THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Efficacy of Post-Surgical Stereotactic Radiosurgery for Metastatic Brain Disease: A Randomized Trial
2009-0381

Core Protocol Information

Short Title	Resection bed SRS
Study Chair:	Anita Mahajan
Additional Contact:	Donna M. White Toni Williams Victoria Cox
Department:	Radiation Oncology
Phone:	713-563-2300
Unit:	97
Full Title:	Efficacy of Post-Surgical Stereotactic Radiosurgery for Metastatic Brain Disease: A Randomized Trial
Protocol Type:	Standard Protocol
Protocol Phase:	Phase III
Version Status:	Activated 09/24/2013
Version:	16
Submitted by:	Toni Williams--9/13/2013 11:23:24 AM
OPR Action:	Accepted by: Virginia M Gonzales -- 9/24/2013 3:58:08 PM

Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1. To evaluate benefit of post-surgical stereotactic radiosurgery (SRS) on the resection bed in effecting time to local recurrence in comparison to surgical resection alone.
2. Secondary endpoints assessed will include: overall survival, development of distant brain metastases and complications related to treatment .

2.0 Background and Significance

Metastatic brain disease is a significant medical problem with an estimated 170,000 to 200,000 new cases annually [1, 2]. For a single, surgically accessible brain metastasis, the standard of care has been established as surgical resection followed by Whole Brain Radiation Therapy (WBRT)[2, 3]. WBRT is known to decrease local recurrence at the surgical site. Stereotactic radiosurgery (SRS) is a well established, effective technique used to treat small intracranial targets and has been used with or without WBRT in patients with brain metastasis, particularly those that are small and surgically inaccessible. In a prospective randomized trial investigating SRS with or without WBRT Aoyama et all reported that even though there was a difference in local control and brain control in the group randomized to WBRT, there was no statistical difference in overall survival between the two groups. This finding suggests that subsequent therapies, including repeat SRS or delayed WBRT for new metastatis is effective with no detriment in patient survival. In practice, WBRT is often withheld due to various reasons including: reports of its negative impact on cognition[4, 5], possible interruption of chemotherapy, and prolonged fatigue lasting 1-2 months. The results from Aoyama and multiple retrospective studies support the approach of avoiding or delaying WBRT without an impact on survival and so at this institution, this strategy is commonly used. In order to minimize the chances of local recurrence after surgery, SRS is now being used to radiate the surgical bed instead of WBRT. Although small series have appeared in the literature[6-8], there are no prospective randomized trials to definitively support the use of post-operative SRS to the surgical resection cavity.

2.1 The Technique of Stereotactic Radiosurgery

Stereotactic radiosurgery is a method of eradicating intracranial lesions by delivering multiple, small, well collimated beams of ionizing radiation to stereotactically localized lesions. In 1951 at the Karolinska Institute in Sweden, Lars Leksell originally developed the technique for the treatment of functional disorders of the brain by ablating specific sites[9]. With the development of CT in the 1970s and MRI in the 1980s, the application of stereotactic techniques for treating other neurological disorders rapidly developed and many other uses of stereotactic radiosurgery were explored. Stereotactic radiosurgery has now been shown to be effective against vascular abnormalities, particularly arteriovenous malformations, and against some brain tumors, such as

acoustic neuromas.

The stereotactic radiosurgery system developed by Leksell has become known as the Gamma Knife. More recently, technical advances in the design of conventional radiotherapy units allowed them to be used as radiosurgery units. Specifically, modern linear accelerators have the ability to generate high-energy beams of x-rays that can be well collimated. These machines can administer arc photon beams precisely around a fixed point. The LINAC-based stereotactic radiosurgery technique allows delivery of high doses of radiation to stereotactically defined targets with a steep dose gradient at the edge of the lesions and a minimal dose to the surrounding brain10. At the University of Texas MD Anderson Cancer Center (UTMDACC), LINAC-based stereotactic radiosurgery technique has been available since 1991 and our multidisciplinary team comprised of neurosurgeons, radiation oncologists and radiation physicists treat over 200 patients per year.

Stereotactic radiosurgery has several theoretical advantages. First, radiosurgery is non-invasive. It requires placing a stereotactic head frame under local anesthesia and treatments are delivered in a short period of time to conscious patients. Consequently, radiosurgery is better tolerated than surgery in patients with medical conditions that make general anesthesia undesirable. Second, radiosurgery can be delivered to lesions that may be considered surgically inaccessible. Although modern surgical technologies have made most tumors accessible to the surgeon, some lesions may still be considered unsafe for surgical resection, particularly when eloquent normal brain must be transgressed to reach the lesion.

2.2 Surgical Management of Metastatic Brain Tumors

Two randomized controlled trials definitively showed a benefit to surgical resection followed by whole brain radiation2, 3. In the 1990 study by Patchell et al., surgical resection followed by postoperative radiation was significantly superior to biopsy followed by radiation (local recurrence rates were 20% vs. 52 % respectively, $p < 0.02$). Median overall survival was superior as well (40 weeks vs. 15 weeks respectively, $p<0.01$). In a subsequent study, the same authors showed that the addition of whole brain radiation to a surgically resected single brain metastasis was superior to resection alone. In this study, the local recurrence rates were 10% versus 46% respectively ($p<0.001$). At MDACC, surgical resection is frequently employed for treatment of metastatic brain disease and we have specific expertise in this area. Our neurosurgeons make use of state of the art techniques (including frameless stereotactic navigation), and achieve complete resection of the tumor in 95% of cases.

