Stereotactic irradiation for treatment of acoustic neuromas

Irradiação estereotáctica no tratamento de neurinomas de acústico

Michael T. Selch

ABSTRACT

Stereotactic cerebral irradiation is a radiotherapeutic technique for precise delivery of ionizing irradiation to an intracranial target with simultaneous sparing of adjacent parenchyma. Treatment can be administered by a multi-source cobalt-60 device (gamma knife) or a dedicated linear accelerator. The target dose can be delivered in a large, single fraction (stereotactic radiosurgery SRS) or in multiple, daily increments (stereotactic radiotherapy SRT). The latter approach combines the physical dose localization advantages of SRS with the radiobiologic benefits of dose fractionation. This literature review will present the rationale and clinical results of SRS and SRT for the treatment of acoustic neuromas. Emphasis will be placed on tumor control, imaging outcome and cranial nerve preservation. The findings demonstrate that SRS and SRT represent reasonable therapeutic options for patients with acoustic neuromas.

Key-words: acoustic neuromas, stereotactic radiosurgery, fractionated stereotactic radiotherapy.

SUMÁRIO

A radiação cerebral estereotáxica é uma técnica para aplicação precisa de radiação ionizante para um alvo intracraniano com preservação simultânea do parênquima cerebral adjacente. O tratamento pode ser administrado por equipamentos que utilizam múltiplas fontes de cobalto-60 (gamma-knife) ou através de aceleradores lineares. A dose ao alvo pode ser administrada através de uma alta fração única (radiocirurgia estereotáxica - SRS) ou através de múltiplas frações diárias (radioterapia estereotáxica - SRT). A última combina as vantagens físicas de localização dosimétrica da SRS com os benefícios radiobiológicos do fracionamento de dose. Esta revisão de literatura apresenta as indicações e resultados clínicos da SRS e SRT para o tratamento dos neurinomas do acústico. Ênfase foi dada para o controle tumoral, resultados de imagem e preservação de nervos cranianos. Os resultados demonstram que a SRS e a SRT representam importantes opções terapêuticas para pacientes com neurinomas do acústico.

Palavras-chave: neurinomas do acústico, radiocirurgia estereotáxica, radioterapia estereotáxica fracionada.
Acoustic neuromas are benign Schwann cell neoplasms affecting the vestibular branch of the eighth cranial nerve. Properly termed “vestibular Schwannomas”, their histologic appearance belies a potentially aggressive clinical course. Unchecked tumor growth results in compression of the brainstem and adjacent cranial nerves. Microsurgery has represented the standard of care for these tumors. Local relapse rates following total removal are <5% but microsurgery may result in deafness and facial paresis in some cases. Treatment of acoustic neuromas represents one of the success stories of stereotactic irradiation. This review will describe the rationale and management of acoustic neuromas by stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT).

**RATIONALE FOR SRS**

Stereotactic cerebral irradiation was developed by Swedish neurosurgeon Lars Leksell in 1951. Treatment of acoustic tumors by this technology was proposed in published form in 1971. Subsequent reports from the Karolinska Institute provide radiobiologic credence to SRS. Karolinska Institute cranial nerve V and VII function and retention of speech discrimination despite some decrement in pure tone threshold.

The hallmark of stereotactic irradiation is a steep falloff in dose deposition measured from the center of the field to the periphery. This physical principle is exploited to irradiate minimally invasive benign tumors without risk of marginal relapse while simultaneously protecting uninjured adjacent parenchyma. SRS can be delivered by the gamma-knife or a dedicated linear accelerator. Each device has vocal proponents. Arguments concerning superiority of one device over another with respect to dose delivery are spurious. Dose deposition can be analyzed according to the steepness or shallowness of dose falloff in a particular plane of view. Analysis of this parameter for a single isocenter demonstrates no appreciable difference between a gamma unit and a linear accelerator using either multiple fixed beams or arcs. When assessing minimum and maximum falloff distances, gamma-knife and linear accelerator SRS demonstrate similar dose profiles.

