Christopher Ulrich, MD, Chair SHCC  
North Carolina State Health Coordinating Council  
c/o NC Division of Health Service Regulation  
Healthcare Planning and Certificate of Need Section  
2704 Mail Service Center  
Raleigh, NC 27699-2704

Re: Wake Forest Baptist Health Comments regarding Atrium Petition for a Special Allocation for one Gamma Knife in the Western Portion (HSAs I, II, and III) of North Carolina

Dear Dr. Ulrich:

Wake Forest Baptist Health ("WFBH") appreciates the opportunity to comment on the Petition submitted by Charlotte-Mecklenburg Hospital Authority d/b/a Atrium Health ("Atrium" or the "Petitioner") for a special allocation for one Gamma Knife in the Western Portion (HSAs I, II, and III) of North Carolina submitted to the State Health Coordinating Council (SHCC) on March 6, 2019.

WFBH operates one of the two existing gamma knife units in North Carolina and has done so continuously since 1999. WFBH has nearly 20 years of gamma knife experience and leading experts in the fields of Radiation Oncology, Neurosurgery, Radiation Physics, and Stereotactic Radiosurgery ("SRS").

Based on its review of the petition, WFBH urges the SHCC to deny this petition for the following reasons:

1. The Petitioner claims an additional gamma knife is needed to improve inadequate gamma knife access but fails to demonstrate that access to radiosurgery is truly limited in the Western Portion of North Carolina and provides insufficient evidence about the number of potential radiosurgery cases in this region.

2. The Petitioner incorrectly asserts that gamma knife is the preferred radiosurgery platform for patients with four or more brain metastases.

3. The Petitioner incorrectly states that a gamma knife is a more efficient treatment modality than a linear accelerator or CyberKnife.

4. The Petitioner states they do not have a dedicated radiosurgery machine, but fails to disclose that they already own a CyberKnife (which is an alternative linear accelerator-
based radiosurgery platform) and provides no data about the number of cases they have treated with either linear accelerator or the CyberKnife.

Attached are two articles that 1) demonstrate equivalent dose profile for gamma knife and linac-based SRS (Attachment 1) and 2) demonstrate that in North Carolina linac-based radiosurgery is being practiced successfully (Attachment 2).

The Petitioner claims that “there are only two gamma knife units in North Carolina and as a result the state, particularly the western portion, has inadequate access to this technology”. The Petitioner does not demonstrate any indicators of genuine inadequate access to gamma knife services in North Carolina, such as: patients seeking treatment at the two existing gamma knife units but unable to obtain treatment due to capacity constraints; treatment delays due to inadequate capacity on the two existing gamma knife units; patients opting for alternative treatments as a result of inadequate capacity on the two gamma knife units; and percent available capacity the of the two gamma knife units.

Moreover, the more important question is whether patients in the Western Portion of North Carolina have adequate access to radiosurgery services. Gamma knife is one type of radiosurgery device. An SRS-equipped linear accelerator (“linac”) or linac-based CyberKnife can accomplish equivalent outcomes for the same indications, so the critical issue is access to radiosurgery technologies and services, rather than access to gamma knife per se. The Petitioner provides no data to support the claim that access to radiosurgery services in the Western Portion of North Carolina is limited or inadequate. The Petitioner also fails to mention the existence of a CyberKnife at Carolinas Healthcare System NorthEast (“CHS-NE”), an Atrium Health facility located just 25 miles from Carolinas Medical Center in Charlotte.

WFBH offers the following points and supplemental information in response to information gaps and misleading statements within the Atrium petition that were used in its determination of “inadequate gamma knife capacity” in the Western Portion of North Carolina.

1. The Petitioner provides misleading or incomplete information about treatment options by failing to disclose Atrium Health’s possession of a CyberKnife (at CHS-NE) and the capabilities of linac-based SRS as compared to a gamma knife.

Atrium Health possesses an underutilized CyberKnife at its CHS-NE facility in Concord, NC – just 25 miles from Carolinas Medical Center in Charlotte. Both gamma knife and CyberKnife are dedicated SRS treatment technologies. Based on data reported in the 2018 hospital license renewal application for CHS-NE, it appears just 39 CyberKnife procedures were performed at CHS-NE during federal fiscal year 2018. Please reference Attachment 3, volume reported for CPT Code 77372.
Gamma knife and CyberKnife both provide a noninvasive alternative to intracranial surgery by using radiation technology. In these techniques, small beams of radiation are carefully programmed via the aid of diagnostic imaging such as CT and MRI scans, then locked onto a target to converge on a finely pinpointed spot. When these beams meet at the designated point, they create a therapeutic level of radiation.

Gamma Knife treatment uses 192 beams from Cobalt-60 sources focused on the same spot. The engineering of the gamma knife allows for sharp falloff between the region being treated and the surrounding normal tissues. CyberKnife is a linear accelerator mounted on a robotic arm. In general, CyberKnife uses over 100 beams to treat a region of interest. It is also engineered to produce a sharp falloff of radiation dose between the region treated and the normal tissues. There are several functional and theoretical differences between the gamma knife and CyberKnife. CyberKnife is a more versatile treatment machine as it can also be used to treat lung tumors and spinal tumors (in addition to most of the same lesions that are treated within the brain with a gamma knife). Gamma knife is limited to treating conditions above the ear and in the cervical spine. Gamma knife mostly uses a headframe attached to the patient’s skull in order to keep the patient in the proper position for the treatment. CyberKnife uses a rigid mask, and tracks patient positioning throughout their treatment. Because of the differences between sharpness of dose falloff and how to immobilize patients for their treatment, there are a few indications for which gamma knife has a theoretical advantage over CyberKnife. These are essentially the disorders that require a very high dose (>70 Gy) of radiation (trigeminal neuralgia, essential tremor). In spite of the theoretical advantage, there are reports of CyberKnife being used successfully for trigeminal neuralgia. Moreover, Asheville uses their CyberKnife to treat trigeminal neuralgia, while Duke uses a linac-based radiosurgery to treat trigeminal neuralgia.

The following nationally renowned academic sites utilize CyberKnife as their de-facto SRS technology:

- John Hopkins
- Stanford
- UNC
- Fox Chase
- USC-Norris
- Beth Israel - Harvard
- University of Texas - Southwest

CyberKnife sites in North Carolina include:

- University of North Carolina at Chapel Hill
• Cape Fear Valley Health System
• Vidant Health
• Carolina’s Medical Center NorthEast
• Mission Health

Linac SRS sites in the Western Portion of North Carolina include, but are not limited to:

• Novant Health Presbyterian Medical Center
• Carolinas Medical Center
• Novant Health Forsyth Medical Center
• Cone Health

In its comparison of gamma knife to linac-based SRS, the Petitioner makes several false or misleading claims:

• The Petitioner claims that gamma knife is superior to linac-based SRS. However, to the contrary, new randomized evidence states that gamma knife and linac-based SRS have equivalent local control rates¹.

• The Petitioner claims that “approximately 20 percent of patients with brain metastases have between 5 and 10 lesions at diagnosis. These patients are not currently eligible for SRS on most linacs but these patients could be treated on a gamma knife.” This is not correct; plenty of linac-based centers are treating between 5 and 10 lesions, including centers in North Carolina² ³. In fact, the Petitioner goes on to contradict its own statement, but subsequently notes that “these patients are not currently eligible for SRS on most (emphasis added) linacs....”

• The Petitioner states “Atrium rejected this alternative because linear accelerators configured to perform SRS are not capable of providing the same level of precision and efficiency as gamma knife for patients with intracranial pathologies.”

¹ E Clerici, P Navarria, C Franzese, G A Carta, P Mancosu, G Reggiori, P Picozzi, L Attuati, S Tomatis, M Scorsetti; OS6.5 Randomized phase III trial comparing GAMMA KNIFE (GK) and linac based (EDGE) radiosurgery for brain metastases from solid tumors: results from the GADGET trial, Neuro-Oncology, Volume 20, Issue suppl_3, 19 September 2018, Pages ii227, https://doi.org/10.1093/neuonc/noy139.042
However, linac-based radiosurgery has been proven to be more efficient for patients with multiple metastases⁴.