2.3 Stereotactic Radiosurgery after Surgical Resection

While no randomized trials are available for the use of SRS after surgery for brain metastasis, at least three retrospective studies have been performed6-8. The patient population in these studies is low ranging from seven to forty. Each of these studies verifies the feasibility of post surgical SRS to the resection cavity. Mathieu et al.

reported a local control rate of 73% after SRS was used to treat the resection bed after removal of a brain metastasis. This is comparable, although not as compelling, as the 90% local control rate reported by Patchell when WBRT was applied after surgical resection. Nevertheless, these patients presumably avoided the potential deleterious consequences of WBRT, and could have potentially received WBRT as salvage therapy. Distant brain failure remains the risk of local treatment. It is unclear from the data from these studies whether or not local failure occurred prior to distant brain failure. There are two randomized trials comparing SRS and WBRT which can be used to indirectly identify the risks of local brain failure1, 11. Aoyama et al. compared SRS alone to SRS plus WBRT1. In this study, the authors found that local control was significantly better with the addition of WBRT (p=0.02). Andrews et al. (RTOG 9508) compared SRS and WBRT to WBRT alone for treatment of one to three newly diagnosed brain metastases11. They found that local failure was significantly reduced with the combination of the two (p=0.01). However, overall brain failure rates were not statistically different (p=0.12). Taken together, these studies support the use of radiation for minimizing the potential for local and distant brain failure after treatment of a brain metastasis. These results form the basis for the hypothesis of our study: can SRS replace WBRT in delaying or preventing local recurrence after surgical resection of a brain metastasis.

Value of a Prospective Trial

Currently, there are no prospective trials supporting the use of SRS to the post operative surgical cavity. Anecdotal evidence abounds to suggest that post-operative SRS decreases local recurrence rates. Validating post operative SRS in a prospective randomized fashion can be accomplished at MDACC given the volume of cancer patients with metastatic brain disease treated with both surgery and radiosurgery.

3.0 Patient Eligibility

The study will be a controlled prospective randomized trial in which eligible patients (see Human Subjects section 9) will be randomized to one of two arms, conventional surgery followed by stereotactic radiosurgery to the resection bed or conventional surgery alone.

3.1 Inclusion Criteria

3.1.1 Patients must be older than 3 years of age (radiosurgical frames cannot be placed on children younger than age 3).

3.1.2 Patients must have 3 or fewer newly diagnosed metastatic lesions in the brain with a complete resection of at least one lesion as determined the study neuroradiologist.

3.1.3 The resection cavity must have a maximum diameter of $\leq$ 4cm (will be determined by the study radiologist).

3.1.4 Additional unresected brain metastases (up to 2) must have a maximum diameter of $\leq$ 3 cm.

3.1.5 Patients must be considered candidates for SRS within 30 days of surgical resection.
3.1.6 Patients must have a Karnofsky Performance Scores $\geq$ 70 at the first post operative visit. Patients under 18 years of age must have a Lansky Performance Score of $\geq$ 70.
3.1.7 Patients must be able to undergo an MRI scan.
3.1.8 Patients must agree to randomization as documented by signing the Institutional Review Board (IRB) approved consent form.

3.2 Exclusion Criteria

3.2.1 Patients who have received prior radiation therapy to the brain for any reason.
3.2.2 There is radiographic evidence of leptomeningeal disease prior to study entry.
3.2.3 The primary tumor is small-cell lung cancer, lymphoma, leukemia, or multiple myeloma.
3.2.4 For females, if they are pregnant or breast-feeding (The exclusion is made because gadolinium may be teratogenic in pregnancy).

4.0 Pretreatment evaluation

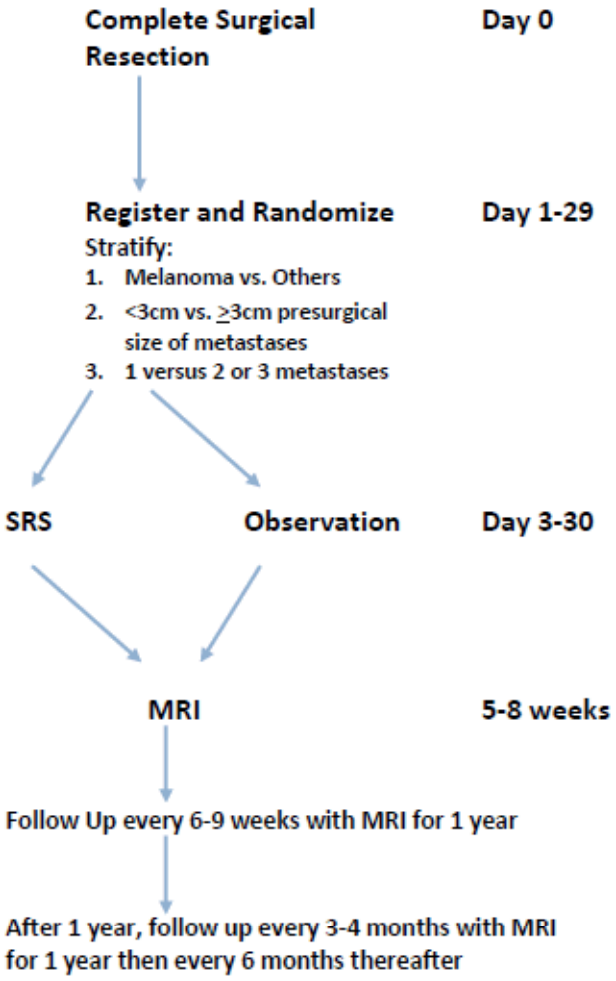
Patients will be enrolled in the study and randomized within 1-29 days after surgical resection (typically during the first post operative clinic visit). The patient's complete history (including details of prior chemotherapy, radiotherapy, or surgery for systemic disease, and concurrent non-malignant disease), general physical exam, complete neurological exam, and determination of the KPS, will be reviewed prior to consent. The extent of the systemic (noncerebral) disease should be evaluated and the activity of the systemic disease will be characterized as progressing, stable, or no evidence of disease based upon a CT of the chest/abdomen and pelvis or PET imaging performed within 3 months of randomization.

They will undergo a volumetric MRI within seven days of scheduled SRS treatment for planning purposes. Patients randomized to receive SRS will undergo the procedure 3 to 30 days after surgical resection.