In vitro and in vivo laboratory models of human acoustic neuromas provide radiobiologic credence to SRS. Karolinska Institute investigators, using an in vitro organ culture system, analyzed cellular changes after single-doses of 30-150 Gy. Irreversible cellular injury was noted at the earliest post-exposure period (ie, 3-5 hours). Alterations included vesiculation, appearance of myelin bodies and basal membrane disintegration. Alterations progressed over two weeks with the time of maximum injury dependent upon dose. Linskey et al analyzed volume reduction of neuromas implanted into the subrenal capsule of athymic mice 2-12 weeks following 10-40 Gy. Significant volume reductions of 33-45% were recorded following 20 and 40 Gy but no significant change occurred after 10 Gy. Volume reductions were not accompanied by evidence of necrosis. This may be a result of insufficient time for appearance of this finding. Human autopsies following SRS for acoustic tumors reveal central tumor necrosis/fibrosis but the interval to histologic analysis in these cases is longer than that used by Linskey and associates. Results of these investigations suggest single dose ionizing irradiation in the range used for acoustic neuromas produces cellular injury on a time scale not compatible with reproductive cell death due to radiation-induced double strand DNA breakage. Traditional DNA injury likely does result from SRS and contributes to control of acoustic neuroma. Given the low proliferative capacity of acoustic neuromas, the time course required for reproductive cell death is longer than that used in the laboratory models.

Despite decades of implementation, use of SRS for acoustic neuromas remains empiric. Level I evidence from randomized trials comparing microsurgery to SRS is absent. Retrospective series confirm superiority of SRS with respect to retention of useful hearing, preservation of VII nerve function and quality of life. Pollock et al published a non-random, prospective, blinded observational comparison of 46 gamma-knife patients versus 36 microsurgery patients. After a mean 42 month follow-up, 96% of SRS patients had normal VII nerve function compared to 75% of microsurgery patients (p<0.01). Preservation of useful hearing (Gardner-Robertson Grade I-II) occurred in 63% of SRS patients compared to 54% of microsurgery patients (p=0.001). The microsurgery group demonstrated significant decline in one or more quality of life indicators. Serious morbidity was more common in the microsurgery patients: 14% CSF leak, 17% requiring intervention for eyelid protection procedure. There were no tumor relapses in the microsurgical patients compared to 4% failure after SRS (p=0.5). Kaylie et al evaluated 11 microsurgery and 8 gamma-knife SRS series involving 2579 and 875 patients, respectively in a meta-analysis. Local control rate with microsurgery was 98% compared to 91% for SRS with no significant differences in preservation of facial nerve function or useful hearing. The microsurgery group demonstrated significantly lower rate of overall morbidity (22% versus 35%) and major morbidity (5% versus 16%). The meta-analysis is flawed by inclusion of patients irradiated from 1969 onward, reflecting SRS techniques no longer considered optimal. There were seven perioperative fatalities in the microsurgical group compared to no treatment-associated mortality after SRS. Available retrospective and prospective series support use of SRS as an alternative to mi-
crosurgery for selected neuromas in the absence of a definitive randomized clinical trial.

**GAMMA-KNIFE SRS RESULTS**

Kondziolka et al reported the initial United States gamma-knife experience with 162 patients (Table 1). Patients were treated with >1 isocenter and the 50-70% isodose line at the margin of the lesion43. This planning philosophy resulted in a conformal dose distribution at the cost of tumor dose homogeneity. Initial experience was characterized by prescribed doses in the range of 14-20 Gy (median 17 Gy). Prescribed dose was never established through the mechanism of a phase II dose-searching trial. Tumor growth or regression was defined as ± 2 mm change. This arbitrary criterion represented approximately twice the error in determining the size of an acoustic neuroma with available imaging studies50. The definition may overestimate the impact of SRS on acoustic tumors. Several natural history studies document growth rates of untreated acoustic neuromas <2 mm/year8,102. Battaglia et al compared the growth rate of untreated acoustic neuromas to untreated acoustic neuromas following an average of 38 months with control rates reported in the SRS literature6. The average growth rate of untreated tumors was 0.7 mm/year. Enlargement <1 mm/year was recorded in 82% and 18% enlarged >1 mm/year. The authors reported an 87% “local control” rate in the observed patients using the University of Pittsburgh definition of relapse.