2. The Petitioner Inflates the Number of Potential Gamma Knife Cases in North Carolina

On page three of the petition, Atrium provides a methodology to estimate the number of potential gamma knife cases in North Carolina and in the Eastern and Western portions of the state. The methodology grossly overstates the estimated gamma knife demand in North Carolina. The overstatement is in part driven by the petitioner's neglect to acknowledge that a portion of patients with each of the identified conditions will never receive treatment. Therefore, applying the petitioner's "percent indicated for treatment" to the total prevalence of the identified conditions overstates the potential demand for gamma knife services. For example, if 50% of patients with benign tumors are ever treated and 50% of those treated are indicated for gamma knife treatment, then the percentage of patients indicated for gamma knife treatment is 50% * 50% = 25%. In addition, in most of these conditions there is no clinical improvement seen for patients treated with gamma knife versus other linear accelerator-based SRS such as CyberKnife or linear accelerators equipped with SRS. Therefore, the "percent indicated for gamma knife" would be more appropriately labeled "percent indicated for SRS". WFBH addresses each identified condition below:

Meningioma

Given a prevalence of 975 meningiomas, only 50% of these cases will receive any treatment as half of meningiomas are chronically dormant and non-progressive⁵. Of those meningiomas that are in fact treated, many are treated with surgery given the advantage of surgery to decompress symptoms and yield tissue diagnosis of the grade. Tumors greater than 3 cm are inappropriate for gamma knife due to the risk of post-treatment brain swelling. Many of the more aggressive tumors (WHO grade II and III tumors) are inappropriate cases for gamma knife as they experience tumor re-growth just outside of the gamma knife treatment volume⁶. It is estimated that the true proportion of meningiomas that are appropriate for gamma knife are 70% of tumors that require treatment. Therefore, an appropriate "percent indicated for treatment" to apply to the total

⁴ Comparison of Plan Quality and Delivery Time between Volumetric Arc Therapy (RapidArc) and Gamma Knife Radiosurgery for Multiple Cranial Metastases Evan M Thomas, M.S.,1 Richard A Popple, Ph.D.,1 Xingen Wu, Ph.D.,1 Grant M Clark, M.D.,1 James M Markert, M.D.,2 Barton L Guthrie, M.D.,2 Yu Yuan, Ph.D.,1 Michael C Dobelbower, M.D., Ph.D.,1 Sharon A Spencer, M.D.,1 and John B Fivash, M.D.1


prevalence is 35% (50% of patients will be treated * 70% of patients treated appropriate for gamma knife = 35% of total prevalence of patients with meningiomas indicated for gamma knife treatment). There is no clinical improvement seen in patients treated with gamma knife vs. linac-based SRS (Cyberknife or linear accelerators equipped with SRS) for this indication.

Vestibular Schwannoma

Similar to meningioma, not all vestibular schwannoma cases require treatment. In cases that are observed, usually only 50% of patients will ultimately require treatment as some of these tumors either do not grow or spontaneously decrease in size. Moreover, of the cases that require treatment, not all are eligible for stereotactic radiosurgery. Some tumors are large enough to require surgery. Others occur in patients with neurofibromatosis type II, and may not be good candidates for radiosurgery given the concern for becoming cancerous as a result of radiation exposure. In all, approximately 80% of patients that require treatment (40% of the population of vestibular schwannomas) will be treated with stereotactic radiosurgery. As with meningioma, there is no clinical improvement seen in patients treated with gamma knife vs. linac-based SRS (Cyberknife or linear accelerators equipped with SRS) for this indication.

Brain Metastases

The percent of patients with brain metastases indicated for gamma knife treatment is well below the 90% estimate provided in the Atrium petition. This estimate ignores the proportion of patients that have 1) large numbers of brain metastases, 2) small cell lung cancer, and 3) leptomeningeal involvement (cancerous involvement of the meningeal covering of the brain). These are scenarios in which gamma knife is inappropriate and in combination comprise well above 10% of the population of patients with brain metastases. These conditions are more appropriate for whole brain radiotherapy. In addition, some brain metastasis patients have such poor performance status or limited life expectancy, that they are not appropriate for any treatment as the gamma knife treatment would never impact their survival or quality of life. Moreover, there is emerging data that many patients with small asymptomatic brain metastases may be managed with systemic therapy (immunotherapy or targeted agents) alone instead of treatment with any form of radiation. Should these findings be validated, it would dramatically decrease the number of brain metastases treated with SRS.

The team from Atrium incorrectly state that patients with 5-10 brain metastases are ineligible for linear accelerator-based SRS. Single-isocenter center multi-target linear

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accelerator-based SRS is increasingly available at multiple centers in the southeast including Duke University. Sites in North Carolina including Mission Health, UNC-Chapel Hill, Cape Fear Valley Health System, Vidant Health and CMC-NEall have access to CyberKnife which can be used to treat multiple lesions (even breaking up treatments over several days to avoid long treatments). Linear accelerator-based SRS is considered to be as effective for treatment of brain metastases as gamma knife. When taking into account linear accelerator-based platforms such as CyberKnife and brainlab, the true access to SRS issue is dramatically less than what is presented in Atrium’s petition.

Research led by Dr. Eric Chang, a world recognized authority on brain metastases, illustrates that at some point, SRS can't keep increasing due to a population of patients that are not appropriate. This number is on the order of 25% of patients (due to poor life expectancy, large numbers of metastases, and small cell lung cancer or leptomeningeal disease). Based on this information, an appropriate “percent indicated for treatment” is likely closer to 75% of patients having brain metastases.

With regards to the assertion that alternative linear accelerator platforms would be insufficient to treat patients with multiple brain metastases, there is actually clinical data that demonstrates that linear accelerator platforms deliver equivalent plan quality and potentially higher efficiency (depending on the platform acquired) than the gamma knife. A recent prospective randomized trial of in Italy compared linac-based SRS to gamma knife and found comparable local control, but increased rate of radiation necrosis in gamma knife as compared to linac-based SRS. Modern international clinical trials including those led by Dr. Asher and those led by Wake Forest investigators (CE.7) treat gamma knife and linac-based SRS as equivalent modalities.

**Arteriovenous Malformations**

Arteriovenous malformation is a condition for which there are several treatment options, including surgery as well as stereotactic radiosurgery (in cases that are in non-operative locations). Gamma knife is a good treatment option for this condition, though linac-based radiosurgery has been reported for this indication and is commonly practiced at Duke University. WFBH agrees with the estimate in Atrium’s petition that approximately 70% are indicated for gamma knife.

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8 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5707418/#__fn_sectitle
10 https://academic.oup.com/neuro-oncology/article/19/suppl_3/iii5/3743820
11 https://jamanetwork.com/journals/jama/fullarticle/2536637
12 https://clinicaltrials.gov/ct2/show/NCT03550391
Trigeminal Neuralgia

Trigeminal neuralgia represents a treatment indication in which gamma knife may be superior to linac-based approaches. This is because of the very small size of the nerve that is targeted by radiosurgery (approximately 4 mm in caliber). Linac-based approaches (while sometimes used, and often used in Charlotte) for this indication have demonstrated comparable clinical outcomes but in small retrospective series with limited follow-up. The level of error estimated with linac-based approaches lead to the question of whether its accuracy is sufficient to hit such a small target which is also in close proximity to the brainstem. This is a point of current controversy at the present time.

However, prior to a patient requiring gamma knife or other radiosurgery for trigeminal neuralgia, patients should be first treated with medications. Many patients who are first managed with medications will go into spontaneous remission and can have medicines withdrawn. Many patients are successfully treated with medications chronically over time. Patients who fail medical management ultimately are treated with either radiosurgery or surgery. Surgery has been shown to be more cost efficient than gamma knife because of its greater durability of pain relief (5 years of pain relief for gamma knife, often permanent pain relief for surgery)\(^1\). As such, surgery is considered the first line treatment for patients with trigeminal neuralgia that fail medications if they are young/fit enough for it. This generally eliminates at least 50% of the population of patients with trigeminal neuralgia who fail medications. The resulting “percent indicated for treatment” is more realistically 25% patients with trigeminal neuralgia. Moreover, the incidence of trigeminal neuralgia is not increasing, and thus, with two gamma knife centers in North Carolina that are not at capacity, access to gamma knife should also be stable.

The substitution of these more realistic estimates of the percentage of patients that are indicated for gamma knife results in range of potential North Carolina gamma knife cases of 1,380 to 2,305. This compares to Atrium’s estimate of 2,042 to 3,484. In the Western Portion of North Carolina, the estimated potential range of cases is 717 to 1,197 compared to Atrium’s estimate of 1,060 to 1,809. Again, it is important to note that in the vast majority of these conditions there is no clinical improvement seen for patients treated with gamma knife versus other linear accelerator-based SRS such as CyberKnife or linear accelerators equipped with SRS. As such, the “Potential Gamma Knife Cases” truly represents the potential cases indicated for SRS treatment which could come in the form of linac-based SRS or gamma knife.

\(^1\) https://www.ncbi.nlm.nih.gov/pubmed/15951649
Table 1
Estimated SRS Demand, North Carolina

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
<th>Annual Incidence (per million)</th>
<th>Prevalence (per million)</th>
<th>% Indicated for Gamma Knife</th>
<th>Potential NC Gamma Knife Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>High</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Benign Tumors*</td>
<td>Meningioma</td>
<td>74.4</td>
<td>975</td>
<td>35%</td>
<td>271</td>
</tr>
<tr>
<td></td>
<td>Vestibular Schwannoma</td>
<td>19</td>
<td>200</td>
<td>35%</td>
<td>69</td>
</tr>
<tr>
<td>Malignant Tumors*</td>
<td>Metastases</td>
<td>83</td>
<td>143</td>
<td>75%</td>
<td>648</td>
</tr>
<tr>
<td>Vascular Abnormalities*</td>
<td>Arteriovenous Malformations</td>
<td>8.9</td>
<td>13.4</td>
<td>70%</td>
<td>65</td>
</tr>
<tr>
<td>Functional Disorders</td>
<td>Trigeminal Neuralgia</td>
<td>126</td>
<td>289</td>
<td>25%</td>
<td>328</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total Potential Gamma Knife Cases</td>
<td>1,380</td>
</tr>
</tbody>
</table>

*these indications are treated in an equivalent manner using CyberKnife (UNC, Asheville, Atrium) or other linac-based stereotactic radiosurgery (Novant, Duke).

