Medical Advances Using SRS Technology Lead to New Treatment Guidelines for Brain Metastases

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Abstract

Among the most common sites for cancers to metastasize is the brain. According to the American Cancer Society, 20-40% of all cancer patients develop metastatic tumors in the brain. This is the single most common type of intracranial tumor. In the US alone, around 150,000 people are diagnosed with brain metastases each year. The incidence continues to increase as advances are made in the treatment of systemic cancer. The most common primary sources of brain metastases are lung (17%), renal cell (10.5%), and breast (5.2%) cancer and melanoma (8%). Brain cancer metastases (mets) represent a significant burden on the U.S. healthcare system, comprising 25 percent of the total number of newly diagnosed cancer cases per year (1.4 million), and with an incidence almost five times greater than that of primary brain tumors. The impact of brain metastases on an individual is no less significant.

Advanced treatment modalities utilizing stereotactic radiosurgery (SRS) technology such as Leksell Gamma Knife® Perfexion™ have recently resulted in the publication of new treatment guidelines for this increasingly common and difficult to treat condition. This paper reviews both the clinical challenge of brain metastasis treatment and presents a promising outlook for improved metastasis management using SRS modalities, particularly Leksell Gamma Knife® and Leksell Gamma Knife Perfexion.
Introduction
Not only can there be severe neurologic sequelae and death as a direct result of brain metastases, but the treatments themselves also can be associated with significant morbidity. Recent medical advances, however, have changed overall management of mets. Whereas in the past, palliation of symptoms was the primary goal, clinicians increasingly consider metastatic disease a chronic condition and manage these cases accordingly, often with curative intent. In concert, median survival (defined as the time over which half the treated population is alive) has in some cases extended to years, and quality of life has likewise improved.

Medical advances have emerged on a number of fronts. The greatest leaps have come from the surgical, stereotactic and radio-surgical arenas. The availability of technologies that have allowed focused radiation beams, i.e. fractionated stereotactic radiosurgery performed with a linear accelerator or single fraction stereotactic radiosurgery using Leksell Gamma Knife Perfexion, has lead to significant therapeutic progress and completely changed the medical landscape.

Managing brain mets with SRS technology using Leksell Gamma Knife® Perfexion™
Leksell Gamma Knife Perfexion dramatically streamlines workflow and expands the treatable volume through an automated, multi-source collimator. System benefits include faster set-up and treatment delivery to one or more tumors in a single session, and the potential to treat lesions in the paranasal sinuses, orbits and upper cervical spine—even paraspinal metastases and laryngeal tumors. Perfexion allows treatment of a wider range of targets faster and more efficiently than ever before.

The radiosurgery system’s unique collimator is a permanent device divided into movable sectors, ensuring superior conformity, accuracy and dosimetry while reducing residual dose to unintended areas. Integrated and intuitive treatment planning software facilitates creation of even the most complex plans (e.g., a donut-shaped dose distribution) by configuring composite shots that avoid overexposure to critical structures. Perfexion is fine-tuned to the task, resulting in fast, efficient treatments.

This unique advance in the treatment of brain metastases has resulted in significant time savings, workflow improvement and enhanced patient comfort as shown in Figure 2.

Figure 1. Multiple mets case requiring a multi-target dose conformity (22 mets - 10,368 beams)
Four Brain Metastases Treated in Less Than Two Hours
All Steps Included

1. Patient in.
2. Frame attachment for maximum stereotactic accuracy. 10 min.
3. Imaging, MR. 20 min.
4. Treatment planning with Leksell GammaPlan® PFX. 20 min.
5. Treatment. Leksell Gamma Knife® PERFEXION™. One session. 60 min.
6. Treatment completed. Patient returns home.

Leksell Gamma Knife® PERFEXION™
Treat 4 brain metastases in less than 2 hours!

Four brain metastases eccentrically located (Frontal anterior, far lateral and posterior fossa)*

*Courtesy of Prof. J. Régis La Timone Univ. Hospital, Marseille, France 2007

Gamma Knife surgery – preferred for a reason

Figure 2. Improving workflow with Leksell Gamma Knife® Perfexion™
Figure 3. Patients with multiple lesions can now be followed with repeated Gamma Knife surgery in a whole new way. Shown is a brain mets patient pre Gamma Knife treatment, and then six months post op.
New guidelines for brain mets treatment now published

Many questions and significant controversy have surrounded the use of stereotactic radiosurgery for treatment of brain metastases. In medicine, such questions are generally addressed in the form of clinical trials examining the utility of the treatment. No such trials are perfect, and even well constructed studies leave questions unanswered. Trials that include patients treated with SRS technology are no exception. In the case of brain metastases, dozens of SRS technology studies have been conducted and published.

A great deal of interest has been generated regarding the relative clinical efficacy of SRS approaches, prompting investigations that explore whether SRS is superior to surgical resection or whether surgical resection alone or with SRS is the best treatment. Head to head comparisons of SRS using systems such as Gamma Knife have spurred a confusing mosaic of medical recommendations, often lacking consistency and rarely based on consensus.

In response to this situation, a multidisciplinary committee of medical experts was recently assembled with the goal to produce a set of clinical practice guidelines for management of metastatic brain tumors. The results of their efforts recently have been published in the Journal of Neurooncology. This landmark publication not only codifies the approach to management of brain metastases, but it also establishes a foundation for development of follow-up guidelines as the field advances. A summary of this comprehensive and detailed report is as follows:

Experts

The panel consisted of 17 physicians (neurosurgeons, radiation oncologists, medical oncologists and neurologists) from all over the United States, many of whom are Elekta customers and all of whom are considered leading experts in the field. The final report was endorsed by the major stakeholder professional societies, including AANS, CNS, SNO and ASTRO.

