Clinical Investigation

Interval From Imaging to Treatment Delivery in the Radiation Surgery Age: How Long Is Too Long?

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Summary

We evaluated intervals from treatment planning image acquisition, consultation, simulation, and insurance authorization to stereotactic radiation surgery (SRS) for brain metastases and the potential clinical impact these intervals had on efficacy. Patients treated with SRS based on magnetic resonance imaging completed ≥14 days prior to treatment demonstrated reduced local control. Future studies should monitor and evaluate the impact of timing from imaging acquisition to treatment delivery.

Purpose: The purpose of this study was to evaluate workflow and patient outcomes related to frameless stereotactic radiation surgery (SRS) for brain metastases.

Methods and Materials: We reviewed all treatment demographics, clinical outcomes, and workflow timing, including time from magnetic resonance imaging (MRI), computed tomography (CT) simulation, insurance authorization, and consultation to the start of SRS for brain metastases.

Results: A total of 82 patients with 151 brain metastases treated with SRS were evaluated. The median times from consultation, insurance authorization, CT simulation, and MRI for treatment planning were 15, 7, 6, and 11 days to SRS. Local freedom from progression (LFFP) was lower in metastases with MRI ≥14 days before treatment (P = .0003, log rank). The 6- and 12-month LFFP rate were 95% and 75% for metastasis with interval of <14 days from MRI to treatment compared to 56% and 34% for metastases with MRI ≥14 days before treatment. On multivariate analysis, LFFP remained significantly lower for lesions with MRI ≥14 days at SRS (P = .002, Cox proportional hazards; hazard ratio: 3.4, 95% confidence interval: 1.6-7.3).

Conclusions: Delay from MRI to SRS treatment delivery for brain metastases appears to reduce local control. Future studies should monitor the timing from imaging acquisition to treatment delivery. Our experience suggests that the time from MRI to treatment should be <14 days. © 2015 Elsevier Inc. All rights reserved.

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Supplementary material for this article can be found at www.redjournal.org.
Introduction

As treatment planning and delivery increase in complexity, the number of steps to safely and accurately treat patients has increased. Patients undergo consultation, simulation, and imaging acquisition, followed by image fusion, target delineation, treatment planning, quality assurance, and finally treatment delivery. This process requires communication and coordination between and within departments that can contribute to delays. In addition, the timeliness of insurance authorization can be highly variable, further contributing to delays.

Analysis of workflow and its impact on patient care is a topic of increasing importance but is often ignored. Studies have been conducted and provide guidance for the interval from surgery to radiation therapy in the post-operative setting (1). Delays in treatment for other aggressive cancers can also directly affect prognosis (2). However, reports to date have not assessed the impact of interval from imaging for treatment planning to the start of treatment.

Currently, there are no formal recommendations regarding the timing of high-resolution imaging used for treatment planning, such as magnetic resonance imaging (MRI) before stereotactic radiation surgery (SRS). Patients often arrive at consultation with recent imaging that potentially could be used for treatment planning, but delays following consultation may render these scans effectively obsolete by the time the treatment can be delivered. Another option is to obtain a new MRI at the time of simulation, but in the era of rising medical care costs due to increasing use of high-resolution imaging, obtaining new imaging is not trivial (3).

Computerized tomography (CT), MRI, and positron emission tomography allow for increasingly focused and precise radiation therapy, first with 3-dimensional (3D) technology, intensity modulated radiation therapy, and now with SRS. Given the reduced margins used in these treatments, high-resolution cross-sectional imaging is essential for SRS planning. Even in cases where a new MRI is acquired specifically for planning, delays in workflow could make imaging inadequate for SRS planning. In the treatment of fast-growing malignancies, intervals from imaging and treatment delivery could have significant clinical impacts, which include both a delay in systemic therapy and a potential for a marginal miss as the tumor continues to grow, but this has not been previously evaluated.

This article is a retrospective single-institution review of all patients treated with frameless SRS for brain metastases. Analysis was done measuring the timing between the MRI used for treatment planning and radiation therapy delivery. In addition, we evaluated our entire workflow to find potential sources of delay and reduced efficacy. To our knowledge, this paper represents the first attempt in peer-reviewed publication to quantify the workflow delays in treatment planning and delivery and the effect of delay from MRI with or without contrast-enhanced CT imaging on patient outcomes in the SRS setting.