Table 2
Estimated SRS Demand, Western (HSA I, II, III) and Eastern (HSA IV, V, VI) Portions of NC

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
<th>HSA I, II, III</th>
<th>Potential Gamma Knife Cases</th>
<th>HSA IV, V, VI</th>
<th>Potential Gamma Knife Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Benign Tumors*</td>
<td>Meningioma</td>
<td>141</td>
<td>141</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Vestibular Schwannoma</td>
<td>36</td>
<td>36</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Malignant Tumors*</td>
<td>Metastases</td>
<td>336</td>
<td>579</td>
<td>311</td>
<td>536</td>
</tr>
<tr>
<td>Vascular Abnormalities*</td>
<td>Arteriovenous Malformations</td>
<td>34</td>
<td>51</td>
<td>31</td>
<td>47</td>
</tr>
<tr>
<td>Functional Disorders</td>
<td>Trigeminal Neuralgia</td>
<td>170</td>
<td>390</td>
<td>158</td>
<td>361</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total Potential Gamma Knife Cases by HSA</td>
<td>717</td>
</tr>
</tbody>
</table>

*these indications are treated in an equivalent manner using CyberKnife (UNC, Asheville, Atrium) or other linac-based stereotactic radiosurgery (Novant, Duke).

3. Population per Gamma Knife is an Inaccurate and Incomplete Measure to use in Determining Appropriate Access

The Petitioner sites the population per gamma knife as the primary driver of its determination of inadequate gamma knife capacity in North Carolina. While North Carolina ranks well below the neighboring southeastern states based on the ratio of gamma knife units per population, geographic accessibility to the two existing gamma knife units in North Carolina in terms of travel time are in-line with these neighboring states. In fact, Virginia which has a significantly lower population to gamma knife ratio than North Carolina (2,129,421 in VA versus 5,191,810 in NC) and the second lowest population to gamma knife ratio of the five nearby surrounding states has the greatest travel time from the farthest distance to the nearest gamma knife unit. Reference Table 3.

Population per gamma knife alone cannot be the sole factor in determining adequate treatment accessibility. Treatment accessibility must also consider accessibility to linac-based SRS. In particular, Atrium does not indicate the number of linac-based SRS
procedures performed in each state, including North Carolina. Atrium also does not provide data on the number and location of linear accelerators equipped with SRS or the number and location of CyberKnife systems.

Travel distance to the nearest gamma knife unit, capacity and utilization of existing units, and demonstrated access concerns with existing units should also be factored into determining if inadequate access truly exists. In addition, accessibility to and utilization of linac-based SRS must be considered when evaluating whether or not adequate access exists.

Table 3
Farthest distance to nearest Gamma Knife
North Carolina and Neighboring Southeastern States

<table>
<thead>
<tr>
<th>State</th>
<th>Population per Gamma Knife</th>
<th>Travel Time</th>
<th>Start Point (Address or Latitude, Longitude)</th>
<th>End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA</td>
<td>2,103,895</td>
<td>3 hours, 3 minutes</td>
<td>1099 Gopher Hill Rd, Darien, GA 31305</td>
<td>Augusta University Medical Center</td>
</tr>
<tr>
<td>VA</td>
<td>2,129,421</td>
<td>5 hours, 31 minutes</td>
<td>36.6596399, -83.4144922</td>
<td>University of Virginia Medical Center</td>
</tr>
<tr>
<td>SC</td>
<td>2,542,064</td>
<td>2 hours, 57 minutes</td>
<td>Bull Sluice Rd, Long Creek, SC 29658</td>
<td>Richland Memorial Hospital</td>
</tr>
<tr>
<td>TN</td>
<td>3,385,005</td>
<td>3 hours, 39 minutes</td>
<td>1676 Ardmore Hwy, Taft, TN 38488</td>
<td>Fort Sanders Regional Gamma Knife Center</td>
</tr>
<tr>
<td>NC (Western Portion)</td>
<td>5,191,810</td>
<td>4 hours, 34 minutes</td>
<td>35.0515005, -84.2902344</td>
<td>Wake Forest Baptist Medical Center</td>
</tr>
<tr>
<td>NC* (Western Portion)</td>
<td>5,191,810</td>
<td>2 hours, 33 minutes</td>
<td>35.0515005, -84.2902344</td>
<td>Mission Health</td>
</tr>
</tbody>
</table>

Source: Google Maps; Elekta; Atrium Petition
*Represents the farthest distance to the nearest CyberKnife: when accounting for distance to nearest Cyberknife (located at Mission Health), the travel time is reduced to 2 hours, 33 minutes

4. The Petitioner Fails to Demonstrate Access Issues for Patients Seeking Treatment on the Two North Carolina Gamma Knife Units

The petitioner makes an assumption that there is inadequate gamma knife capacity in North Carolina based upon its analysis of gamma knife units per population and estimated gamma knife demand in North Carolina. However, the petitioner makes no claim in its petition that patients seeking gamma knife treatment at the NCBH gamma knife unit are unable to obtain that treatment as a result of capacity limitations. In addition, the petitioner makes no statements in its petition regarding patients experiencing delays in treatment or selecting alternative treatments as a result to capacity limitations at the NCBH gamma knife.
The NCBH gamma knife unit was established to be a regional resource for patients in need of gamma knife treatment. Per the conditions of its Certificate of Need for one gamma knife unit, NCBH

"shall provide the Certificate of Need Section with copies of written policies establishing the gamma knife unit as a regional resource having no administrative, clinical or charge requirements which would impede physician referrals for whom gamma knife procedures would be appropriate".

To meet the conditions of its Certificate of Need, NCBH, which by and large has a closed medical staff consisting of only Wake Forest School of Medicine faculty providers allows for the privileging of non-faculty providers to provide access to and utilization of the gamma knife unit at NCBH. In fact, Dr. Tony Asher was once privileged at NCBH, along with four other radiation oncologists and neurosurgeons from Chapel Hill, Raleigh and Charlotte, and utilized the NCBH gamma knife for treating his patients. These privileges could be reestablished at NCBH gaining Dr. Asher (and/or other providers) access to utilize the existing gamma knife unit at NCBH. Please see Attachment 4 for the CON.

5. The Petitioner Fails to Demonstrate Existing Gamma Knife Utilization and Capacity in Comparison to Gamma Knife Demand

The Petitioner provides historic gamma knife unit volumes for NCBH and Vidant, the state’s two gamma knife providers. However, the Petitioner makes no mention of how the utilization compares to gamma knife unit or linac-based SRS capacity. As demonstrated throughout these comments, linac-based SRS is a clinically equivalent treatment for most of the conditions identified within the Atrium petition.

The state of North Carolina does not have an established methodology to estimate gamma knife utilization. As such, NCBH offers the following definition of full utilization in the methodology outlined below based on its experience as a leading gamma knife provider with nearly 20 years of expertise. In addition, the optimal utilization per gamma knife unit identified below is supported by utilization data provided by the gamma knife vendor, Elekta. Please reference Attachment 5. Worldwide data from Elekta demonstrates that 700-800 procedures per unit per year is about the maximum capacity.

\[
\text{Maximum capacity for patients treated per day * treatment days per year * target utilization threshold} = \text{annual gamma knife unit capacity}
\]
| Maximum Patients Treated per Day: | 4 | Source: WFBH gamma knife clinical and operational experts |
| Treatment Days per Year:          | 260 | Business days per calendar year |
| Target Utilization Threshold:     | 75% | Source: WFBH gamma knife clinical and operational experts |
| Annual Gamma Knife Unit Capacity: | 780 procedures |

NCBH estimates that target full utilization of one gamma knife unit is equivalent to 780 procedures per unit per year. Based upon this capacity calculation, the two existing North Carolina gamma knife units are operating well below this threshold at a combined utilization of 41%. The NCBH gamma knife, which performed 496 procedures during FFY 2018, is at 64% of optimal capacity and the Vidant Health gamma knife, which performed 164 procedures during FFY 2017, is at 19% of optimal capacity.\(^4\)

Combined, the two existing North Carolina gamma knife units have capacity to perform a total 1,560 procedures annually. Given that the identified conditions can be appropriately treated on one of the five CyberKnife systems in NC, a linear accelerator equipped with SRS, or a gamma knife unit, there is sufficient capacity in the state to meet the needs of the estimated 1,380 to 2,305 patients per year that would benefit from SRS treatment.

In the Western Portion of NC, the gamma knife unit at NCBH has capacity to perform a total 780 procedures annually. The estimated demand for SRS-based treatments in the Western Portion of North Carolina ranges from 717 to 1,197 procedures. Given that the identified conditions can be appropriately treated on one of the two CyberKnife systems in the Western Portion of NC, a linear accelerator equipped with SRS, or the NCBH gamma knife unit, there is sufficient capacity in Western North Carolina state to meet the needs of the estimated 717 to 1,197 patients per year that would benefit from SRS treatment. Reference Table 4 (below) which summarizes the gamma knife capacity and estimated demand for North Carolina. Again, note that most conditions identified in determining demand for gamma knife services may and are appropriately treated with linac-based SRS.