5.0 Treatment Plan

Patients who have undergone resection of at least one lesion (who have less than three total), who meet the inclusion criteria will be randomized to receive post operative SRS to the resection cavity within 30 days of the craniotomy or to observation alone. Patients will be stratified by the following variables: primary tumor histology, size of metastasis (pre-resection tumor volume), and single versus multiple metastases (2 or 3). All other unresected brain metastasis will be treated with SRS between day 3 and 30 after surgery whether or not they are randomized to the post-op surgical bed SRS. All unresected lesion(s) and/or surgical bed will be

treated with SRS on the same day.



Changes in patients' clinical courses will be treated as deemed medically necessary. Treatment of the systemic disease will be left to the discretion of the primary medical oncologist.

5.1 Evaluation During Study

All patients will be undergo an MRI at 5-8 weeks post craniotomy then every 6-9 weeks for 1 year. After 1 year, follow up every 3-4 months for 1 year then every six months thereafter. Patients will be removed from the study once they develop a local recurrence or develop distant brain metastases requiring WBRT, but will be followed for overall survival purposes. Patients who develop a distant brain lesion that is treatable by local therapy, without the use of WBRT, will remain on study. WBRT will be administered at the discretion of the treating physicians.

Patients will be evaluated clinically and radiographically at approximately 5-8 weeks after the craniotomy, and approximately every 6-9 weeks thereafter by staff from the

Departments of Neurosurgery and Radiation Oncology. Corticosteroid doses will be adjusted based on clinical and radiographic criteria. Requirements for more frequent evaluation will be carefully documented. Data on unscheduled follow-ups will also be documented.

5.2 Outcome evaluation

Endpoints to be assessed include: local failure, distant brain recurrence and overall survival. Recurrence in the brain will be considered to be local (at the site of resection/HOU/UTMDACC) or distant (at brain sites separate from the treated site). Local recurrences will include radiographic evidence of a new contrast-enhancing lesion (specifically any new progressive enhancing nodularity) at the site of surgical resection and will be reviewed by the study neuroradiologist.

Evaluation of local tumor recurrence or progression (i.e., treatment failure) after radiosurgery is complex because the treatment may induce transient radiographic changes such as increased enhancement size or increased edema, representing tumor necrosis rather than tumor growth. These radiographic changes may be associated with transient neurological worsening. Because palliation of symptoms is a main goal of treatment, an increase in the size of the lesion with associated worsening of the patient's neurological condition (based on the KPS and the assessment of the neurosurgeon and radiation oncologist participating in the study), and despite increases in steroid dose, will be considered to be a local failure. These radiosurgical failures may be treated surgically if the patient has stable or responding systemic disease is medically fit to undergo general anesthesia. Clinical intervention will be based on the clinical symptoms of the patient and the assessment of the neurosurgeon and the radiation oncologist. Patients will be treated using the same criteria as outlined earlier.

5.3 Off Study

Patients will be off study if they require WBRT, develop a local recurrence or die.

6.0 Radiation Technique

The target volume for SRS will include the surgical cavity with a 1mm margin. Linear accelerator SRS with either circular collimation or mini-multileaf collimation or Gamma Knife (GK) SRS will be allowed. The tumor volume ratio (TVR) should be evaluated for final treatment plan acceptance. Normal tissue doses through dose volume histogram (DVH) analyses of the brain stem and optic chiasm should be evaluated. The maximum point dose to the optic apparatus should not exceed 9Gy. More than 1cc of the brain stem should not exceed 12 Gy. The prescribed dose should be modified to respect the above normal tissue constraints. The prescribed

dose to the isodose line surrounding the target volume will be as follows:

0-10cc	16Gy
10.1-15cc	14Gy
>15cc	12Gy

Radiosurgery treatment planning will be based on stereotactic MRI scan with or without a planning CT, which is the current standard practice.

7.0 Statistical Considerations

7.1 Accrual Goal:

A total of 132 patients will be recruited from both genders, all races, and ages 3 years and above.

7.2 Randomization procedure:

Patients will be block randomized equally between SRS and observation using CORe. The randomization will be stratified on three factors: histology (melanoma vs. others), size of metastases (<3cm vs. >/= 3cm), and number of metastases (1 vs. 2 or 3).

Sample size calculations: The sample size calculations are based on the primary endpoint - time to local recurrence (TTLR). Local recurrence after surgical resection is expected to occur in 50% of patients within 6 months. After the application of SRS to the surgical cavity, the available literature indicates that local recurrence will occur in 25% of patients within 6 months. Based on the exponential distribution, this implies that a median TTLR of 6 months in the surgical resection arm and 14.45 months in the SRS arm (hazard ratio of 0.415). Based on this hazard ratio under the alternative hypothesis for a log rank test, a two-sided type I error of 0.05, and 2 interim futility looks, a total of 132 patients (61 to surgery alone and 61 to radiosurgery) will have 99.6% power to detect differences in based on a hazard ratio of 0.415 and approximately 80% power to detect differences based on a hazard ratio of 0.596. With accrual rate of 2-3 patients per month, the projected completion time for the study is 44-66 months.

7.3 Post-entry exclusion:

There will be no post-entry exclusions. All patients randomized to the study will be included in the analysis.

7.4 Statistical analyses:

The primary analysis for TTLR will be intent to treat analysis that A) will include all randomized patients; B) preserve the original treatment assignment; and C) is based on the stratified log-rank test.