Methods and Materials

Patient selection and radiation surgery technique

All brain metastases treated with frameless SRS at our institution were retrospectively reviewed, from 2005 through 2011, which included 93 total patients. Resection cavities were excluded, limiting our analysis to 82 evaluable patients with 151 lesions.

Our radiation surgery technique and patient selection methods were previously described (4). SRS was accomplished with a radiation surgery system (Cyberknife Robotic Radiosurgical System model G3, Accuray, Sunnyvale, CA). Please see Appendix E1 (available online at www.redjournal.org) for details of this method.

Statistical analysis

Demographic, lesion, and patient parameters were scored at the time of treatment, including lesion volume. All patients were advised to undergo surveillance imaging every 3 months after SRS. In follow-up, a lesion size surrogate was measured in 3 orthogonal dimensions, and the product of the 3 diameters divided by 2 was used as the surrogate for lesion volume and was compared using the same technique at the time of treatment to assess local failure. To cross-compare different hypofractionated schemes, we calculated the biologically effective dose (BED) assuming $BED = \left[ n \times d \times (1 + d/\left(\alpha/\beta\right)) \right]$, $\alpha/\beta = 10$.

Interval analysis for patients without MRI within 30 days of treatment was analyzed with considered to have MRI 30 days from treatment as to not weight outliers, but raw numbers are reported in Table 1. Planning time was measured from the time at which all planning imaging was obtained to first treatment, both MRI and CT simulation, to assess workflow analysis for treatment planning. Overall survival (OS) and local freedom from progression (LFFP) were determined from the start of SRS using Kaplan-Meier methodology. LFFP was assessed by lesion, and OS was assessed by patient. Lesion failure was scored if the lesion volume surrogate increased by 25% from the nadir volume, the volume of the lesion at maximal response of each lesion separately. Patients with questionable local recurrence versus adverse radiation effect were evaluated by MRI perfusion imaging as well as by close follow-up of sequential MRI.

Statistical analysis was performed with Stata/IC version 10.0 software (Statacorp, College Station, TX) for Macintosh (Apple, Inc, North Hollywood, CA). Parameters were assessed for significance by using univariate and multivariate Cox proportional hazards analysis and log-rank, rank-sum, and $\chi^2$ tests with a level of significance.
at P<.05. Multivariate models were evaluated with stepwise regression analysis to evaluate and select the best predictors of local control. We included either CT simulation or planning time in each model, as these variables were highly correlated.

Results

Workflow

The median times from consultation, insurance authorization, CT simulation, and MRI to treatment were 15 (interquartile range: 10-21 days), 6 (interquartile range: 4-10 days), 6 (interquartile range: 5-10 days), and 11 days (interquartile range: 6-23 days) by patient, respectively. Planning time was longer in patients with longer times from MRI to treatment. MRI was obtained on the same day as simulation in 34 patients (41%). In 5 patients, MRI was obtained after simulation, and in 43 patients, a new MRI was not acquired at or after simulation. Treatment for only 7 patients with 17 lesions was planned with outside MRIs. Of the lesions with planning based on outside imaging, only 8 lesions had any follow-up, with a maximum follow-up of 3 months. Of these lesions planned with outside MRIs, all but 2 lesions were accompanied with a delay from MRI to treatment of at least 14 days, and 5 lesions failed.
Timing for the availability of insurance authorization was limited to only 42 patients and 80 lesions and was therefore excluded from analysis of local control and survival. Time from consultation to insurance authorization varied from 0 to 42 days (median, 4 days; interquartile range: 4-10 days).

A total of 5 patients experienced a medical event between MRI and treatment that could have influenced the start of treatment (2 were related to brain metastases requiring medical intervention and stabilization, and 3 were related to delays secondary to disease outside the brain). Of the patients experiencing a medically related event, 2 patients underwent a new MRI for planning, 1 was expedited to start treatment without a new MRI, and 2 patients had significant delays from MRI to SRS of 16 and 25 days, respectively.

**Local control and overall survival**

Initial analysis revealed a divergence in local control with increasing time periods between imaging and treatment at 2- and 3-week intervals from imaging to treatment. We therefore hypothesized that LFFP would be worse in patients with interval from MRI to treatment of ≥14 days. Patients with intervals of ≥14 days between MRI and treatment also had significantly longer times from consultation, larger target volumes, lower BED, longer planning times, and greater usage of contrast at the time of CT simulation (Table 1). There was a trend toward differences in type of primary tumor among patients with longer intervals, but divergence in local control by MRI to treatment of ≥14 versus <14 days persisted across major primary sites and histology types.