<table>
<thead>
<tr>
<th></th>
<th>Supply: Gamma Knife Capacity</th>
<th>Demand: SRS Estimated Demand (Low)</th>
<th>Demand: SRS Estimated Demand (High)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Portion</td>
<td>780</td>
<td>717</td>
<td>1,197</td>
</tr>
<tr>
<td>Western Portion</td>
<td>780</td>
<td>663</td>
<td>1,198</td>
</tr>
<tr>
<td>Total</td>
<td>1,560</td>
<td>1,380</td>
<td>2,305</td>
</tr>
</tbody>
</table>

\(^4\) Data source for NCBH and Vidant gamma knife volumes is Atrium petition
With regard to value, as demonstrated throughout these comments, the Petitioner fails to demonstrate inadequate access to SRS treatment for the Western Portion of North Carolina. The addition of a costly piece of medical equipment will not promote healthcare value as it represents an imprudent expenditure of resources. Patients in the Western Portion of North Carolina have adequate access to linac-based or SRS treatments. This is evidenced by the 41% utilization of the gamma knife located at NCBH, the low utilization of the CyberKnife at CHS-NE, and the additional availability of linac-based SRS including CyberKnife at other providers in the Western Portion of North Carolina.

For the reasons stated above, WFBH respectfully requests the SHCC deny this petition. Thank you for the opportunity to comment on our concerns regarding the petition.

Sincerely,

[Signature]

Marisa Barone
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Comparison of Plan Quality and Delivery Time Between Volumetric Arc Therapy (RapidArc) and Gamma Knife Radiosurgery for Multiple Cranial Metastases

BACKGROUND: Volumetric modulated arc therapy (VMAT) has been shown to be feasible for radiosurgical treatment of multiple cranial lesions with a single isocenter.

OBJECTIVE: To investigate whether equivalent radiosurgical plan quality and reduced delivery time could be achieved in VMAT for patients with multiple intracranial targets previously treated with Gamma Knife (GK) radiosurgery.

METHODS: We identified 28 GK treatments of multiple metastases. These were replanned for multiarc and single-arc, single-isocenter VMAT (RapidArc) in Eclipse. The prescription for all targets was standardized to 18 Gy. Each plan was normalized for 100% prescription dose to 99% to 100% of target volume. Plan quality was analyzed by target conformity (Radiation Therapy Oncology Group and Paddick conformity indices [CIs]), dose falloff (area under the dose-volume histogram curve), as well as the V4.5, V9, V12, and V18 isodose volumes. Other endpoints included beam-on and treatment time.

RESULTS: Compared with GK, multiarc VMAT improved median plan conformity (CI VMAT = 1.14, CI GK = 1.65; P, .001) with no significant difference in median dose falloff (P = .269), 12 Gy isodose volume (P = .500), or low isodose spill (P = .49). Multiarc VMAT plans were associated with markedly reduced treatment time. A predictive model of the 12 Gy isodose volume as a function of tumor number and volume was also developed.

CONCLUSION: For multiple target stereotactic radiosurgery, 4-arc VMAT produced clinically equivalent conformity, dose falloff, 12 Gy isodose volume, and low isodose spill, and reduced treatment time compared with GK. Because of its similar plan quality and increased delivery efficiency, single-isocenter VMAT radiosurgery may constitute an attractive alternative to multi-isocenter radiosurgery for some patients.

KEY WORDS: Gamma Knife, LINAC, Multiple metastases, Plan quality, Radiosurgery, RapidArc, TrueBeam STx, Treatment efficiency

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capable of volumetric modulated arc therapy (VMAT), coupled with improved planning strategies, is now available. Therefore, we investigated whether improved VMAT technology and planning technique provide sufficient merit to reevaluate this conclusion.

To assess the clinical feasibility of such an approach, we retrospectively evaluated plan quality and efficiency of treatments for consecutive patient cases at our institution who received GK therapy for multiple metastases to the brain. We then replanned each case for different types of VMAT delivery and compared plan quality and prospective treatment efficiency. Our hypothesis was that VMAT could deliver plan quality clinically equivalent to GK with a significant increase in treatment efficiency.

METHODS

Treatment Planning

With approval from the University of Alabama at Birmingham Institutional Review Board, we identified 28 consecutive multiple-target cases with 112 total targets that had been treated on our Leksell Model C (Elekta) GK with SRS. No other selection criteria were used. Each of the plans had been designed by an experienced GK physicist and approved by an attending neurosurgeon and radiation oncologist. The GK’s source was less than 2 years old over the entire range of treatments. Source activity was at least 77% of initial activity for all treatments. Treatment times and beam times were those of the actual date of treatment and not normalized to a specific source age. Descriptive statistics for the cases and individual targets are shown in Table 1. All patients received magnetic resonance (MR) imaging with contrast for planning. Four-, 8-, 14-, and 18-mm collimators were used for treatment planning. As a general rule, our institution prefers using multiple shots to emphasize conformity, rather than fewer shots to minimize treatment time. We strive for each plan to cover at least 99% of the target volume with the prescription dose, but occasionally a clinical judgment call is made in the setting of a nearby organ at risk to accept 95% volume coverage with the prescription dose. Once acceptable coverage and conformity is achieved, optimal gradient is pursued. To optimize dose falloff and normal tissue background dose, the prescription isodose line was between 50% and 60% for most targets. If warranted, higher and lower isodose lines (max: 86%, min: 40%) were occasionally used (eg, for very small or particularly large targets).

To ensure congruent planning, quality comparison between modalities, the prescription for all tumors was standardized to 18 Gy in a single fraction, and any GK cases with heterogeneous prescriptions were renormalized accordingly. We transferred each GK session’s imaging set and all corresponding structure contours from Leksell Gamma Plan version 10.1 into Eclipse via the Digital Imaging and Communications in Medicine–radiotherapy (DICOM-RT) protocol. Because a computed tomographic (CT) volume is required for treatment planning within Eclipse, we generated an equispaced (\(z = 0.25\) cm) phantom CT image set into which all structure contours were replicated. In the manner of our previously described technique, we constructed 1-arc, 2-arc, and 4-arc (Figure 1) single-isocenter VMAT plans in 10MV flattening filter free (FFF) mode for simulated delivery with the TrueBeam STx (Varian) in high-intensity FFF mode with HD120 MLC high definition–multileaf collimators. Jaw tracking was enabled. High-intensity FFF mode operates at up to 2400 monitor units/minute. We included additional optimization criteria to emphasize conformity and dose falloff as well as reduced low-dose spill. Plans were optimized with the RapidArc PRO3 algorithm. We normalized each plan such that 100% of prescription dose was delivered to \(\geq 99\%\) of target volume. In contrast to GK plans where normalization is performed for each isocenter to optimize gradient for
that particular target, single-isocenter RapidArc uses a single cumulative plan normalization. Each plan received appropriate physician and physicist review to ensure clinical acceptability with regard to accepted standards for target coverage and risk of neurological complication, particularly radionecrosis. Upon initial analysis, we observed that 4-arc plans consistently generated plan quality superior to 1- and 2-arc plans and confined intermodality comparison to the 4-arc VMAT and GK plans for increased statistical power.

**Plan Comparison Evaluation**

We quantitatively assessed both modalities’ plan quality with Radiation Therapy Oncology Group (RTOG) and Paddick conformity indices: 18, 12, 9, and 4.5 Gy isodose volumes ($V_{18}$, $V_{12}$, $V_{9}$, $V_{4.5}$); mean dose; and the area under the dose-volume histogram (DVH) curve between the 50% and 100% prescription isodoses ($AUC_{50-100}$). We limited conformity analysis to targets with volume $\geq 0.025$ cm$^3$.

$$\text{RTOG CI} = \frac{PV}{TV}$$

$$\text{Paddick CI} = \frac{(TV_{PV})^2}{PV \times TV}$$

$$AUC_{100\% - 50\%} = \int V_{structure} d\text{dose},$$

where $TV$ = target volume; $PV$ = prescription volume; $TV_{PV}$ = target volume within the prescribed isodose cloud; $V_{structure}$ = volume of structure (absolute or relative %); $d\text{dose}$ = 50% to 100% prescription dose range.

Beam-on time and treatment time were also compared. For GK, treatment time was defined to be the duration between treatment room

![FIGURE 2. Distribution of RTOG and Paddick conformity indices for individual targets and overall plans. RTOG, Radiation Therapy Oncology Group; VMAT, volumetric modulated arc therapy.](image)

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$^a$RTOG, Radiation Therapy Oncology Group; VMAT, volumetric modulated arc therapy.
entry and frame removal as recorded in the medical record. Because the difference between delivered and replanned GK beam-on times were negligible compared with treatment time, we used the clinical treatment times for the replanned GK cases. The institutional average delivery time was utilized for simulated VMAT plan treatment time. With the use of a single-isocenter approach, for a given prescription, VMAT beam-on time is independent of target number and only varies with the number of arcs.

Statistical analysis was performed with Origin 9.0 and SAS 9.3. Direct comparison was performed via paired Wilcoxon signed-rank test; multivariate regression was performed via least-squares regression with an identity link function.

RESULTS

All plans met our standards for clinical acceptability, including target coverage, dose falloff, moderate isodose spill, and critical structure exposure. Figure 2 shows the distributions of RTOG and Paddick conformity indices for both individual target and overall plan conformity. Table 2 details their respective descriptive statistics. Conformity was more favorable in multiarc VMAT plans than GK.

Figure 3 shows the distribution of 4.5, 9, 12, and 18 Gy isodose volume levels and Figure 4 illustrates the mean brain dose distributions for both modalities. Over the entire distribution of cases, no statistically significant difference was detected in 4.5, 9, and 12 Gy isodose volume levels or mean dose.