For the primary and secondary endpoints, censoring will be done as follows: For recurrence, patients dying without evidence of CNS recurrence will be censored; for site-specific recurrence, patients recurring first in another site will also be censored; finally, in all analyses, patients remaining free of the entity under study at the end of

follow-up will be censored. For all time to event endpoints, a univariate test between groups will be conducted using a log rank test of Kaplan-Meier survival estimates and multivariate analyses will be conducted via the Cox proportional hazards model. The hazard ratio comparing radiosurgery to surgery will be computed for each endpoint with and without adjustment for other covariates. Confidence intervals (95%) will be computed for the hazard ratio estimates. The proportions of patients experiencing neurological complications will be computed via univariate and multivariate logistic regression analysis. The proportion of complications resulting in prolongation of hospital stay will also be computed. The odds ratios comparing radiosurgery to surgery will be computed with and without adjustment for other covariates. Confidence intervals (95%) will be computed for the odds ratio estimates. Secondary analyses will include a competing risk analysis using local CNS recurrence, distant CNS recurrence requiring WBRT, other CNS recurrence, and death without CNS recurrence as competing risks. We will estimate the cumulative incidence functions by treatment arm for each mode of failure. We will estimate the cumulative incidence hazard ratio comparing the two treatment arms with 95% confidence intervals with and without adjustment for potential confounding factors using the Fine-Gray proportional hazards model. We will perform similar analyses for LMD (leptomeningeal disease) treating death without LMD as a competing risk. We will also perform subset analyses according to the three stratification factors (histology, size of metastases, and number of metastases), nature of the resection (en bloc vs. piecemeal), and Graded Prognostic Assessment score (Sperduto, 2012).

7.5 Interim analyses

The maximum sample size to be accrued is 132 patients with 2-3 patients accruing per month. Differences in TTLR will be monitored at 3 timepoints and will take place: 1) after a total of 39 events occur; 2) after 77 events occur**;** and 3) after at least 115 events occur. The test statistic used will be based on the stratified log-rank test. Early stopping rule for futility will serve as guidance for early termination of patient accrual. The interim stopping rule consists of a group sequential test based on a Gamma family Type I error spending function. We will stop early at the first interim look if the two-sided p-value from the stratified log-rank test is greater than 0.9866. In addition, will stop early after the second interim look if the two-sided p-value from the stratified log-rank test is greater than 0.4692. Results from the interim analysis will be reported to an independent Data Monitoring Committee (DMC) convened at MD Anderson Cancer Center, The DMC will assess the along with supportive data including other efficacy outcomes, and safety data. It will use this data to possibly recommend early stopping or other study modifications.

8.0 Data and Protocol Management

To ensure protocol compliance, the neurosurgeon, principal investigator, radiation oncologist, neuroradiologist and research nurse will review the patient data and MRI films prior to randomization. All required pretreatment data should be available before a decision to enroll the patient on the protocol is made.

All data will be collected by the research nurse in charge of the protocol. This includes pretreatment, treatment, and post treatment data. The principal investigator will act as the final arbitrator of all study parameters should a difference of opinion exist. Patients who meet eligibility criteria will be registered in CORe .

9.0 Human Subjects

9.1 Sources of research material

The results of physical, neurological, patient histories, and neuroimaging studies will constitute the research material of the study. These evaluations do not step beyond what is required for regular patient care.

9.2 Recruitment of subjects

Patients who meet the inclusion/exclusion criteria will be recruited for the study by the principal investigator and collaborators. The principal investigator will describe the specifics of the study, its aims, associated risks, and anticipated benefits.

9.3 Potential risks

Stereotactic radiosurgery has risks associated with it. The risks of radiosurgery include tumor swelling, pin site infection, neurological worsening, and edema.
Surgery and SRS are currently the two most recommended treatment modalities for single brain metastases in patients with similar characteristics to those eligible for the proposed study. Adverse treatment reactions will be reported to the IRB as per the guidelines shown in Appendix A.

9.4 Procedures for minimizing risks

Standard monitoring procedures to detect and treat postoperative complications will be followed. Interim analyses of the data will be performed. All attempts will be made to preserve patients' confidentiality. Patient records will be kept in secure file cabinets and handled only by responsible personnel.

9.5 Anticipated benefits versus risks

The main potential benefit of the study is to determine the value (if any) of adding stereotactic radiosurgery to a resected brain metastasis to delay or prevent local recurrence. The short-term risks associated with each procedure are minimal. However, it is not known if duration of local tumor control, survival, and functional abilities are affected. These issues may be of prime importance to the patient and could, if found different, have a major impact on the treatment and management of patients

with brain metastases.

10.0 References

1. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *Jama.* Jun 7 2006;295(21):2483-2491.
2. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *Jama.* Nov 4 1998;280(17):1485-1489.
3. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* Feb 22 1990;322(8):494-500.
4. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys.* Aug 1 2007;68(5):1388-1395.
5. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology.* Jun 1989;39(6):789-796.
6. Bahl G, White G, Alksne J, Vemuri L, Spear MA. Focal radiation therapy of brain metastases after complete surgical resection. *Med Oncol.* 2006;23(3):317-324.
7. Mathieu D, Kondziolka D, Flickinger JC, et al. Tumor bed radiosurgery after resection of cerebral metastases. *Neurosurgery.* Apr 2008;62(4):817-823; discussion 823-814.
8. Do L, Pezner R, Radany E, Liu A, Staud C, Badie B. Resection followed by stereotactic radiosurgery to resection cavity for intracranial metastases. *Int J Radiat Oncol Biol Phys.* Feb 1 2009;73(2):486-491.
9. Leksell L. The stereotaxic method and radiosurgery of the brain. *Acta Chir Scand.* Dec 13 1951;102(4):316-319.
10. Alexander E, 3rd, Loeffler JS. Radiosurgery using a modified linear accelerator. *Neurosurg Clin N Am.* Jan 1992;3(1):167-190.
11. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet.* May 22 2004;363(9422):1665-1672.

Original Version (#1, 6-11-2009)

7.4 Statistical analyses:
The primary analysis for TTLR will be intent to treat analysis that A) will include all randomized patients; B) preserve the original treatment assignment; and C) is based on the stratified log-rank test.