The initial University of Pittsburgh experience confirmed earlier Karolinska Institute findings. Response rate increased with follow-up. Respective 1-, 2-, 3-, 4- and 5- year rates were 26%, 47%, 59%, 64%, and 76%. Tumor progression, whether transient or permanent, occurred only during the first three years of follow-up. Respective 1-, 2- and 3- year rates were 0.7%, 4.7% and 3.1%. Surgical salvage of failed SRS was not more challenging than a de novo tumor77. Retention of pretreatment VII nerve function occurred in 79% of all patients and 85% of those with initial normal nerve function. Respective rates of preserving cranial nerve V function for the entire population and among those with normal initial function were 73% and 84%. Useful hearing was preserved in 49% of patients.

Subsequent analyses of this initial demonstrated that neither tumor minimum nor maximum doses significantly influenced local control rate20,50. By contrast, injury of cranial nerves V, VII and VIII was significantly related to dose, a finding confirmed in many other centers32,37,61,80. Rates of freedom from injury to either cranial nerve V or VII were 100% among those receiving <14 Gy, 82% receiving 14-15 Gy and 65% for those receiving >15 Gy20. Cranial neuropathy was also strongly related to tumor size, a finding confirmed by investigators at Charlottesville60,80. The rate of fifth nerve injury was 0% for lesions with a pons-petrous tumor dimension of ≤1cm compared to 52% for larger lesions. The rate of seventh nerve injury was 5% for tumors with mid-porous transverse diameter of ≤2cm compared to 47% for larger lesions51. The incidence of cranial neuropathy was significantly related to use of reformatted CT imaging.

**Table 1 - Outcome Following Gamma-Knife SRS for Acoustic Neuromas**

<table>
<thead>
<tr>
<th>Series</th>
<th># Pts.</th>
<th>Dose (Gy)</th>
<th>Follow-up (mos)</th>
<th>Local Control</th>
<th>Imaging Response</th>
<th>Retention</th>
<th>VII Injury*</th>
<th>V Injury*</th>
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* Any degree of injury, transient or permanent.
for treatment planning as compared to MRI, a finding also reported by Mayo Clinic investigators. Among those planned with CT, the rate of cranial nerve V injury was 36% compared to 8% for those with MRI-based planning (p<0.0001). Seventh nerve injury occurred in 27% with CT planning compared to 8% for MRI-planned patients (p=0.0001). Total loss of hearing occurred in 51% with CT planning versus 14% with MRI planning (p<0.001).

These findings led to an evolution in technique and the current approach at the University of Pittsburgh has become a clinical standard. The recommended minimum peripheral dose has been reduced to 12-13 Gy although some have cautioned that follow-up of patients receiving “low dose” is too short to conclude that the long-term local control rate will equal that of the “high dose” era. MRI became the main imaging study used in treatment planning. In truth, use of MRI alone may not be sufficient given the geometric image distortion inherent in this procedure. Coregistering CT and MRI results in a further significant reduction in three-dimensional targeting error compared with either nonregistered CT fiducial scans or MRI images.

Flickinger et al reported results with these changes in a series of 190 patients. The 5-year actuarial rate of freedom from any imaging evidence for enlargement was 91%. The 5-year rate of freedom from salvage surgery was 97%, a figure equivalent to local control rates reported in microsurgery series. Actuarial rates of injury to cranial nerves V and VII, whether transient or permanent, were 2.6% and 1.1%. All injuries were recorded within 15 months of treatment. The actuarial rate of preserving useful hearing was 71%. Imaging response rate was 35%, a manifestation of dose reduction and a shorter follow-up period compared to the initial series.