The distribution of the $V_{18}$ was more favorable for VMAT than for GK, as would be expected from the observed difference in conformity. Because the $V_{12}$ has become a benchmark predictor for risk of radionecrosis, we also constructed a generalized linear model of $V_{12}$’s dependence on total gross tumor volume (GTV), tumor number, as well as modality to ensure that the former 2 were not confounding variables. The model was well-fitted to the data ($R^2 = 0.97$, $P < .001$) and found $V_{12}$ to be significantly correlated with both total GTV ($P < .001$) and tumor number ($P = .013$), but not modality ($P = .14$). Dropping the nonsignificant modality correlate left an equally well-fitted model ($R^2 = 0.97$, $P < .001$) of $V_{12}$ vs total GTV and tumor.
number that can be visualized conveniently in a contour fit plot (Figure 5). Paddick and Lippitz\(^9\) stated in their original postulation of the metric that the gradient index is inherently unsuited to comparison of dose falloff in plans with incongruent conformity. However, the rapidity of the prescription dose falloff, especially in the 9 to 18 Gy range, is an important property in radiosurgical plan evaluation. We therefore sought a more robust metric that was insensitive to individual isodose volume differences between plans. We chose to compare the area under the dose volume histogram curve (AUC-DVH) in our range of interest for each modality, a metric that has been used principally for predicting normal tissue toxicity in genitourinary and gastrointestinal treatments,\(^11-13\) but not previously for comparative SRS plan evaluation. Matlab was used to integrate each absolute dose/volume DVH curve of the body from 9 Gy to 18 Gy to obtain the AUC-DVH\(_{9-18}\). A case example and the distribution for each modality are shown in Figure 6. Distributions of plan dose falloffs was not significantly different (\(P = .44\)) between GK (range, 7.97-520.0; median, 81.5 cGy-cc) and VMAT (range, 16.18-328.7; median, 80.8 cGy-cc).

Figure 7 shows the difference in beam-on time and treatment time between GK and multiarc VMAT. For high-intensity mode FFF VMAT, at prescriptions that average less than 24 Gy/360° of arc rotation, the dose rate is determined by the gantry rotation speed, and the beam-on time will not vary with target number or prescription. For the 4-arc geometry we used here, beam-on time will always be approximately 2.5 minutes. The remainder of treatment time is constituted by positioning verification and table adjustments. Treatments range from 12 to 22 minutes.\(^3\) One table rotation is necessary for each noncoplanar arc. GK beam-on times ranged from 17.5 to 121.2 minutes (median, 45.1; mean, 55.3 minutes). GK treatment times ranged from 60 to 310 minutes (median, 125; mean, 148 minutes).

**DISCUSSION**

Ma et al found that peripheral isodose volumes are several times lower for GK (Perfexion) than arc-based therapy multimet SRS on both the Novalis\(^6\) and the TrueBeam STx platform in...
4 target-arrangement permutations of a 12 metastasis case. We report here, in a 28-case series of treated patients, that with sufficiently advanced planning technique, VMAT can in fact deliver plans clinically equivalent in terms of both conformity and moderate isodose spill to plans we are currently delivering with our GK. A comparative DVH curve for a 9-metastasis case is shown in Figure 8.

Comparative isodose contour maps of the 9-metastasis case, a 6-metastasis case, and a 2-metastasis case are shown in Figure 9.

At increasing numbers of very small targets (eg, >9 tumors, 0.01-0.1 cm³), GK may retain a small advantage to VMAT with respect to very low isodose spill (ie, dose < Rx₂₅%). This difference may be plan independent and due to collimator leakage, scatter dose, and/or the much larger area of the cranium throughout which the GK's beam entry points are spread. Or, the advantage may be an artifact of the relatively short duration of time VMAT has been used to treat multiple metastases. In any case, the absolute differences between the 2 modalities seem to be very small, and the authors of this study are aware of no work establishing any clinical sequelae to this very low isodose region. Even so, as our VMAT treatment strategy has evolved, we have studied a variety of methods to reduce the low-dose spill as much as possible; these include jaw-tracking and high-priority low-dose spill constraints (eg, 2.5× optimization priority of other parameters).

In this series of patients, we noted that utilizing jaw tracking on the LINAC resulted in a small but consistent 2% to 5% reduction of the mean dose without any compromise to other dosimetric parameters. Although not necessary for a high-quality plan, if available, this feature should not be neglected when treating multiple targets. Our unique Matryoshka (Russian nesting doll) shell technique to emphasize conformity and reduce falloff also likely contributes to our favorable low-dose spill results. However, including a heavily weighted low-dose constraint within the treatment optimization criteria is necessary for a high-quality plan, and we have found it to be the single most effective contributor to reducing low-dose spill.

We have invested additional study into using a custom collimator angle selection program to further reduce low-dose spill. This technique involves iteratively summing the cumulative space between collinear targets in each leaf-pair opening of the beam’s eye projection for all control points across the entire path of each arc. The collimator angle with the least total leaf-pair space is selected for each of the arcs in the designated field geometry. Although this technique was not used for the results presented here, we believe it may enable us to continue improving the low-dose profile of VMAT plans.
A high-quality multimet VMAT SRS plan must utilize beam geometry and optimization criteria that not only achieve the required target coverage, but also emphasize conformity, rapid falloff, minimal moderate isodose, and minimal low isodose spill.

The planner must realize that VMAT is an entirely different paradigm of SRS than GK. In VMAT, the use of separate isocenters and arc(s) for each target no longer makes sense when a single-isocenter plan can achieve the same coverage. When
additional isocenters are used, redundant monitor units are delivered, additional collimator leakage is accumulated, and peripheral dose to normal issue is needlessly increased.\(^7\)

Achieving rapid falloff from the prescription volume can be difficult, especially in the setting of closely situated targets. However, we have found the Martyoshka method of imposing decreasing dose ceilings on increasing diameter concentric shells about the GTV\(^4\) to be effective. On occasion, an additional artificial tuning structure between 2 targets may be necessary to mitigate moderate isodose bridging that occurs when 1 target is eclipsed by another for a large portion of the arc path. This phenomenon, which only occurs in GK plans with very closely situated targets, is referred to as island blocking.\(^17\)

We believe our choice of the area under the DVH region in the 9 to 18 Gy (or any 50%-100% isodose range) is an ideal substitute to the Paddick gradient index for comparing the dose falloff between plans with disparate conformity. It is robust with respect to interplan differences of singular points within the DVH (eg, \(V_{18Gy}, V_{5Gy}\)), and instead provides the planner a quantitative perspective of the entire range of falloff in the important moderate-to-high isodose region. Further study is merited to validate this parameter as a meaningful predictor of SRS treatment toxicity.

Limitations

One limitation to our study was the comparison of VMAT plans with highly refined plan geometry and optimization schema to routine clinical GK plans that had previously been delivered without any particular exhortation to the physicists to generate the absolute best plan they could. Because we desired to know if we could replicate with VMAT the high plan quality we were already achieving with GK, this was an unavoidable consequence of the study design. Slight additional improvements to GK may therefore be possible; however, our institution’s GK planning priorities already tend to emphasize conformity and falloff over efficiency, so it is unlikely these gains would have been meaningful.

One other limitation of our study was that the GK Perfexion was unavailable for our comparison. Perfexion delivers improvement in both irradiatable area and ease of planning and delivery over the model C/4C. The ability of Perfexion to more easily use hybrid shots to tailor the shape of the dose cloud to eccentrically shaped targets or in the vicinity of organs at risk is another advantage\(^18\) over its predecessor. However, its beam profile has been shown to be nearly identical to the model C/4C,\(^19,21\) and indeed was a design feature. Therefore, in this study of mostly spherical targets, we do not expect our use of the model C instead of Perfexion had a meaningful dosimetric impact on the results of our comparison. Technical improvements also allow treatments to be more efficiently delivered on the Perfexion than the model C/4C. In a prospective, randomized 200-patient comparison between the Perfexion and the model 4C, Régis et al\(^21\) found that the median time in the treatment room was reduced from 65 to 45 minutes.\(^22\) However, that improvement is still very modest compared with the delivery efficiency of using 10MV FFF VMAT. Almost all such treatments can be delivered in less than 20 minutes, regardless of total GTV or number of tumors.

CONCLUSION

We found that VMAT can achieve clinically similar plan quality to GK plans that we have been delivering at substantially increased treatment efficiency, especially with a high-intensity LINAC. Across all clinically delivered GK plans we studied, multiarct VMAT rendered improved conformity, equivalent dose falloff, equivalent moderate and low isodose spill, and equivalent mean dose for multiple metastasis treatments. For some, the single-isocenter VMAT approach may constitute an attractive substitute to multiple isocenter methods.