For the primary and secondary endpoints, censoring will be done as follows: For cause-specific death analysis, patients dying from other causes will be censored; for recurrence, patients dying without evidence of CNS recurrence will be censored; for site-specific recurrence, patients recurring first in another site will also be censored; finally, in all analyses, patients remaining free of the entity under study at the end of follow-up will be censored. For all time to event endpoints, a univariate test between groups will be conducted using a log rank test of Kaplan-Meier survival estimates and multivariate analyses will be conducted via the Cox proportional hazards model. The hazard ratio comparing radiosurgery to surgery will be computed for each endpoint with and without adjustment for other covariates. Confidence intervals (95%) will be computed for the hazard ratio estimates. The proportions of patients experiencing neurological and non-neurological complications will be computed for each group via univariate and multivariate logistic regression analysis. The proportion of complications resulting in prolongation of hospital stay will also be computed. The odds ratios comparing radiosurgery to surgery will be computed with and without adjustment for other covariates. Confidence intervals (95%) will be computed for the odds ratio estimates.

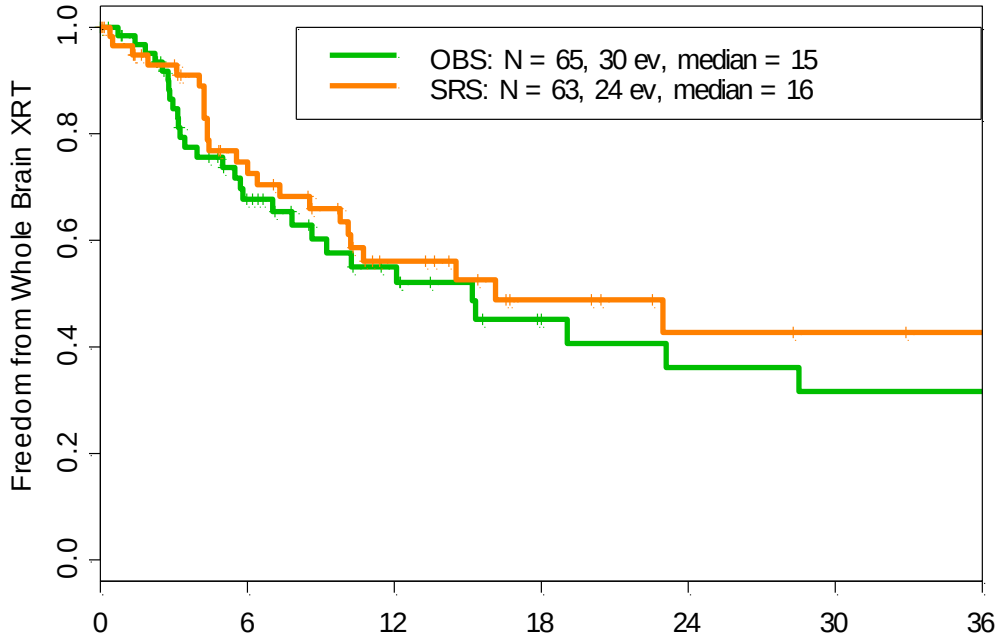
Final Version (#20, 3/22/2016)

7.4 Statistical analyses:
The primary analysis for TTLR will be intent to treat analysis that A) will include all randomized patients; B) preserve the original treatment assignment; and C) is based on the stratified log-rank test.

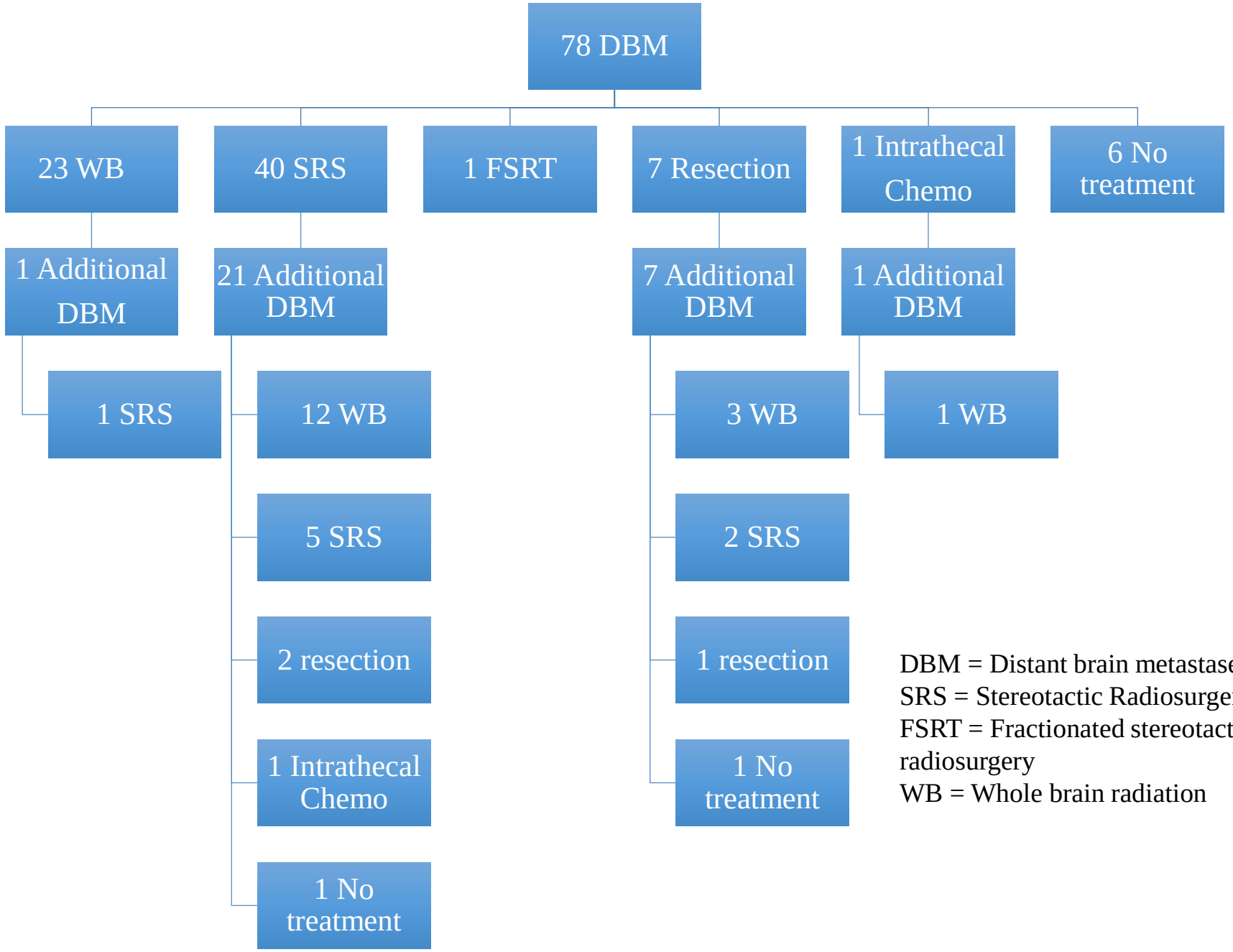
For the primary and secondary endpoints, censoring will be done as follows: For recurrence, patients dying without evidence of CNS recurrence will be censored; for site-specific recurrence, patients recurring first in another site will also be censored; finally, in all analyses, patients remaining free of the entity under study at the end of follow-up will be censored. For all time to event endpoints, a univariate test between groups will be conducted using a log rank test of Kaplan-Meier survival estimates and multivariate analyses will be conducted via the Cox proportional hazards model. The hazard ratio comparing SRS to observation will be computed for each endpoint with and without adjustment for other covariates. Confidence intervals (95%) will be computed for the hazard ratio estimates. The proportions of patients experiencing neurological complications will be computed via univariate and multivariate logistic regression analysis. The proportion of complications resulting in prolongation of hospital stay will also be computed. The odds ratios comparing SRS to observation will be computed with and without adjustment for other covariates. Confidence intervals (95%) will be computed for the odds ratio estimates. In the case of many delayed neurological complications, we will also analyze time to first neurological complication treating death without complication as a competing risk. Secondary analyses will include a competing risk analysis using local CNS recurrence, WBRT, and death without local CNS recurrence or WBRT as competing risks. We will estimate the cumulative incidence functions by treatment arm for each mode of failure. We will estimate the cumulative incidence hazard ratio comparing the two treatment arms with 95% confidence intervals with and without adjustment for potential confounding factors using the Fine-Gray proportional hazards model. We will perform similar analyses for LMD (leptomeningeal disease) treating death without LMD as a competing risk. We will also perform similar analyses using a composite of local CNS recurrence and WBRT as events and death without these events as competing risks. We will analyze time to local CNS recurrence between treatment groups but treating intervening WBRT as a time-dependent covariate. We will compare overall survival between treatment groups. We

