined with WBRT prolongs both OS and PFS compared with surgery alone*" and "*Whether SRS alone is as effective on OS as WBRT…*" they are correct only in the context of a PFS benefit. For OS, the reverse is certainly true: surgery has a survival benefit when added to radiation (6)—mostly in the setting of stable extracranial disease (7)—which has led to surgery with adjuvant WBRT becoming the standard treatment for patients with limited brain metastases, and not because of the aforementioned trials that did not show an OS benefit when radiotherapy was added to surgery. In this context, the motivation to power the Kayama *et al.* trial for OS may have been misguided.

Adjuvant radiosurgery *vs.* adjuvant WBRT

The NCCTG N107C/CEC.3 trial by Brown *et al.* (5) investigated adjuvant SRS *vs.* WBRT for patients with ≤4 brain metastases (77% single metastasis) with at least a partial resection of 1 lesion, and with a <5 cm cavity. The trial asked: does adjuvant SRS increase OS or cognitive decline free survival (CDFS) compared to adjuvant WBRT? For OS, the answer—again—was no. However, replacing WBRT with SRS did improve CDFS. Interestingly, there was no difference in OS despite a difference in intracranial tumor progression rates, with WBRT being associated with a better overall and distant intracranial tumor control (unsurprisingly) and better local control (which was unexpected, but may reflect inadequate targeting of the surgical cavity with SRS). That OS was not adversely impacted by worse intracranial tumor control with the omission of WBRT is a consistent theme that was also demonstrated in the aforementioned studies by Patchell, the EORTC and MDACC, as well as in studies investigating

SRS alone *vs.* SRS and WBRT for limited brain metastases (which are not discussed here).

In summary, randomized evidence suggests that adjuvant SRS (Brown *et al.*) or salvage SRS (Kayama) are both acceptable alternatives to upfront adjuvant WBRT with regards to OS and that SRS is superior with regards to preservation of cognitive dysfunction.

Is a "watch and wait" approach able to spare toxicity?

Taken as a whole, the studies of postoperative radiation in *Table S1* suggest that an observation or salvage approach with either WBRT (2,3) or SRS (1,4) should not affect OS, and will spare a large percentage of patients from unnecessary toxicity, expense, and time in the setting of a terminal disease.

In the trials of postoperative treatment (*Table S1*), the rates of salvage WBRT in the observation/salvage arms include 31% in Kocher *et al.*, 37% in Kayama *et al.*, and 46% in Mahajan *et al.*, suggesting that delaying radiotherapy may spare 1/2 to 2/3 of patients from WBRT. For the adjuvant SRS/cavity SRS arms, the rates of salvage WBRT were 20% in Brown *et al.* and 38% in Mahajan *et al.*, suggesting that even with adjuvant SRS, between 1/5 to 2/5 of patients will eventually need WBRT. Thus, regardless of the WBRT-sparing postsurgical treatment approach, there is a reasonably high rate of salvage WBRT and the difference between these two ranges may describe a therapeutic window that describes a "true" proportion of patients who would have done well with "watch and wait" approach that may include salvage SRS, as Kayama *et al.* suggest. While the median time to salvage WBRT for Kayama *et al.* was <6 months, 20% of the patients who underwent salvage WBRT were able to delay this treatment for at least 13 months; both arms in the Mahajan *et al.* trial also had a relatively long median time to WBRT of 15–16 months.

The most feared early treatment failure of a surgery alone approach is leptomeningeal disease (LMD), which is thought to occur due to contamination of the dura vessels by tumor during surgery. Retrospective studies suggest LMD after postoperative SRS occurs in the 13–17% of patients compared to 5% after SRS for intact brain metastases (8-10). Consequently, one might have expected LMD to be on the higher range in the prospective trials discussed above, particularly after cavity SRS instead of WBRT. While none of the studies were powered to detect statistically significant differences in LMD, it is interesting that there were minimal numerical differences between the treatment arms in the development of LMD in Kayama *et al.* (12% for salvage SRS *vs.* 13% for WBRT) and Brown *et al.* (7% at 1 year for SRS *vs.* 5% at 1 year for WBRT), with Mahajan *et al.* showing a larger gap that remained statistically insignificant (16% at 1 year for observation *vs.* 28% at 1 year for cavity SRS, P=0.46), as shown in *Table S1*. Thus, it seems that an increase in LMD is not seen in a "watch and wait" setting compared to immediate adjuvant treatment. It is also possible that the relative equivalence in LMD rates seen in the prospective data compared to the retrospective data may be the result of significant variation in contouring postoperative SRS cavities, which has led to recent expert consensus guidelines with recommendations for preoperative MRI fusion, surgical tract coverage, and CTV margins (11). Another possibility for the equivalence is that initial surgery sufficiently contaminates the surrounding dura such that any postoperative radiotherapy is unable to prevent manifestation of LMD. This hypothesis is supported by retrospective studies showing LMD rates from 0–3% in preoperative SRS compared to 17% seen postoperatively (12,13).