Disclosure

Drs Fiveash, Popple, and Thomas have received honoraria from Varian Medical Systems to discuss the University of Alabama at Birmingham experience in treating patients with the TrueBeam STx. Drs Fiveash and Popple have served as consultants for Varian Medical Systems in development and implementation of treatment planning methods and technology. Dr Thomas is further supported by an NIH T32 training grant maintained by the University of Alabama at the Birmingham Medical Scientist Training Program. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

The study here describes a dosimetric comparison between Gamma Knife (GK) 4C and VMAT using Flattening Filter Free (FFF) delivery mode. It has been proven\(^1\) that the Gamma Knife Perexion (PFX) can achieve better planning than the GK 4C in terms of conformity, percentage of coverage, and dose gradient index. With improvements between 4C and PFX, the user does not have to compromise with the number of isocenters and plug-in patterns. Differences between GK 4C and PFX in a dosimetric point of view are meaningful, but the automation of the bed and collimators have considerably expanded the possibilities of GK SRS.\(^2\) So, in terms of a dosimetric comparison, 4-arc VMAT may constitute a desirable alternative to GK 4C stereotactic radiosurgery (SRS). But a recent study shows that GK PFX is still the most powerful system\(^3\) for SRS. The study here describes a dosimetric comparison. We can assume that with more than 20 years of experience and clinical outcome, GK SRS is a reliable system. Despite dose measurements with ion chamber, study of the dose distribution with local gamma index or Monte Carlo comparison, we cannot be assured by the quality of the delivered treatment with the author’s Varian TrueBeam STx for this kind of treatment (multiple brain metastasis) and parameters (4 noncoplanar arc, small asymmetric fields, very high dose rate). Plans on Eclipse were optimized on the same volume as the GK, ie, CTV. This leads to the question of the patient immobilization and positioning, which is essential in LINAC-based SRS. A recent study\(^4\) shows that it is possible to treat without taking any margin but only with a high-quality of stereotactic masks, well-calibrated and optimized image guidance, and an experienced team (radio oncologist, neurosurgeon, medical physicist, and therapist) in stereotactic radiotherapy procedures. Unless that, it seems not reasonable to treat LINAC-based SRS without taking any CTV margin.\(^5\)\(^6\)

**COMMENTS**

This is an important manuscript in that it demonstrates the possibility of a VMAT plan in producing a plan with a sharp dose falloff with relatively low dose to the surrounding brain. The plans appear to be equivalent to what one may see with a Gamma Knife plan. While the dose used for each lesion for plan comparison were all 18 Gy, it is not far off to develop plans that use more standardized brain metastases dosing which varies by size. The technique, I am sure, is being refined. Very small lesions measuring a few millimeters in diameter may be an advantage of Gamma Knife over this technique. I look forward to more research with this technique, particularly for smaller lesions and variable dosing based on size.

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Because the new generation of linear accelerators is now available using the VMAT technology, it becomes very apparent that there exist numerous options for providing radiosurgery for this patient population. It would be interesting to see if this improvement would stand up in a comparison with the Gamma Knife Perfexion system in comparison with the model C/4C used in this manuscript. That being said, the key to an effective treatment strategy truly depends on a collaborative approach between the neurosurgeon, radiation oncologist, and physicist. The treatment team must be able to provide effective QA of the system being used and deliver the highest quality of treatment regardless of which delivery system that team chooses to use.

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Jonathan H. Sherman
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Single fraction stereotactic radiosurgery for multiple brain metastases

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Abstract
Introduction: Due to the neurocognitive side effects of whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS) is being used with increasing frequency. The use of SRS is expanding for patients with multiple (>4) brain metastases (BM). This study summarizes our institutional experience with single-fraction, linear-accelerator-based SRS for multiple BM.

Methods and materials: All patients who were treated between January 1, 2013, and September 30, 2015, with single-fraction SRS for ≥4 BM were included in this institutional review board–approved, retrospective, single-institution study. Patients were treated with linear accelerator–based image guided SRS.

Results: A total of 59 patients with ≥4 BM were treated with single-fraction SRS. The median follow-up was 15.2 months, and the median overall survival for the entire cohort was 5.8 months. The median number of treated lesions per patient was 5 (range, 4-23). Per patient, the median planning target volume (PTV) was 4.8 cc (range, 0.7-28.8 cc). The prescribed dose across all 380 BM for the 59 patients ranged from 7 to 20 Gy. The median of the mean dose to the total PTV was 19.5 Gy. Although the number of treated lesions (4-5 vs ≥6) did not influence survival, better survival was noted for a total PTV <10 cc versus ≥10 cc (7.1 vs 4.2 months, respectively; P = .0001). A mean dose of ≥19 Gy to the entire PTV was also associated with increased survival (6.6 vs 5.0 months, respectively; P = .0172). Patients receiving a dose of >12 Gy to ≥10 cc of normal brain had worse survival (5.1 vs 8.6 months, respectively; P = .0028).

Meeting information: This work was presented in poster format at the 2016 Annual Meeting of the American Society for Radiation Oncology, September 25-28, 2016, Boston, MA.

Sources of support: This research was supported by Varian Medical Systems, Grant Number 283-0092.

Conflicts of interest: John Kirkpatrick and Justus Adamson own Clearsight Radiotherapy Products LLP. Justus Adamson reports a consulting arrangement with Immunolight LLC. Both of these relationships are unrelated to the study. Fang-Fang Yin, John Kirkpatrick, and Grace Kim have received research funding from Varian Medical Systems.

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Conclusion: In single-fraction SRS for patients with multiple BM, smaller total tumor volume, higher total dose, and lower volume of normal brain receiving >12 Gy were associated with increased survival. These data suggest that using SRS for the treatment of multiple BM is efficacious and that outcomes may be affected more by total tumor volume than by the number of lesions.

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Introduction

Brain metastases (BM) can occur in up to 10% to 40% of patients with cancer.1,2 Despite advances in diagnosis and treatment, BM are typically associated with a limited life expectancy.3,4 Surgery and whole brain radiation therapy (WBRT) may improve local control and survival for patients with a limited number of BM.1,2 However, WBRT causes late neurocognitive deficits without offering a survival advantage compared with a more focal radiation therapy approach such as stereotactic radiosurgery (SRS).5,6 The use of SRS alone provides very high rates of tumor response and local control.7,8,9

SRS is recommended for patients with a limited number (ie, 1-3) of BM.10,11 Evolving radiation therapy and imaging technology and recognition of the long-term side effects associated with WBRT have increased interest in SRS for patients with larger numbers of BM.12 A prospective trial examining SRS alone for up to 10 BM demonstrated no survival or local recurrence differences in patients who were treated for 2 to 4 BM versus 5 to 10 BM.13 In fact, cumulative tumor volume and largest treated tumor diameter were more significant predictors of outcome than the number of treated lesions.

An obstacle to the use of SRS for larger numbers of BM is the treatment time required when each lesion is treated with a separate radiation therapy plan. Single-isocenter, multitarget (SIMT), volumetric modulated arc therapy (VMAT) for SRS planning and delivery enables the simultaneous treatment of several lesions. This technique was shown to substantially reduce treatment time, with possible improvements in conformity indices and normal brain dose, compared with multiple isocenter plans.14,15 Data on clinical outcomes using this technique are sparse, with one study showing high local control and a 6-month overall survival (OS) rate of 60%.16

The choice between SIMT and WBRT for the treatment of patients with ≥4 BM remains an unresolved issue. This study was performed to explore our institutional experience with SIMT for the treatment of multiple BM to identify those patients who might benefit the most from this procedure.

Methods and materials

Study population

This study was a retrospective review performed at the Radiation Oncology Department of Duke University Medical Center in Durham, North Carolina. From a chart review, we identified patients who underwent SRS as a treatment for ≥4 BM between January 1, 2013, and September 30, 2015. The study was approved by our institutional review board. Inclusion criteria were age ≥18 years, ≥4 BM treated with single-fraction SRS, and histologically proven extracranial malignancy. Primary brain tumors were excluded, and BM biopsy was not required.

Collected data included patient demographics; disease characteristics; Karnofsky Performance Status; initial and salvage brain treatments; number and volume of treated BM; and dosimetric parameters such as technique, planning target volume (PTV) dose, and dose to organs at risk (OARs). Recursive partitioning analysis (RPA) and Graded Prognostic Assessment scores for BM were calculated from these clinical data.3,18 Survival status and the date of death or last follow-up were documented.

Treatment

All patients underwent a computed tomography (CT) simulation with a frameless SRS thermoplastic mask (BrainLAB, Munich, Germany). A thin-cut (1 mm) CT scan of the brain was fused with a thin-cut, gadolinium contrast–enhanced, axial, 3-dimensional, T1-weighted magnetic resonance imaging (MRI) scan. Gross tumor volume included the enhancing lesions on the contrast-enhanced T1 sequence on the MRI scan. PTV was created by adding a 1-mm margin to the gross tumor volume. The dose was normalized so that the 100% isodose line encompassed all or nearly all of the target volume (typically >99%) such that the maximum dose ranged between 110% and 125%. This corresponded to selecting the 80% to 90% isodose line when the dose is normalized to be 100% at the maximum dose point.