will also perform subset analyses according to the three stratification factors (histology, size of metastases, and number of metastases), nature of the resection (en bloc vs. piecemeal), and Graded Prognostic Assessment score (Sperduto, 2012). Additional potentially confounding factors to be studied include: age at randomization, sex, race, resection cavity volume, KPS at randomization, and systemic disease status at randomization (stable vs. progressive), We will construct event charts to graphically illustrate the relative timing of these various events in each patient.

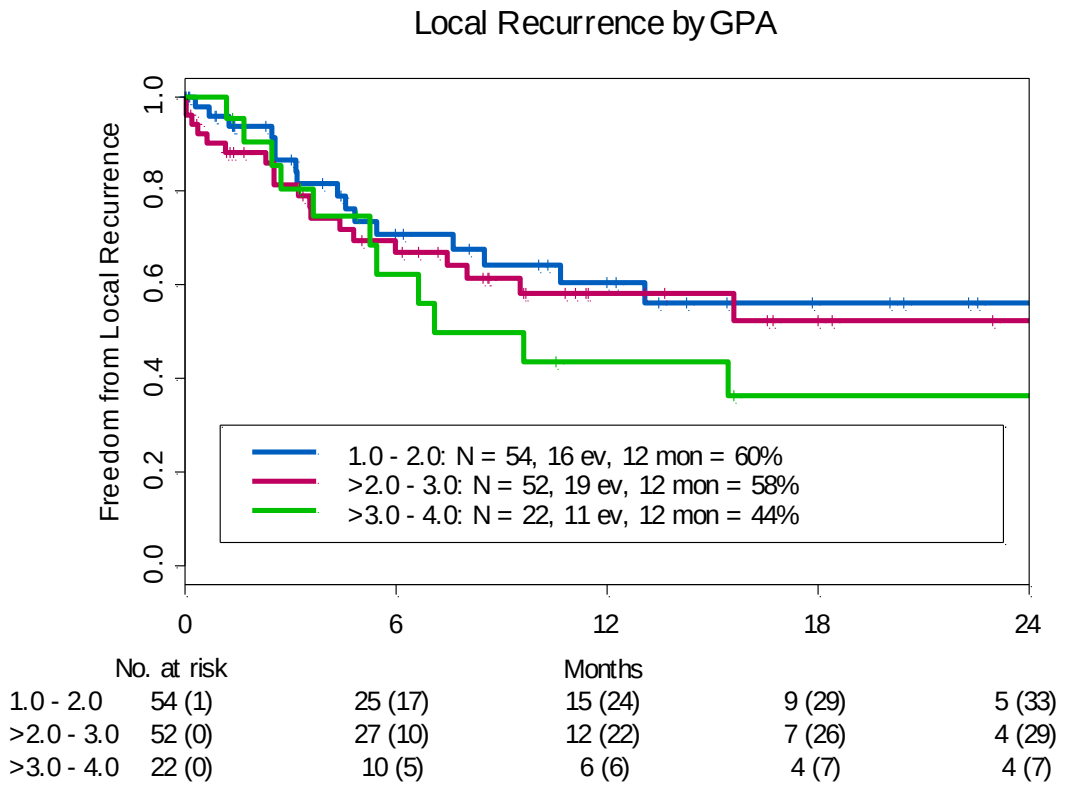
Freedom From Whole Brain XRT by Randomization Arm



