Brain metastases are a common complication of some of the most prevalent cancer types including those of the lung and breast. The management of metastatic disease to the brain has included surgery, WBRT, and chemotherapy, as well as stereotactic radiosurgery. Stereotactic radiosurgery, by virtue of its noninvasive nature and high lesion control rates, has emerged as a key method for treatment of brain metastases.²,²⁷ Radiosurgery has been demonstrated to result in superior local control compared with WBRT alone. Furthermore, in patients with a single brain metastasis, the use of radiosurgery in conjunction with WBRT has shown survival benefit. Patients with oligometastases also may have benefit to quality of life from the addition of radiosurgery to WBRT. Frame-based methods of radiosurgery using either LINAC or gamma unit devices are well established.

Frameless image guidance as applied to radiosurgery describes a method whereby high-resolution imaging is obtained at the time of treatment for patient positioning purposes and implies that patient immobilization is not obtained with rigid skeletal fixation, but rather with the noninvasive use of a mask. A number of solutions for...
IGRS have been devised and are currently available for clinical use. These systems have used stereoscopic x-ray imaging as well as on-board CT imaging.

Frameless image-guided methods in the setting of single-fraction radiosurgery have as their primary advantage the potential for improved patient comfort. As there is no sedation or anesthesia is used, no vital monitoring is required. The use of noninvasive patient immobilization and image-guided fiducialization also allows temporal decoupling of the various phases of treatment set-up, allowing for imaging, fiducialization, treatment planning, quality assurance, and dose delivery to be performed in separate sessions, if needed. This can improve convenience for both the patient and the treating team.

Frame-based radiosurgery methods have a long history, and the reliability of these methods is not in dispute. In contrast, since image-guided methods are relatively new, few reports are available detailing clinical results for common applications of this technology. Significant controversy exists as to the relative merits of image-guided techniques in comparison with frame-based methods.

The geometrical accuracy of frameless image-guided methods in phantom testing has been well described by a number of groups using different IGRS implementations.\(^3,10,22,30\) Reports have been presented regarding the accuracy of Novalis frameless IGRS with ExacTrac (BrainLAB) in particular.\(^18,38\) Ultimately, however, the usability of frameless methods in comparison with traditional frame-based methods must be determined on the basis of clinical outcomes.

The relative accuracy of stereotactic methods depends on large part on the size of the target. Small target volumes are less forgiving with respect to geometrical error. Small departures from ideal localization may result in significant underdosing of the targeted lesion that may result in treatment failure. Such reduced accuracy in brain metastasis radiosurgery may result in an anomalous increase in failures for very small–volume lesions.

We report our initial results using frameless IGRS for the control of brain metastases and in particular examine the role of size in overall lesion control using these techniques.

### Methods

This study was reviewed and approved by the Kaiser Permanente regional research committee.

#### Patient Population

Patients were referred to our regional radiosurgery service from 12 affiliated medical centers. Patients were offered treatment for metastatic disease to the brain with 4 or fewer metastases and a Karnofsky Performance Scale score of 70 or greater at time of initial presentation to our section clinic. Over a 15-month period, 54 patients harboring 108 lesions were treated. There were 4 patients who underwent a total of 6 repeated radiosurgery sessions for treatment of new lesions. The median age at time of treatment was 58.9 years. There were 32 female and 22 male patients in the study population. The distribution of primary tumor types is presented in Table 1.

The median time from cancer diagnosis to development of brain metastasis was 12 months (range 0–144 months). The median time from diagnosis of brain metastasis to initial radiosurgery was 108 days (range 10–869 days). The median tumor volume was 0.98 cm\(^3\) (range 0.03–19.07 cm\(^3\)). The median prescription dose was 18 Gy to the 80% isodose line (range 14–20 Gy). Patients were followed-up with postradiosurgery MR imaging every 2–3 months.

The RTOG RPA classification is useful in describing the overall condition of patients undergoing treatment. In this series, 10 patients were classified as RPA Class 1, 42 patients Class 2, and 2 patients Class 3.

In this series, most patients underwent WBRT at some point during their course of treatment. Thirty-two patients underwent WBRT more than 2 months prior to SRS, and were treated with SRS for either lesion progression or new lesions. Eleven patients received WBRT for boost purposes during the first 2 months after SRS. Three patients had WBRT more than 2 months following SRS for treatment of additional brain lesions. Eight patients did not have WBRT during the study period.

#### Radiosurgery Technique

Prior to radiosurgery, patients underwent high-resolution MR imaging using 1-mm-thick contrast-enhanced 3D-spoiled gradient recalled sequences (GE Excite 1.5 T, GE Medical Systems).