Analysis of prognostic factors in this modern series demonstrated no impact of dose on local control. The freedom from resection rate was 98% for those receiving ≤13 Gy compared to 97% for those receiving >14 Gy. The rates of strict imaging local control were 91% in each dose category. With dose reduction, tumor size no longer correlated with induction of V/ VII neuropathy.

Gamma-knife results for acoustic neuromas have been reported from other centers (Table 2). Local control rates, whether based on strict imaging definition or need for surgical salvage, vary from 91-100%. Imaging response rates vary from 33-76%. Preservation of useful hearing varies from 33-83%. Rare complications reported after SRS include facial spasm, communicating hydrocephalus, worsening tinnitus and chewing difficulties. Local relapse in these series typically occurs within three years of SRS, although recurrence at longer intervals has been reported. Neurofibromatosis may predispose to delayed relapse. Hasegawa et al reported that tumor size and morphology were significant predictors of local control. Actuarial 10-year local control rates for tumors <15 cc were 95% compared to 57% for lesions >15 cc (p<0.001). Local control rates for Type A lesions (intracanalicular), Type B lesions (ce-rebellopontine) and Type C lesions (brainstem compression) were 96% compared to 74% for tumors deviating the fourth ventricle or Type D (p=0.008). Lee et al reported that absence of loss of heterozygosity on chromosome 22q may predispose to relapse after SRS.

Prasad and colleagues examined the extent of volume reduction following SRS. Tumor volume reduction >75% of pretreatment value was seen in 13% of responding patients. Tumor volume decrease of 50-75% was encountered in another 15% of responding patients. The remainder of responding patients demonstrated volume reductions of 15-50%. The findings emphasize that SRS can not be relied upon to provide tumor decompression equivalent to microsurgery. Results reported by Prasad et al also indicate that defining response as a tumor dimension reduction of 1-2 mm is too generous and overestimates the rate of clinically significant volume reduction following SRS.

The rate of neuropathy is significantly higher in those with prior microsurgery compared to those undergoing primary SRS. Neurofibromatosis significantly reduces the rate of preserving useful hearing but has no impact on V/VII injury rates. Aside from the impact of tumor size on local control, irradiated volume is a predictor of symptomatic necrosis. Korytko et al reported the risk of symptomatic necrosis was related to the 12 Gy volume of the treatment plan and the risk increased significantly with a 12 Gy volume >10 cc.

LINEAR ACCELERATOR SRS RESULTS

Linear accelerator SRS was introduced in 1983 by Betti. In a series of 295 patients, Freidman et al reported a 98% control rate. Control was not correlated with tumor volume, prior microsurgery, SRS dose or neurofibromatosis. The 2-year actuarial incidences of facial and trigeminal neuropathies were 11.8% and 9.5%, respectively. The strongest multivariate predictor of neuropathy was dose to the brainstem, suggesting that cranial nerve nuclei and/or the transition zone from oligodendroglial to Schwann cell myelination is the critical SRS target for neuropathy. Prescription dose was also a significant predictor. The incidence of either V or VII deficits was 2% if prescription dose was <12.5 Gy compared to 24% if dose exceeded 12.5 Gy (p<0.0003). Similar to gamma-knife series, prior microsurgery was a significant predictor of neuropathy. In a series of 44 patients, Speigelmann et al reported a 98% local control rate and 71% rate of useful hearing preservation. Both tumor volume (<4 cc versus >4 cc) and prescribed dose (<15 Gy versus >15 Gy) influenced the rate of facial...
neuropathy in this series. In a series of 27 tumors receiving a median 13 Gy, Combs et al reported actuarial 5- and 10-year local control rates of 91%\textsuperscript{17}. Treatment-associated trigeminal and facial nerve deficits occurred in 8% and 5%, respectively.