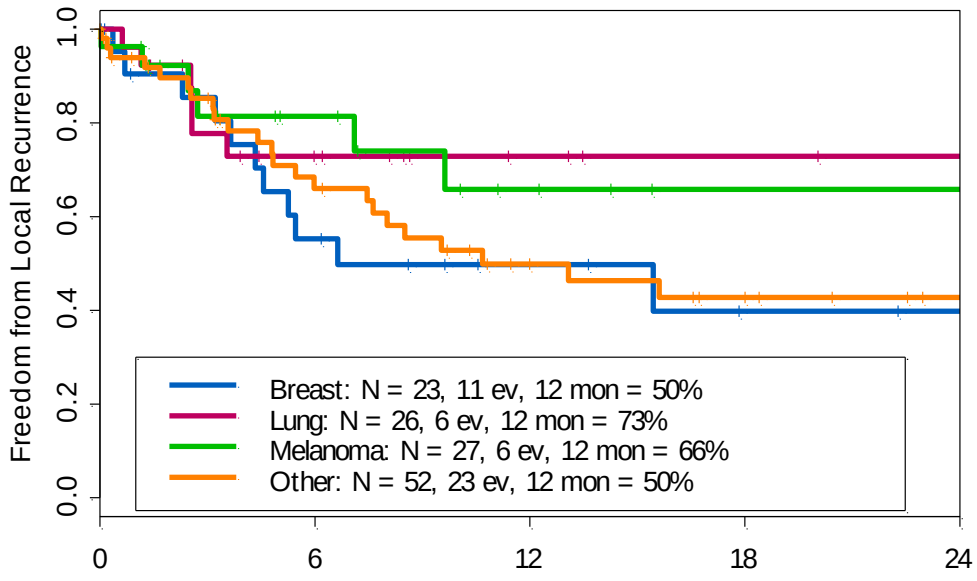
No. at risk							
OBS	65 (1)	33 (14)	19 (23)	11 (28)	8 (29)	7 (29)	7 (29)
SRS	63 (0)	35 (15)	19 (23)	11 (29)	7 (32)	6 (33)	5 (34)



DBM = Distant brain metastases
SRS = Stereotactic Radiosurgery
FSRT = Fractionated stereotactic radiosurgery
WB = Whole brain radiation

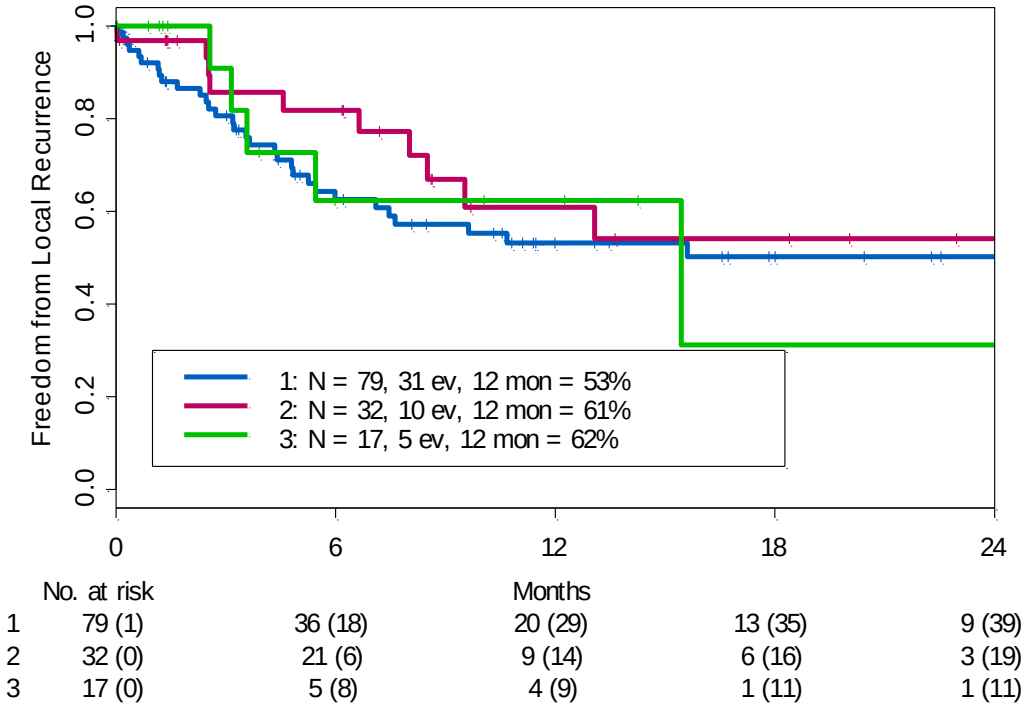

Local Recurrence by GPA
Freedom from Local Recurrence
0.0
0.2
0.4
0.6
0.8
1.0
1.0 - 2.0: N = 54, 16 ev, 12 mon = 60%
>2.0 - 3.0: N = 52, 19 ev, 12 mon = 58%
>3.0 - 4.0: N = 22, 11 ev, 12 mon = 44%
0
6
12
18
24
Months
No. at risk
1.0 - 2.0 54 (1) 25 (17) 15 (24) 9 (29) 5 (33)
>2.0 - 3.0 52 (0) 27 (10) 12 (22) 7 (26) 4 (29)
>3.0 - 4.0 22 (0) 10 (5) 6 (6) 4 (7) 4 (7)