Patient immobilization was accomplished by custom-fitting patients with a BrainLAB bivalve-style thermoplastic mask incorporating a bite bar. A high-resolution CT scan using 1.25-mm slices was then used for fiducialization (GE LightSpeed RT 16, GE Medical Systems).

Imaging data were then transferred via a local area network to a planning workstation running BrainScan v.5 software (BrainLAB). Structures at risk as well as target lesions were then contoured. Target lesions were contoured with no additional margin.

Treatment plans were created using forward-planning methods incorporating either dynamic multileaf collimated noncoplanar arcs or circular collimated noncoplanar arcs. The median prescription dose was 18 Gy to the 80% isodose line (range 14–20 Gy to the 80% isodose line). A single isocenter per lesion was used for all treatments.

### Table 1: Distribution of tumor types in 54 patients

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. of Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>breast</td>
<td>17</td>
</tr>
<tr>
<td>choriocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td>colon</td>
<td>1</td>
</tr>
<tr>
<td>esophageal</td>
<td>2</td>
</tr>
<tr>
<td>lung, non–small cell</td>
<td>19</td>
</tr>
<tr>
<td>lung, small cell</td>
<td>3</td>
</tr>
<tr>
<td>melanoma</td>
<td>6</td>
</tr>
<tr>
<td>renal</td>
<td>2</td>
</tr>
<tr>
<td>gastric</td>
<td>2</td>
</tr>
<tr>
<td>unknown primary</td>
<td>1</td>
</tr>
</tbody>
</table>

* Pts = patients.
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The median conformity index (RTOG method: prescription isodose volume/target volume) was 1.6. A typical treatment plan utilizing dynamic noncoplanar arcs and a follow-up MR image are presented in Fig. 1.

Treatment data were transferred by local area network to the LINAC control station and the ExacTrac patient positioning system. The patient was then placed in a supine position on the treatment table and the head was placed into the mask immobilizer. An optical tracking array was then applied to the head mounting system (Fig. 2).

For each lesion, the optical tracking system was used for initial patient positioning. Stereoscopic x-ray imaging was then performed and the results fused with digitally reconstructed radiographs based on CT imaging via the ExacTrac system. A positioning offset was then calculated. Patient positioning corrections were made for each of 6 degrees of freedom using a robotically actuated couch in concert with the real-time optical tracking system. Treatment was initiated when linear offsets were no more than 0.5 mm and angular offsets were 1° or less. Treatment time was typically under 20 minutes per lesion.

Following completion of dose delivery, patients were released from the mask and discharged home with anticonvulsant and corticosteroid medications where appropriate.

Patients were followed up with contrast-enhanced MR imaging at 6–8 weeks following SRS treatment and then every 2–3 months until the end period of data collection or patient demise. Patients demonstrating evidence of lesion progression underwent dedicated brain FDG-PET to differentiate between necrosis and tumor progression.

Data Analysis

Survival and lesion control were calculated using Kaplan-Meier actuarial curves. Univariate analysis was conducted using the Fisher exact test and the Mann-Whitney U-test.

The measured end points were freedom from targeted lesion progression, freedom from new metastases and overall survival. Lesion progression was determined if there was evidence of tumor enlargement following treatment regardless of whether surgery was undertaken. New metastases were dated from the time of the first imaging study demonstrating their presence. A separate end point of complete response was determined by surveillance imaging demonstrating complete resolution of contrast enhancement within a previously treated volume.

Survival functions were calculated using Kaplan-Meier survival curves. Univariate analyses were calculated using the Fisher exact test for contingency tables and the Mann-Whitney U-test for continuous variables. Survival comparisons were calculated using the log-rank method.

Results

The median duration of follow-up at the time of data acquisition was 9 months (range 0–20 months).

Overall Survival

At the time of data analysis, 20 of the 54 patients in our study group were still alive, 33 had died during the reporting period, and 1 had been lost to follow-up (with
survival data unavailable). The actuarial median survival was reached at 8.6 months (Fig. 3). A univariate analysis of survival demonstrated no significant effect for sex, time from diagnosis, primary disease site, RPA (Class 1 vs Class 2 or 3), number of lesions (1 vs > 1), or use of WBRT. A multivariate analysis was conducted using the same criteria and demonstrated a significant effect only for RPA (p = 0.04).

Lesion Control

There were 108 individual brain metastases treated during this study. Nine patients, who had a total of 18 lesions, died or were lost to follow-up before follow-up imaging studies could be performed, leaving a population of 90 lesions in 45 patients for analysis. The median lesion volume was 0.98 cm³ (range 0.03–19.0 cm³). Progression was observed in a total of 9 lesions in 8 patients during follow-up.