The treatment planning approach in linear accelerator SRS centers emphasizes tumor dose homogeneity. This concept involves minimizing both the maximum absolute target dose and the internal dose gradient by use of a single isocenter and the highest possible isodose line encompassing the target. At UCLA, virtually all targets are irradiated with dose prescribed at the 90-95% isodose line resulting in homogeneity indices of 1.05-1.11. The impact of dose homogeneity on tumor control and morbidity remains among the most contentious issues within the field of stereotactic irradiation. According to Nedzi et al, dose inhomogeneity >5-10 Gy was the most significant factor associated with morbidity following SRS for a variety of intracranial lesions\textsuperscript{64}. Foote and colleagues found that use >5 isocenters was a significant predictor of risk of neuroma relapse (univariate p=0.002)\textsuperscript{24}. Others document no impact of dose inhomogeneity or number of isocenters on tumor control or morbidity\textsuperscript{20,36,61}.

There is debate whether the conformality of single isocenter linear accelerator SRS treatment plans can match that of multiple isocenter gamma-knife plans. A measure of conformality is a ratio of the volume of tissue encompassed by the prescription isodose compared to the volume of the target (ie, conformality index). Isodosimetric comparisons demonstrates a significant conformality advantage for the gamma-knife compared to a linear accelerator equipped with fixed diameter, circular beam collimation\textsuperscript{73,105}. In a modeling study, gamma-knife SRS conformality advantage is associated with a reduced risk of normal tissue injury\textsuperscript{73}. Beegle et al reported no significant influence of treatment plan conformality on incidence of cranial nerve injury or local control\textsuperscript{9}.

**IMAGING CHANGES FOLLOWING SRS**

Transient increase in tumor size associated with decrease in contrast enhancement typically follows SRS for acoustic neuromas (Figure 1).

There is debate whether the conformality of single isocenter linear accelerator SRS treatment plans can match that of multiple isocenter gamma-knife plans. A measure of conformality is a ratio of the volume of tissue encompassed by the prescription isodose compared to the volume of the target (ie, conformality index). Isodosimetric comparisons demonstrates a significant conformality advantage for the gamma-knife compared to a linear accelerator equipped with fixed diameter, circular beam collimation\textsuperscript{73,105}. In a modeling study, gamma-knife SRS conformality advantage is associated with a reduced risk of normal tissue injury\textsuperscript{73}. Linear accelerator conformality can be improved by use of a micro-multileaf collimator (MMLC) with leaf width <5 mm\textsuperscript{62,91}. Dynamically altering the shape of a MMLC- collimated field during linear accelerator arc SRS further improves conformality\textsuperscript{93}. These advances have narrowed the conformality difference between gamma-knife and linear accelerator. In a study of eight patients with acoustic neuromas, Perks et al demonstrated the mean conformality index for a gamma-knife was 1.38 compared to 1.78 for conformal static accelerator beams and 1.65 for dynamic arcs\textsuperscript{70}. Although the differences are small, the gamma-knife index remains significantly lower than either linear accelerator value (p<0.02). The dynamic index is significantly lower than the static field approach (p<0.05). The clinical impact of differences in conformality index remains uncertain. Beegle et al reported no significant influence of treatment plan conformality on incidence of cranial nerve injury or local control\textsuperscript{9}.

**Table 2 - Outcome Following Linear Accelerator SRS for Acoustic Neuromas**

<table>
<thead>
<tr>
<th>Series</th>
<th># Pts.</th>
<th>Dose (Gy)</th>
<th>Follow-up (mos)</th>
<th>Local Control</th>
<th>Imaging Response</th>
<th>Retention Useful Hearing</th>
<th>VII Injury*</th>
<th>V Injury*</th>
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<td>Combs, 2006\textsuperscript{52}</td>
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<td>-</td>
<td>55</td>
<td>8</td>
<td>5</td>
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</table>

\* Any degree of injury, transient or permanent.