Local Recurrence by Site of Primary



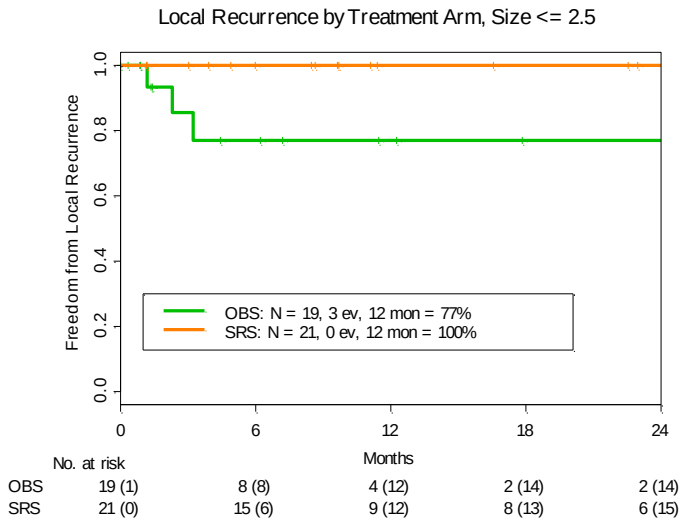
No. at risk					
Breast	23 (0)	11 (3)	6 (7)	3 (9)	2 (10)
Lung	26 (0)	12 (8)	7 (13)	5 (15)	4 (16)
Melanoma	27 (0)	12 (11)	6 (15)	3 (18)	3 (18)
Other	52 (1)	27 (10)	14 (17)	9 (20)	4 (25)

Local Recurrence by Number of Brain Metastases

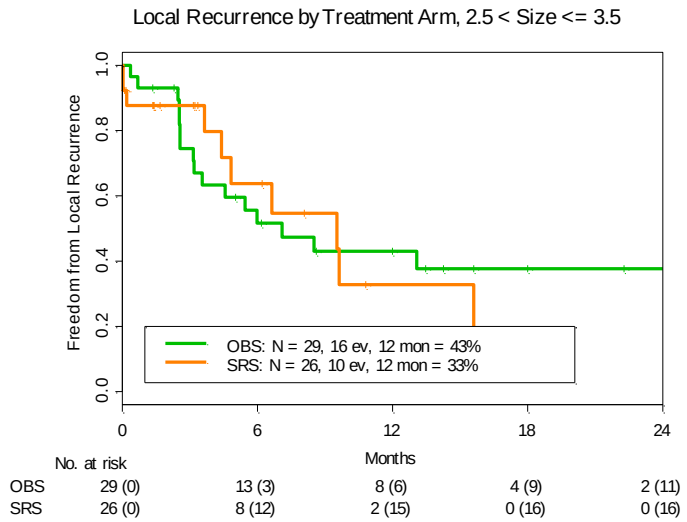


No. at risk					
1	79 (1)	36 (18)	20 (29)	13 (35)	9 (39)
2	32 (0)	21 (6)	9 (14)	6 (16)	3 (19)
3	17 (0)	5 (8)	4 (9)	1 (11)	1 (11)

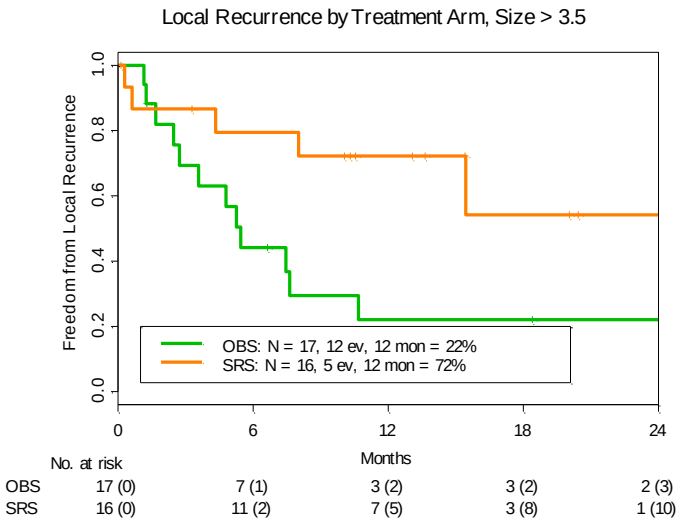
A


Local Recurrence by Treatment Arm, Size <= 2.5
Freedom from Local Recurrence
0.0
0.2
0.4
0.6
0.8
1.0
OBS: N = 19, 3 ev, 12 mon = 77%
SRS: N = 21, 0 ev, 12 mon = 100%
0
6
12
18
24
Months
No. at risk
OBS 19 (1) 8 (8) 4 (12) 2 (14) 2 (14)
SRS 21 (0) 15 (6) 9 (12) 8 (13) 6 (15)

B


Local Recurrence by Treatment Arm, 2.5 < Size <= 3.5
Freedom from Local Recurrence
0.0
0.2
0.4
0.6
0.8
1.0
OBS: N = 29, 16 ev, 12 mon = 43%
SRS: N = 26, 10 ev, 12 mon = 33%
0
6
12
18
24
Months
No. at risk
OBS 29 (0) 13 (3) 8 (6) 4 (9) 2 (11)
SRS 26 (0) 8 (12) 2 (15) 0 (16) 0 (16)

C


Local Recurrence by Treatment Arm, Size > 3.5
Freedom from Local Recurrence
0.0
0.2
0.4
0.6
0.8
1.0
OBS: N = 17, 12 ev, 12 mon = 22%
SRS: N = 16, 5 ev, 12 mon = 72%
0
6
12
18
24
Months
No. at risk
OBS 17 (0) 7 (1) 3 (2) 3 (2) 2 (3)
SRS 16 (0) 11 (2) 7 (5) 3 (8) 1 (10)

Variable	N	OBS 12-m LCR	SRS 12-m LCR	HR (95% CI)	Covariate Interaction
Melanoma	27	57%	77%	0.4 (0.1-2.5)	P=0.98
Non-melanoma	98	40%	71%	0.4 (0.2-0.9)	
Single metastasis	79	37%	71%	0.4 (0.2-0.9)	P=0.79
Multiple metastases	49	54%	73%	0.4 (0.2-1.3)	
Size <3 cm	60	59%	86%	0.2 (0.1-0.8)	P=0.086
Size ≥3 cm	68	34%	58%	0.7 (0.3-1.4)	

Variables influencing local control rate by study arm with treatment-covariate interaction.