Target coverage was similar between the cohorts, with 98.6% (interquartile range: 95.5-99.4%) of the prescription isodose line (IDL) in those <14 days versus 97.2% (interquartile range: 95.4%-98.6%) for lesions with ≥14 days from MRI to treatment. Although treatments of lesions were generally planned without margins, a 1- to 2-mm margin was used in 7 patients with 9 lesions, 3 of whom experienced local failure. Only 4 lesions with margins experienced an interval from MRI to treatment of ≥14 days, including 2 lesions that ultimately failed, despite a 2-mm margin. The presence of a gap between slices was also higher in patients with an interval from MRI to treatment of ≥14 days as well as a trend toward larger slice thickness (Table 1).

LFFP by lesion was higher if the MRI was obtained <14 days from the start of SRS. The 6- and 12-month LFFP probability rates were 95% and 75% in lesions with <14 days from MRI to treatment (with 50 and 29 lesions at risk) compared to only 56% and 34% in those with ≥14 days from MRI to treatment (with 13 and 5 lesions at risk). The median LFFP by lesion was 27.2 versus 10.1 months in lesions with <14-day interval from MRI to treatment versus ≥14 days from MRI to treatment (P=.0003, log-rank) (Fig. 1). Median survival time by patient revealed a trend for reduced survival in patients with MRI at ≥14 versus <14 days (5.9 vs 10.3 months, P=.05; with 26 vs 16 patients being at risk at 6 months) (Fig. 2).

Analysis was then limited to those lesions with MRI obtained <14 days or those with MRI obtained ≥14 days before treatment but with contrast usage at CT simulation to assess whether inclusion of contrast at the time of simulation mitigated the delayed treatment. CT with contrast did not appear to improve local control in the patients with a delayed treatment of ≥14 days from MRI, with a median LFFP of 5.4 months compared to 27.2 months in lesions for those with a more recent MRI (P≤0.001, log rank).

Target volume and target coverage by prescription were also associated with LFFP, whereas time from consultation to treatment, MRI slice thickness, presence of a gap between slices, year of treatment, total dose, and BED were not associated with local control (Table 2). There was a trend for lesions with longer time from CT simulation to treatment or longer planning time and better local control.
In multivariate models, despite differences in target volumes and BED between cohorts, the interval from MRI to treatment remained the dominant factor for improved local control ($P = .002$, Cox proportional hazards; hazard ratio: 3.4; 95% CI: 1.6-7.3; $\chi^2 = 0.002$) (Table 3). Inclusion of other unbalanced factors such as slice thickness, gap, and timing from CT simulation and BED in multivariate models of local control without the stepwise technique did not alter the final results, suggesting that the interval from MRI to treatment was the most important factor for local control in this cohort.

### Discussion

SRS is often used in the single- or oligometastatic setting for brain metastasis to avoid side effects associated with whole-brain radiation therapy while providing good local control for selected lesions (5-8). Use of SRS has expanded dramatically over the last 2 decades, but there are no recommendations regarding the timing of imaging used for treatment planning. Some would consider a 14-day interval from imaging to treatment as relatively long, and likely, the ideal timing from imaging to SRS is shorter than this cut off. However, in the absence of any current recommendations or reporting of accepted workflow patterns, our finding of worse local control with MRI obtained $\geq$14 days from treatment is a relevant starting point.

Our analysis suggests that clinical workflows that fail to optimize efficiency of SRS delivery could undermine treatment efficacy. MRI could be acquired before or after CT simulation, which may explain the trend for shorter times from CT simulation to treatment in lesions with local control as well as represent a desire of treating practitioners to accelerate treatment planning in patients with a less recent MRI. There is no way to quantify all metrics of imaging quality, although inclusion of contrast as CT simulation did not eliminate the risk of a delayed treatment from MRI. Together these 2 findings suggest that the time from CT simulation to treatment was essentially a treatment planning time point rather than a targeting one, the median of 6 days from simulation to treatment for treatment planning was not the driving cause of local recurrence, and contrast administration did not obviate the need for a more recent MRI. Although MRI slice thickness and presence of a 1-mm gap were not associated with reduced local control in this cohort, a dedicated SRS planning MRI appears necessary. In our workflow, obtaining a new MRI at or after the date of simulation seems reasonable to ensure that patients will have recent imaging for treatment planning and delivery. Although this would not prevent delays between MRI acquisition, treatment planning, and SRS delivery, these appeared much less likely sources of clinically significant delay than the time between MRI and SRS, which was the most important factor for local recurrence in this cohort.