Doses were prescribed on the basis of lesion size and volume. The Radiation Technology Oncology Group 90-05 dosing guidelines19 were typically followed, but doses were decreased at the treating physician’s discretion according to tumor location (ie, brainstem), V12Gy for the brain, and doses to OAR from previous radiation treatments. All patients were contoured using the BrainLAB iPlan RT Image software (BrainLAB, Munich, Germany). VMAT treatment plans were then prepared with the Varian Eclipse (Varian Medical Systems, Palo Alto, CA) treatment planning system, using beam geometry and optimization criteria as previously described.20,21 One patient was treated using
dynamic conformal arcs with a single isocenter per target; the treatment plan was prepared using the BrainLAB iPlan RT Dose treatment planning software. Treatment was delivered on a Novalis TX linear accelerator (Varian Medical Systems) using orthogonal kV imaging and cone beam CT for 6-degree-of-freedom position adjustment prior to treatment.\textsuperscript{22}

### Statistical methods

The primary objective of this retrospective study was to describe OS in this patient population as a function of patient demographics, disease characteristics, and treatment parameters. OS-SRS was defined as the time from SRS until death or last follow-up, if the patient remained alive. OS-SRS was calculated using the Kaplan-Meier estimator. Univariate and multivariate Cox proportional hazards models were used to identify predictors of OS. Given the small sample size, these analyses are intended to be descriptive in nature because the study lacks the power to draw definitive conclusions. On the basis of the study size and number of events (deaths), the multivariate analyses focused on 4 potential predictors: age ($\geq 65/ < 65$ years), total volume of all brain lesions ($\geq 10/ < 10$ cc), mean dose to the entire PTV ($\geq 19/ < 19$ Gy), and the volume of normal brain (total brain volume—PTV) exposed to $\geq 12$ Gy (V12Gy; $\geq 10/ < 10$ cc). The multivariate model using backward variable elimination employed a 0.10 significance level for variable retention. SAS (SAS Institute, Cary, NC) Version 9.3 was used for all analyses.

### Results

Fifty-nine patients met the study inclusion criteria. As of February 6, 2016, the median follow-up was 15.2 months. Patient and treatment characteristics are summarized in Table 1. The average age was 61.8 years (range, 40.5-83.8 years). The most common primary histology was non-small cell lung cancer (35.6%). Most patients had a Karnofsky Performance Status of $\geq 70$ (93.2%), an RPA $\geq 2$ (93.2%), and a Graded Prognostic Assessment $\geq 1$ (71.2%). More than half of patients (54.2%) had undergone previous brain radiation therapy, with 22 patients (37.3%) receiving WBRT alone and 8 (13.5%) previously treated with SRS alone. Four patients (6.8%) had previously

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<td>61.8 (11.1)</td>
</tr>
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<td>Primary Tumor</td>
<td>Non-small cell lung cancer</td>
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<tr>
<td></td>
<td>Breast</td>
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<tr>
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<td>Melanoma</td>
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<tr>
<td></td>
<td>Renal Cell Carcinoma</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Previous brain radiation therapy\textsuperscript{b}</td>
<td>WBRT</td>
</tr>
<tr>
<td></td>
<td>PBRT</td>
</tr>
<tr>
<td></td>
<td>SRS alone</td>
</tr>
<tr>
<td></td>
<td>WBRT + SRS</td>
</tr>
<tr>
<td>Previous surgery</td>
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</tr>
<tr>
<td>Treated lesions</td>
<td>No. of treated lesions, median (range)</td>
</tr>
<tr>
<td></td>
<td>Median volume of all lesions within a patient, median (range), cc</td>
</tr>
<tr>
<td></td>
<td>Total volume of all lesions within a patient, median (range), cc</td>
</tr>
<tr>
<td>Fractionation and dosing</td>
<td>Median dose to all lesions within a patient, median (range), Gy</td>
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<tr>
<td></td>
<td>Mean dose to total PTV, median (range)\textsuperscript{c}, cc</td>
</tr>
<tr>
<td>Treatment technique</td>
<td>Volumetric modulated arc therapy</td>
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<tr>
<td></td>
<td>Dynamic conformal arcs</td>
</tr>
<tr>
<td>Isocenters</td>
<td>Single isocenter</td>
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<tr>
<td>Further treatment</td>
<td>Repeat SRS</td>
</tr>
<tr>
<td></td>
<td>WBRT</td>
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</table>

PBRT, partial brain radiation therapy; PTV, planning target volume; SD, standard deviation; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

\textsuperscript{a} Except where noted otherwise.

\textsuperscript{b} The denominator for these percentages was the 32 patients who received any prior brain radiation therapy.

\textsuperscript{c} Mean dose to the PTV was calculated based on mean dose to the aggregate planning target volume, not the average of the mean doses to the individual lesions.
undergone surgery for BM due to mass effect, symptoms, or size.

A median of 5 lesions were treated per patient (range, 4-23 lesions). The median of the total PTV of all treated lesions in a patient was 4.8 cc (range, 0.7-28.8 cc). Fifty-five patients (93.2%) were treated with a single isocenter. The most commonly used treatment technique was VMAT (98.3%). A single patient was treated using dynamic conformal arc planning with 4 isocenters. The PTV prescription dose across all doses ranged from 7 to 20 Gy. The median of the mean dose to the total treated PTV was 19.5 Gy (range, 12.7-24.5 Gy).

Dose constraints

Doses to OARs were well within normal limits. The median maximum point dose to the brainstem was 3.4 Gy (range, 0.4-12.8 Gy) for the entire cohort of 52 patients (88.1%) who did not have brainstem metastases. For the 3 patients who were treated with 2 isocenters, the median maximum brainstem dose was 2.3 Gy (range, 1.9-5.7 Gy).

The median maximum dose to the optic chiasm was 1.7 Gy (range, 0.3-9.1 Gy). For the 55 patients who were treated with SIMT, the median dose was 1.7 Gy (range, 0.3-9.1 Gy) versus 1.0 Gy (range, 0.5-3.2) for the 4 patients who were treated with more than 1 isocenter.

The median V12Gy was 13.7 cc (range, 3.8-59.5 Gy) for all patients. In the 55 SIMT patients, the median V12Gy was 13.7 cc (range, 3.8-59.5 Gy) versus 6.6 cc (range, 3.9-18.2 Gy) for the 4 patients who were treated with a single fraction but more than 1 isocenter.

Survival analysis

For the entire patient cohort, the median OS was 5.8 months (95% confidence interval [CI], 4.9-6.6; Fig 1). One-year survival was 25.5% (95% CI, 14.2%-38.4%), and 2-year survival was 6.4% (95% CI, 0.6%-22.9%). Univariate analyses provided no evidence of survival differences according to tumor histology, sex, age, prior treatments for BM (WBRT, SRS, or surgery), RPA classification, number of fractions used, or number of isocenters. In addition, the number of treated lesions did not appear to influence survival; no significant difference was found between patients who were treated for 4 to 5 lesions (n = 42) versus patients who were treated for 6 or more metastases (n = 17; median OS: 5.6 months [95% CI, 4.2-8.5] vs 5.8 months [95% CI, 3.4-6.8], respectively; P = .66).

An analysis of parameters related to tumor volume (Fig 2) and dose (Fig 3) revealed potential impacts on survival. While these results need confirmation in a larger study with adequate power to detect true differences, our study provided evidence of a potential increase in survival in patients with a total PTV <10 cc compared with patients with a ≥ 10 cc total PTV (median OS: 7.1 months [95% CI,
5.4-14.4] vs 4.2 months [95% CI, 2.2-5.3], respectively; \( P = .0001 \). Patients whose largest lesion was <5 cc versus ≥5 cc also had improved survival (median OS: 6.8 months [95% CI, 5.2-14.4] vs 4.2 months [95% CI, 2.2-5.3], respectively; \( P = .0006 \)). A combined PTV mean dose of ≥19 Gy versus <19 Gy demonstrated a survival advantage (median OS: 6.6 months [95% CI, 5.2-14.4] vs 5 months [95% CI, 3.4-5.8], respectively; \( P = .0172 \)). V12Gy >10 cc was associated with a poorer survival (median OS: 8.6 months vs 5.1 months; \( P = .0028 \)).

Figure 2  Overall survival according to volume parameters. (A) Overall survival according to total PTV of brain metastases. (B) Overall survival according to largest lesion volume.
From the multivariate analysis including age, total volume of all BM, mean dose to the entire PTV, and V12Gy as potential predictors, the only significant predictor of survival was the total volume of BM, which showed worse survival in patients with a total PTV $\geq 10$ cc (hazard ratio [HR]: 3.34; 95% CI, 1.74-6.43; $P = .0003$).

**Salvage therapy**

Of the 43 patients with post-SIMT SRS imaging, 5 patients had local failure; in all 5, local failure was accompanied by distant failure in the brain. Sixteen of the 59 patients in the study did not undergo post-SRS imaging due to death.
and/or progression of extracranial disease. The crude intracranial local failure rate was 11.6% (5 of 43 patients). All patients who had local failure also presented with distant failure. There were 21 cases of distant failure alone (crude rate, 48.8%). Two cases (4.7%) of radionecrosis were observed.

Sixteen patients (27.1%) underwent further radiation therapy, including 4 patients who received additional treatment with WBRT only, 2 who received WBRT and SRS, and 10 who received additional treatment only with SRS. Of the 12 patients (20.3%) who received additional SRS, 11 had 1 additional course and 1 had 3 additional courses. The median time between the first and second SRS treatments was 4.0 months. For the 6 patients (10.2%) who received post-SRS WBRT, the median time from SRS to WBRT was 4.1 months.

Discussion

As systemic therapy continues to improve with the growing role of immunotherapy, patient survival is improving. Treating BM while minimizing radiation’s impact on quality of life and neurocognition becomes ever more crucial. The use of SRS has been traditionally limited to 1 to 3 BM, as illustrated by the inclusion criteria of pivotal SRS prospective trials. However, advances in treatment delivery and MRI have overcome the technical difficulties of simultaneously treating ≥4 BM. Little has been published on the efficacy of single-fraction, single-isocenter SRS for multiple BM.