Lesions were divided into 2 groups on the basis of volume: ≥ 1 cm³ and < 1 cm³. These groups were found to be similar by univariate analysis in regard to patient age, primary disease site, and RPA class. Lesions of < 1 cm³ were less likely to be solitary in nature (Table 2). Three of 46 lesions demonstrated progression in the group of < 1 cm³ volume and 6 of 44 lesions demonstrated progression in the group of lesions of ≥ 1 cm³ in volume. Of the 9 lesions that showed progression, 5 were associated with breast cancer and 1 each with lung, melanoma, gastric, and renal cancers. Local control survival curves are presented in Figs. 4 and 5 for all of the lesions (pooled data) as well as for the lesions stratified by size (< 1 cm³ vs ≥ 1 cm³). The 6-month actuarial control rate for all lesions was 88 ± 4% (± SE). While there was a trend toward better control in lesions < 1 cm³ in volume, it did not reach statistical significance in this series (p = 0.16, log-rank test). Univariate analysis and multivariate analysis of local control failed to show significant effects for age, RPA, lesion volume, number of coexistent lesions, or sex.

A separate end point of complete response (complete loss of contrast enhancement) was evaluated (Table 3). This was seen in 9 lesions in 7 patients. Complete responses were more likely in lesions of < 1 cm³ in volume (p = 0.01, Mann-Whitney U-test). Radiation necrosis was noted involving 6 lesions in 5 patients with late progression of contrast enhancement but with negative FDG-PET scans. These 5 patients included 3 with lung cancer, 1 with breast cancer, and 1 with melanoma. The median time to formation of necrosis was 28 weeks (range 3–9.9 months). In none of these cases was the radiation necrosis symptomatic and none of the patients underwent surgery or required steroid therapy. At last scheduled follow-up, 2 of the 5 patients had died (at 11.3 and 21.3 months following treatment). The 3 other patients were alive, with an average of 15.6 months of follow-up.

**Freedom From Brain Progression**

Eleven patients (20%) developed new metastases following radiosurgery treatment. The median time from treatment to development of new metastases was 6 months.

**Complications**

Complications were unusual in this series. There

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**TABLE 2: Univariate analysis of patient demographic and clinical characteristics versus lesion volume**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Lesions</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1 cm³ Vol</td>
<td>≥1 cm³ Vol</td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>M</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>age in yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>&lt;65</td>
<td>7</td>
<td>10</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>lung</td>
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<td>9</td>
</tr>
<tr>
<td>breast</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>other</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>RPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>coexistence of lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 lesion</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>&gt;1 lesion</td>
<td>40</td>
<td>27</td>
</tr>
</tbody>
</table>

*All values calculated using Fisher exact test.

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**TABLE 3: Imaging response stratified by lesion size***

<table>
<thead>
<tr>
<th>Response</th>
<th>&lt;1 cm³</th>
<th>≥1 cm³</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>complete</td>
<td>9</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>not complete</td>
<td>37</td>
<td>42</td>
<td>79</td>
</tr>
<tr>
<td>total</td>
<td>46</td>
<td>44</td>
<td>90</td>
</tr>
</tbody>
</table>

*Values represent numbers of lesions. Results of univariate analysis: Fisher exact test, p=0.02; Mann-Whitney U-test, p=0.01.
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were no occurrences of postprocedure seizures or new progressive neurological deficits in the absence of tumor progression. There were no apparent nontarget dose deliveries.

**Discussion**

**Role of Radiosurgery in Management of Brain Metastases**

Brain metastases are a common complication of some of the most common forms of cancer, with an overall incidence estimated to be 8–11 per 100,000.26,37 Radiosurgery has emerged as a key method of providing definitive local control for brain metastases in addition to surgery and WBRT.13 Radiosurgery with WBRT has been consistently shown to improve overall local control in comparison with WBRT alone.2,20 In addition, in comparison to WBRT alone, the combination of WBRT and SRS appears to improve survival in patients with a single brain metastasis and improve functional independence in patients with 3 or fewer metastases.2 Surgery continues to play an essential role in the management of lesions complicated by mass effect or after failure of less-invasive treatment methods.1

Routine use of WBRT in the setting of brain metastases has become controversial.4,8,9 A number of centers have advocated routine use of WBRT, while others typically will defer or withhold WBRT until there is either failure of local control or development of new metastases. While WBRT has been shown to reduce the likelihood of formation of new brain metastases, addition of WBRT to SRS has not been shown to improve overall survival.4,33 Prevention of new metastases with WBRT, however, may result in initial improved preservation of cognitive function. This, however, may be counterbalanced by the increasing incidence of radiation leukoencephalopathy in longer term survivors, particularly those surviving beyond 2 years following WBRT.3 Survival to 24 months is approximately 15–20% in patients with 3 or fewer brain metastases on presentation.2,27 While we have in the past relied on WBRT as an important component of the initial treatment of brain metastases, it is likely that this modality will be used in a more limited fashion as overall survival from metastatic cancer improves. Of interest, new methods of WBRT delivery with sparing of temporal lobe structures may mitigate to some degree late-term cognitive decline.14 Lastly, the role of radiosurgery in the adjuvant therapy of surgically treated brain metastases has been a subject of recent interest and may further expand the role of radiosurgery in the management of cerebral metastases.12,16,23,29,34