Demonstrating an impact on patient outcomes may help radiation oncology departments and insurance companies consider the implications of delayed insurance authorizations on patient care and the necessity for up-to-date imaging. At our institution, we obtain CT simulation only after insurance authorization has been acquired; under this workflow, at least one quarter of patients would experience a delay of 10 days from consultation to insurance authorization alone. This makes it challenging to guarantee that treatment would commence swiftly enough to forego ordering a new MRI at the time of patient consultation, when most patient care decisions are made. Insurance authorization times varied widely suggesting that treating physicians were unlikely to be able to predict when authorization would be approved or when simulation and treatment planning could commence.

The potential sources for reduced efficacy in delayed treatments for any workflow are multiple. The most obvious may relate to the risk of a marginal miss as tumors continue to grow during the time it takes to coordinate the start of treatment. An MRI obtained prior to this process

### Table 2

<table>
<thead>
<tr>
<th>Treatment interval</th>
<th>Cox P value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI to treatment ($&lt; \text{ or } \geq 14$ days)</td>
<td>.001</td>
<td>3.4</td>
<td>1.7-6.8</td>
</tr>
<tr>
<td>CT simulation to treatment (continuous)</td>
<td>.03</td>
<td>1.03</td>
<td>1.03-1.1</td>
</tr>
<tr>
<td>Planning time (continuous)</td>
<td>.08</td>
<td>0.93</td>
<td>0.86-1.0</td>
</tr>
<tr>
<td>Consult to treatment ($\leq \text{ or } &gt; 14$ days)</td>
<td>.2</td>
<td>0.94</td>
<td>0.87-1.0</td>
</tr>
<tr>
<td>Lesion prescription coverage (continuous)</td>
<td>.4</td>
<td>0.75</td>
<td>0.39-1.5</td>
</tr>
<tr>
<td>Fractions (continuous)</td>
<td>.9</td>
<td>1.0</td>
<td>0.96-1.04</td>
</tr>
<tr>
<td>Target volume (quartile)</td>
<td>.01</td>
<td>1.4</td>
<td>1.1-1.9</td>
</tr>
<tr>
<td>MRI slice thickness (continuous)</td>
<td>.6</td>
<td>0.89</td>
<td>0.55-1.4</td>
</tr>
<tr>
<td>Gap between slices (yes or no)</td>
<td>.2</td>
<td>1.8</td>
<td>0.69-4.8</td>
</tr>
<tr>
<td>Year of treatment (continuous)</td>
<td>.5</td>
<td>0.82</td>
<td>0.43-1.6</td>
</tr>
</tbody>
</table>

**Abbreviations:** BED = biological equivalent dose; CI = confidence interval; CT = computed tomography; MRI = magnetic resonance imaging.

### Table 3

<table>
<thead>
<tr>
<th>Treatment interval</th>
<th>Cox P value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI to treatment ($&lt; \text{ or } \geq 14$ days)</td>
<td>.002</td>
<td>3.4</td>
<td>1.6-7.3</td>
</tr>
<tr>
<td>Planning time (continuous)</td>
<td>.1</td>
<td>0.94</td>
<td>0.86-1.01</td>
</tr>
<tr>
<td>Lesion prescription coverage (continuous)</td>
<td>.06</td>
<td>0.97</td>
<td>0.93-1.0</td>
</tr>
<tr>
<td>Target volume (quartile)</td>
<td>.1</td>
<td>1.3</td>
<td>0.94-1.8</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI = confidence interval; MRI = magnetic resonance imaging.
may not be of optimal quality and not necessarily reflective of the tumor burden at the start of treatment. The volume doubling times (VDT) are not uniform. Given the clinical efficacy in the treatment of brain metastases, they rarely go untreated, so estimates of the rate of growth of brain metastases are not available. However, in 209 primary lung cancers initially diagnosed on CT, the average VDT was 158 days for all patients but was widely variable from 40 to 1493 days (9). These findings were similar to those of another single institution’s review of 111 primary lung cancers, where median VDT was 98 days, with an inter-quartile range of 108 days (10). Given the nonmetastatic nature of these patients, we might assume VDT may be shorter in metastatic lesions, although Chojnak et al (11) evaluated 408 presumed metastatic pulmonary nodules in 21 patients who received no cancer treatment and noted a tumor doubling time of 118–21 patients who received no cancer treatment and noted a tumor doubling time of 118 ± 134 days. The VDT was again highly variable, even across patients with the same tumor type. The median VDT for all breast, colon, melanoma, head and neck, and thymoma metastases were >100 days but were much shorter for sarcoma metastases. Recent data suggest it may be dramatically shorter in various sarcoma subtypes, with doubling times ranging from 13 to 29 days, and these lesions may require an even shorter interval from MRI to the start of SRS (12).