Methods

The process by which the panel developed the guidelines was painstaking, and involved exhaustive literature reviews, systematic ranking of studies and strict development of an evidence basis for its findings and recommendations. The highest specific recommendation was assigned a “Level 1”, which generally meant that the determinations were based on evidence from well-conducted randomized clinical trials that were relatively free of flaws. The lowest recommendation was assigned a “Level 4” which meant that they were largely based on expert opinion and were thus considered as clinical options with uncertain utility.

Because of the many individual treatment options and option combinations, the panel examined many therapy permutations. These included combinations of surgical resection (S), whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), stereotactic radiotherapy (SRT) and chemotherapy (CT). Also considered were factors such as the patients’ Karnofsky performance status (KPS), number of metastatic lesions, lesion size, surgical resectability and a host of other medical conditions. Add to this the fact that the outcomes themselves are multi-dimensional, including survival, local control, regional control, quality of life and neuro-cognitive status. The complexity that the panel faced was daunting, and the resultant recommendation should be welcomed by our customers as they help greatly simplify decision-making processes.
**Summary**

Virtually every scenario in which SRS was considered resulted in equal or better outcomes than the compared alternative. In no case in which SRS was considered an option did the panel recommend against its use. This is of paramount importance. The publication represents the most concise and reputable compilation of evidence-based guidelines supporting the use of SRS, which of course can be performed elegantly and efficiently with SRS technology such as Gamma Knife Perfexion. It is likely to have significant impact on the practice patterns for patients with metastatic brain lesions.

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**Recommendations**

A high level summary of the panel’s recommendations is tabulated above (see Table 1). The summary is general in nature and exceptions could exist, for patients with highly radio-responsive tumors—such as germ cell tumors, small cell lung cancer and lymphomas, for patients who are very ill, and for patients who have lesions that, for whatever reason, are contraindicated for the recommended therapy.

**Table 1.** High level summary of the panel’s recommendations. In no case where SRS Technology was considered an option did the panel recommend against its use.

<table>
<thead>
<tr>
<th>Level of Recommendation</th>
<th>Compared Treatments</th>
<th>Primary Endpoint</th>
<th>Caveat/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Surgery + WBRT &gt; Surgery</td>
<td>Local &amp; Brain Control</td>
<td>Applies to solitary lesions</td>
</tr>
<tr>
<td>2</td>
<td>SRS + WBRT – Surgery + WBRT</td>
<td>Survival</td>
<td>However, surgery is generally favored for resectable lesions larger than 3cm</td>
</tr>
<tr>
<td>3</td>
<td>SRS – Surgery + WBRT</td>
<td>Function &amp; Survival</td>
<td>However, there was better local control in WBRT group and evidence-basis weak</td>
</tr>
<tr>
<td>1</td>
<td>Surgery + WBRT &gt; WBRT</td>
<td>Generally, Survival</td>
<td>Solitary lesions in patients with good performance status and limited/controlled extracranial disease</td>
</tr>
<tr>
<td>1-2</td>
<td>SRS + WBRT &gt; WBRT</td>
<td>Local Control &amp; Function</td>
<td>KPS &gt; 70, 1-3 or 4 lesions</td>
</tr>
<tr>
<td>1</td>
<td>SRS + WBRT &gt; WBRT</td>
<td>Survival</td>
<td>KPS &gt; 70, Solitary lesion</td>
</tr>
<tr>
<td>3</td>
<td>SRS + WBRT &gt; WBRT</td>
<td>Survival</td>
<td>2-3 lesions; supportive evidence weak</td>
</tr>
<tr>
<td>3-4</td>
<td>SRS + WBRT &gt; WBRT</td>
<td>Survival</td>
<td>KPS &lt; 70, 1-3 or 4 lesions, but supportive evidence weak</td>
</tr>
<tr>
<td>2</td>
<td>SRS – SRS + WBRT</td>
<td>Survival</td>
<td>Panel cautioned regarding obligation to watch patients treated with SRS alone post treatment because if they recur they may benefit from salvage WBRT</td>
</tr>
<tr>
<td>3-4</td>
<td>SRS + WBRT – Surgery + WBRT</td>
<td>Survival</td>
<td>Relatively strong evidence to suggest that SRS can be substituted for surgery in select cases</td>
</tr>
<tr>
<td>3</td>
<td>SRS – Surgery + WBRT</td>
<td>Function &amp; Survival</td>
<td>SRS roughly equivalent to Surgery + WBRT, but supportive evidence is weak</td>
</tr>
<tr>
<td>3</td>
<td>SRS &gt; WBRT</td>
<td>Survival</td>
<td>Valid up to 3 lesions, but supportive evidence weak</td>
</tr>
<tr>
<td>1</td>
<td>WBRT – WBRT + CT</td>
<td>Survival</td>
<td>No evidence that chemotherapy provides benefit to these patients</td>
</tr>
<tr>
<td>-</td>
<td>Surgery + SRS vs Surgery + WBRT</td>
<td>N/A</td>
<td>Panel indicated that no compelling data exists to make a valid comparison between the two approaches</td>
</tr>
</tbody>
</table>
Conclusion
Treatment with SRS technology has been proven to be an effective alternative for brain metastases and a table of treatment guidelines has been published to guide clinicians in how to use this technology for the best outcomes. Leksell Gamma Knife Perfexion is an SRS technology that is designed for fast and efficient treatment of multiple brain metastases. Today more than 200,000 patients have been treated with Gamma Knife surgery for brain metastases. Based on ease of use, efficiency and long proven history of effectiveness, SRS modalities such as Leksell Gamma Knife Perfexion are perfectly designed to treat multiple brain metastases, as well as other disorders of the head and neck, as well as improve workflow.