**Radiosurgical Instrumentation**

Gamma-unit devices have traditionally had significant advantages over LINAC devices in regard to simplicity of quality control and work flow speed. Linear accelerator devices employing cone-based collimation required more complex treatment planning and work flow. The introduction of multileaf collimation has allowed for development of more conformal and homogeneous treatment plans using single isocenter methods,7,17,32 thereby simplifying the planning and delivery process resulting in more rapid workflow. There appears to be no difference in either overall survival or lesional control of brain metastases using either LINAC or gamma-unit technology.2,36

The use of frame-based skeletal immobilization for stereotactic procedures has a long history dating back to the 1950s with the introduction of stereotactic systems designed by Leksell, Talaraich, Reichert and Mundinger, Todd and Wells, and others.11 Studies have demonstrated that the application accuracy of these devices is on the order of 1 mm.21 In addition to potential errors due to frame application, other aspects of stereotactic treatment can introduce additional errors. These would include errors associated with imaging resolution and distortion as well as fiducialization, image fusion, device isocentricity, and radiation output. Using frame-based methods in the setting of the Novalis LINAC, we have previously demonstrated high accuracy and precision with an overall system error of 0.6 mm.28 While simple and expedient, the use of the stereotactic frame does have some disadvantages including the proce-
dural discomfort for most patients, with awake placement being typically performed with local anesthetic only. Alternatively, frame placement can be performed with sedation, although at our institution this entails mandated close patient monitoring, with consequent labor demands on clinic staff. The use of image-guided techniques can potentially improve the patient experience while at the same time further improve workflow and other logistical issues by making it unnecessary to accomplish all phases of the procedure—including frame placement, imaging, and treatment—at the same location and time. Noninvasive patient immobilization had been accomplished in the past by means of stereotactic devices, such as the Spiegel-Wycis device, which used a plaster cast applied to the head.\(^3\)\(^5\) In the case of the Spiegel-Wycis device and similar devices of the era, intraoperative image guidance is achieved by using ventriculography. The modern implementation of image-guided radiosurgery procedures is therefore analogous to this earlier technique. Rather than relying on ventriculographic methods, however, the ExacTrac and similar systems use image fusion of digitally reconstructed preoperative radiographs with intraoperative skull radiographs, allowing for precise stereotactic positioning.

A number of reports regarding the accuracy of image-guided methods have demonstrated that submillimeter accuracy can be accomplished in bench testing for a variety of IGRS implementations, including the device used in this report.\(^1\)\(^0\)\(^,\)\(^2\)\(^4\)\(^,\)\(^3\)\(^8\)

### Treatment of Brain Metastases With IGRS

While bench testing suggests that image-guided methods are equivalent in accuracy to frame-based methods, clinical data are needed to confirm that outcomes are similar. From the clinical standpoint, the greatest concern is spatial accuracy of dose delivery. This is particularly critical for small lesion targets where geometrical imprecision may have greater effects on the resultant dose delivered to the target volume. One may hypothesize that an anomalous increase in failures involving smaller lesions may result if the technique for patient positioning is inadequate.

In this series, there appeared to be no increase in the risk of failure for patients with lesions of < 1 cm\(^3\) volume.

We are aware of 3 reports in the literature utilizing IGRS techniques for brain metastasis treatments (Table 4).\(^1\)\(^9\)\(^,\)\(^2\)\(^5\)\(^,\)\(^3\)\(^1\) These reports demonstrate that lesion control rates are similar to those obtained with frame-based methods. We are, however, unaware of any other reports specifically addressing lesion control as a function of lesion size with the frameless methods used in the present study.

### Conclusions

We present our early data in regard to control of brain metastases using IGRS methods. The overall rate of freedom from local lesion progression was 88% at 6 months. These data are comparable to those reported by others employing conventional frame-based techniques and alternative IGRS methods. Lesions < 1 cm\(^3\) in volume did not have higher failure rates in comparison to larger lesions, demonstrating that frameless image-guided radiosurgery can be used for reliable and precise targeting of small lesions. It would appear that IGRS using Novalis with ExacTrac is adequate for treatment of the gamut of indicated brain metastases.

### Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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