Extrapolating across these clinically reported estimates of VDT, assuming a 1-cm mass and 14-day interval from MRI to start of treatment, the change in radius for VDT of 200, 150, 100, 50, 25, and 14 days would equate to a diameter of 1.02, 1.03, 1.04, 1.09, 1.16, and 1.26 cm. Considering larger lesions, the geometric miss would increase for the same doubling times. For instance a 2-cm lesion with the same VDT as above would equate to a 2.04-, 2.06-, 2.08-, 2.18-, 2.32-, and 2.52-cm lesion at 14-day intervals, assuming uniform growth. This appears to be a very likely source of reduced efficacy in some patients, especially for those with short to moderate doubling times and larger tumors. The delayed lesions in this paper were larger in volume, although even controlling for tumor size these lesions were still more likely to fail based on delay from MRI to treatment than by lesion size alone. There may not be an ideal cutoff for determining whether an MRI is outdated at treatment as VDTs vary so widely across tumors, but it is clear that delay from imaging to treatment should be minimized.

Other potential causes of reduced local control could result from delayed systemic therapy. However, we would then expect time from consult to treatment to be associated with reduced local control as well. The exceptionally low rates of local control observed in the patients with ≥14 days from MRI to SRS are not consistent with accepted rates of local control throughout literature, while the local control rates in lesions with MRI to SRS of <14 days appear very reasonable (6). This may suggest that reduced local control is more likely due to inadequate treatment coverage of the prescription isodose compounded by furthering marginal coverage of a continually growing metastasis rather than delays to systemic therapy. Simply, it is possible the dose does not matter if an increasing proportion of the target is missed. Alternatively, additional margin could be considered to ensure coverage, although additional margin would potentially increase rates of radiation necrosis based on increased dose to normal brain, particularly in lesions with longer VDT (13). Also, the potential for a marginal miss in spite of planning margin could still exist in the event of asymmetric growth.

Survival, as expected, was less divergent between patients with and without delay from MRI to SRS treatment delivery, as many patients for whom initial therapy failed can be salvaged, and undoubtedly competing factors for survival cannot be ignored. Although there was no divergence, based on MRI timing until nearly 6 months post-SRS when the potential for recurrence and salvage failures would likely be noted in the setting of partial treatment. Treatment profiles in the retreatment setting have a greater risk of complications, so an ineffective treatment may lead to high-risk salvage therapies (14). Overall, the trend toward reduced survival in patients with ≥14 days between MRI and SRS is concerning, as known prognostic factors, such as recursive partitioning analysis classification, appeared similar between groups.

Limitations of this study relate to the retrospective nature with potentially variable image quality for treatment planning, moderate numbers of patients and lesions, as well as limited data on insurance authorization timing and commonly accepted but nonstandardized, fractionation. Based on our findings, our group has undertaken a prospective study to ensure that >75% of patients treated with SRS for brain metastases will have an MRI within 2 weeks of first treatment. We have instituted workflow where an MRI is ordered at consultation and is to be performed on the date of CT simulation, where the median time from simulation to treatment was 6 days. We hope to demonstrate an improvement in patient outcomes with this workflow intervention.

Conclusions

SRS requires recent high-quality imaging, and longer times from MRI to treatment can significantly decrease the efficacy of therapy. CT imaging with contrast may not eliminate the risk with longer times from MRI for treatment planning. The workflow with SRS, where MRI is not acquired on the day of treatment, should be designed and monitored to minimize intervals from imaging acquisition to treatment delivery.

References