This study provided no evidence that patient survival was significantly affected by the number of treated metastases. Although these analyses should be interpreted cautiously given the study’s lack of power and the number of comparisons, the results suggest that volumetric and dose parameters were associated with survival, including total PTV, volume of the largest treated lesion, and normal brain V12Gy. These variables are interrelated and reflect, in essence, the significance of total intracranial tumor volume on survival in the setting of SRS treatment. Mean dose was also associated with improved survival. However, mean dose is inversely related to tumor volume, and patients with a higher PTV received lower delivered doses and exhibited a lower V12. Ultimately, the only factor that was significant in the multivariate analysis was total tumor volume.

Previously published results underscored that the number of intracranial metastases is not a prognostic factor for survival. The significant effect of cranial tumor volume on survival has been demonstrated in both retrospective and prospective trials. Bhatnagar et al treated patients with 4 to 18 BM (median = 5) with SRS, and multivariate analyses indicated that smaller cranial tumor volume was associated with improved survival regardless of the number of tumors. Yamamoto et al demonstrated that the diameter of the largest tumor (≥1.6 cm) and cumulative tumor volume (≥1.9 mL) were each significant in influencing survival, whereas a number of tumors greater than 4 was not significant.

Lower total lesion volume is associated with improved SRS response and may also permit higher treatment doses to each lesion, which is another parameter that is associated with better survival. As reported in other SRS trials for 1 to 3 metastases, local control as well as survival are influenced by the dose to each lesion. A similar impact of dose is also seen in this study, where a mean dose of ≥19 Gy to the entire PTV had a beneficial effect on survival.

Survival was adversely affected by the volume of normal brain receiving doses higher than 12 Gy. Normal brain exposure in SRS treatments as measured by V12Gy has been associated with increased toxicity, including radionecrosis and radiographic changes. To our knowledge, a relationship between V12Gy and other potential side effects, such as neurocognitive toxicity and neurologic death, has not been reported. Similarly, the significance of tumor volume in survival warrants an analysis of whether patients with larger-volume BM are more likely to experience neurologic death or whether these patients have a larger burden of systemic disease that leads to higher mortality rates.

In other trials of patients with multiple BM, median survival after SRS ranged from 6.2 to 8.6 months. Our median survival was 5.8 months and was not comparable to these published studies because approximately 60% of our patients were treated previously with brain radiation therapy, including SRS and WBRT. With improved chemotherapy and immunotherapy, patients face the dilemma of repeat brain radiation with increasing frequency. In patients who previously received WBRT, salvage SRS is often optimal for local control of recurrent BM while maximizing quality of life.

Much has been published about the negative effects of WBRT. Most recently, data from the prospective, randomized QUARTZ trial indicate that in patients with NSCLC and BM, WBRT does not improve survival or quality of life when compared with supportive care alone. Rather than using WBRT, patients may receive multiple courses of SRS safely. Our results also illustrate that appropriately chosen patients with multiple metastases may be treated with repeated courses of SMT SRS. Factors that determine the decision to use repeat SRS versus WBRT for salvage include the number of distant BM, radioreistant histology, time to failure, or previous whole brain administration. Retreatment for each patient is considered on a case-by-case basis, but in general, fewer BM, melanoma or renal cell histology, previous whole brain administration, or longer time to failure would support the use of salvage SRS.

Conclusions

These findings are hypothesis-generating and are limited by the study sample size, lack of power, number of
comparisons, and the study’s retrospective and single-institution nature. To our knowledge, this is the largest reported experience to examine single-fraction SIMT for multiple BM. In our experience, this technique is feasible, readily implemented, and well tolerated by patients, although robust quality assurance and careful correction of translational/rotational deviations in position are essential. SIMT is associated with favorable survival in patients with 4 or more BM, particularly when the total metastatic lesion volume, rather than the number of lesions, is low. A prospective trial examining SIMT in patients with 4 to 10 BM has been opened to better define its efficacy and effect on neurocognition (NCT02886572 at clinicaltrials.gov).

References

32. Sneed PK, Mendez J, Veeman-van den Hoek JG, et al. Adverse radiation effect after stereotactic radiosurgery for brain metastases:


11. Linear Accelerator Treatment Data (including Cyberknife® & Similar Equipment)

Campus – if multiple sites: CHS NorthEast

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<thead>
<tr>
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<tr>
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<td>Radiation treatment delivery</td>
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<tr>
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<td>Radiation treatment delivery (&lt;5 MeV)</td>
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<tr>
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<tr>
<td>77406</td>
<td>Radiation treatment delivery (&gt;20 MeV)</td>
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**Simple Treatment Delivery**

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**Intermediate Treatment Delivery**

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<td>Intensity modulated radiation treatment (IMRT) delivery with or CPT codes 77385 and/or 77386 and/or G6015</td>
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<td>77372</td>
<td>Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; linear accelerator</td>
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<td>77373</td>
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<td>G0339</td>
<td>(Image-guided) robotic linear accelerator-based stereotactic radiosurgery in one session or first fraction</td>
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<tr>
<td>G0340</td>
<td>(Image-guided) robotic linear accelerator-based stereotactic radiosurgery, fractionated treatment, 2nd-5th fraction</td>
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<td>Intraoperative radiation therapy (conducted by bringing the anesthetized patient down to the LINAC)</td>
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<td></td>
<td>Limb salvage irradiation</td>
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<td></td>
<td>Hemibody irradiation</td>
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<td>Total body irradiation</td>
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**Other Treatment Delivery Not Included Above**

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**Total Procedures – Linear Accelerators**

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**Gamma Knife® Procedures**

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<td>Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of one session; multisource Cobalt 60 based (Gamma Knife®)</td>
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Project Identification Number: G-5868-98

Issued to: The North Carolina Baptist Hospitals, Inc.
Medical Center Boulevard
Winston-Salem, NC 27157

The North Carolina Department of Health and Human Services, pursuant to the North Carolina Health Planning and Resource Development Act of 1978, G.S. § 131E-75, et seq., as amended and recodified, G.S. § 131E-175, et seq., hereby finds and certifies that the new institutional health service proposed by the person listed above is consistent with, or as conditioned is consistent with, the plans, standards, and criteria prescribed by the Act and the rules and regulations promulgated thereunder. The findings of the Department are attached hereto and incorporated by reference.

This Certificate affords the person listed above the opportunity to proceed with development of the proposed new institutional health service in a manner consistent with the plans, standards, and criteria prescribed by the Act and the rules and regulations promulgated thereunder. This Certificate includes and is limited to:

SCOPE: The North Carolina Baptist Hospitals, Inc. shall acquire no more than one (1) Leksell Gamma Knife pursuant to Policy No. 8 of the 1998 State Medical Facilities Plan.

CONDITIONS: See Reverse Side

PHYSICAL LOCATION: North Carolina Baptist Hospitals
Medical Center Blvd, Winston-Salem, NC 27157

MAXIMUM CAPITAL EXPENDITURE: $2,895,000

TIMETABLE: See Reverse Side

FIRST PROGRESS REPORT DUE: June 30, 1999

This Certificate is limited to the person listed above and is not transferable or assignable. This Certificate may be withdrawn as provided in G.S. § 131E-189, and the rules and regulations promulgated thereunder.

Issuance of this Certificate does not supplant provisions or requirements embodied in codes, ordinances, statutes other than G.S. § 131E-175, et seq., rules regulations or guidelines administered or enforced by municipal, state or federal agencies or the agent thereof.
CONCLUSIONS:
G-5868-98

1. North Carolina Baptist Hospitals, Inc. shall materially comply with all representations made in its certificate of need application.

2. Prior to issuance of the certificate of need, The North Carolina Baptist Hospitals, Inc. shall provide the Certificate of Need Section with copies of written policies establishing the gamma knife as a regional resource having no administrative, clinical or charge requirements which would impede physician referrals for whom gamma knife procedures would be appropriate.

3. North Carolina Baptist Hospitals, Inc. shall provide, at the request of the Certificate of Need Section, documentation of the number and type of stereotactic radiosurgery procedures performed with the LINAC and the Gamma Knife in accordance with data format and reporting requirements that will be formulated by the Agency.

4. North Carolina Baptist Hospitals, Inc. shall acknowledge acceptance and compliance with all conditions stated herein to the Certificate of Need Section in writing prior to issuance of the certificate of need

A letter acknowledging acceptance and compliance with all conditions stated in the conditional approval letter was received by the Certificate of Need Section on November 10, 1998. Condition 2 was satisfied on November 2, 1998.

TIMETABLE:

Financing
Obtaining funds necessary to undertake project February 5, 1999

Design
Completion of preliminary drawings April 1, 1999
Completion of final drawings and specifications June 1, 1999
Approval of final drawings and specifications by Construction Section, DFS July 1, 1999

Construction
Contract Award August 2, 1999
25% completion of construction August 16, 1999
50% completion of construction September 13, 1999
75% completion of construction October 13, 1999
Completion of construction November 15, 1999
Occupancy/offer of service December 20, 1999

Acquisition of Equipment

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<th>Gamma Knife</th>
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<td>September 22, 1999</td>
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<tr>
<td>Arrival of equipment</td>
<td>November 22, 1999</td>
</tr>
<tr>
<td>Operation of equipment</td>
<td>December 1, 1999</td>
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Leksell Gamma Knife Icon
Average number of treatments per Icon center* and region 2017

Asia: 770, Europe: 730, Middle East & Africa: 379, North America: 591

Average number of treatments per Icon center worldwide: 671

*Based on reports submitted by top 15 Icon centers by treatment volume