Conclusions

The JCOG 0504 trial by Kayama *et al.* joints the growing evidence that a "watch and wait" approach after surgical resection for select patients with a limited number of brain metastases does not impact OS while sparing some patients from toxicity of unnecessary treatment.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Outcomes in survival, patterns of recurrence, LMD, and salvage WBRT in postoperative trials investigating the benefit additional radiotherapy (1-5)

Postoperative radiation trial	Enrollment	Primary treatment	Randomization	n	Survival			Recurrence									LMD	Salvage WBRT	Median time to WBRT (m)	Comments
					MS (m)	1y OS	2y OS	Median IC RFS (m)	1y IC RFS	2y IC RFS	Median LC (m)	1y LC	2y LC	Median DC (m)	1y DC	2y DC				
Univ. of Kentucky. Patchell *et al.*, NEJM 1998	1989–1997	Complete resection for single metastasis	Observation	46	9.9	–	–	6.0	~20%	<15%	6.2	~35%	<25%	12.2	~48%	<45%	–	–	–	
			WBRT	49	11.0	–	–	50.6	~70%	~70%	>11.5	~80%	<80%	50.6	~85%	~75%	–	–	–	
EORTC 22952. Kocher *et al.*, JCO 2011	1996–2007	Complete resection ≤3 lesions. No size limitations for surgery	Observation	79	10.9*	~45%	~25%	3.4*	–	–	~8	~48%	41%	NR	~62%	58%	–	31%	–	Results combined from primary SRS and primary surgery approach
			WBRT	81	10.7*	~45%	~25%	4.6*	–	–	NR	~78%	73%	NR	~85%	77%	–	3%	–	
JCOG 0504. Kayama *et al.*, JCO 2018	2006–2014	Surgery ≤4 lesions with only one lesion >3 cm having been resected	Salvage SRS*	134	15.6	~60%	~35%	4.0	~22%	~15%	–	–	51%	–	–	26%	12%	37%	<6	SRS for any postop residual lesions, recurrences ≤3 cm or ≤10 mL for ≤8 lesions
			WBRT	137	15.6	~60%	~35%	10.4	~40%	~22%	–	–	45%	–	–	39%	13%	–	–	
MDACC. Mahajan *et al.*, Lancet Oncol 2017	2009–2016	Complete resection ≤3 lesions with max cavity ≤4 cm	Observation	68	18	~65%	~40%	–	–	–	7.6	43%	~40%	~8	33%	~25%	16% at 1y	46%	16	
			Cavity SRS	64	17	~65%	~30%	–	–	–	NR	72%	~62%	~6	42%	~30%	28% at 1y	38%	15	
NCCTG N107C/CEC.3. Brown *et al.*, Lancet Oncol 2017	2011–2015	At least partial resection of 1 lesion, ≤4 lesions with max cavity <5 cm	SRS/cavity SRS	98	12.2	~52%	~25%	6.4	37%	–	–	61%	–	–	65%	–	7% at 1y	20%	–	Local salvage: 32% in SRS group, 21% in WBRT group (P=0.12)
			WBRT	96	11.6	~48%	~35%	27.5	72%	–	–	81%	–	–	89%	–	5% at 1y	–	–	

*, see comments; ~, estimated from figure in paper. y, year; IC, intracranial; LC, local control; DC, distant control; LMD, leptomeningeal disease; WBRT, whole brain radiotherapy; SRS, salvage stereotactic radiosurgery; OS, overall survival; RFS, recurrence free survival; MS, median survival.