In a sequential volumetric analysis, Yu et al reported transient volume increase followed by progressive shrinkage in 57 of 91 tumors\textsuperscript{106}. Mean tumor volume increase was 20% but individual tumors increased by 100%. Maximum increase occurred six months after SRS and resolved over 12 months. In a series of 206 Mayo Clinic patients, 30 (14%) demonstrated enlargement
≥2 mm a median of nine months after SRS\(^7\). Loss of tumor contrast enhancement was noted in 93% with enlargement. Resolution of enlargement over the ensuing 12 months occurred in 57% of this group and was associated with return of central homogeneous enhancement (Figure 2).

**Figure 2.** (A) Axial T1-weighted contrast enhanced MRI demonstrating SRS isodose line. The target received 12 Gy prescribed at the 90% isodose line. (B) Axial T1-weighted contrast enhanced MRI six months following SRS for the target displayed in Figure 2A. The image demonstrates loss of tumor enhancement. (C) Axial T1-weighted contrast enhanced MRI 12 months after SRS. There has been return of contrast enhancement and reduction in tumor size.

Enlargement was persistent but not progressive in 29%. Progressive enlargement over 12-48 months was noted in 14% and was significantly associated with tumor size and SRS dose. Surgical intervention was advised only for progressive enlargement. Hasegawa et al defined enlargement as >2 mm in mean tumor diameter in a series of 254 patients\(^3\). Expansion was classified into three morphologic categories: expansion with loss of central enhancement suggesting central necrosis (Type A); solid expansion (Type B) occurring after appearance of necrosis and during the time of return of enhancement; cyst formation or enlargement of a pre-existing cyst (Type C). Overall, 42 patients (17%) demonstrated expansion. Actuarial 1- and 3-year expansion rates were 8% and 15%, respectively. Of those with expansion, Type A, B and C occurred in 33%, 38% and 29%, respectively. Median intervals to Type A, B and C expansion were 9 months, 18 months and 12 months, respectively. On multivariate analysis, tumor volume ≥15 cc was a significant predictor of any expansion. The authors advised observation for those with tumor expansion rather than immediate intervention unless there was significant symptomatology or brainstem compression. Type A expansion was typically transient although resolution could require many months of observation. Type B expansion not preceded by a necrotic phase and Type C expansion characterized by new cyst formation as opposed to enlargement of a pre-existing cyst were most likely to require salvage therapy. Gamma-knife dose inhomogeneity is not solely responsible for these imaging changes. In a series of 46 linear accelerator SRS patients, Okunaga et al reported transient volume increase followed by tumor shrinkage in 45% and overall loss of tumor enhancement in 88%\(^8\).

**MECHANISM OF HEARING LOSS DUE TO SRS**

Proposed mechanisms for hearing decrement following SRS include microvascular occlusion, direct axonal injury, perineurial adhesions and tumor volume change. Cochlear dose has emerged as a significant predictor of hearing loss. According to Linskey et al, the basal turn may be the most susceptible portion of the cochlea to SRS\(^4\). In a retrospective series of 18 patients receiving 14 Gy SRS, doses >12 Gy were delivered to the basal turn near the modiolus and the inferior cochlear portion in 10.8% and 14.8%, respectively. Massager et al reported the median cochlear dose for those with hearing preservation was 3.7 Gy compared to 5.33 Gy among those with hearing loss (p=0.005)\(^9\). Dose-volume histogram analysis revealed that at all dose levels the irradiated cochlear volume of those with hearing loss exceeded that of patients with hearing retention (p<0.0001). Dose to the cochlea, in turn, was correlated significantly with tumor extension into the internal auditory canal (p<0.001). The average mean cochlear dose associated with tumors filling 0-25%, 25-50%, 50-75% and 75-100% of the internal auditory canal was 2.7 Gy, 2.7 Gy, 4.1 Gy and 5.3 Gy, respectively. Respective rates of hearing preservation associated with these degrees of canal filling were 100%, 77%, 65% and 50%. Massager and associates quantified the relationship between intracanalicular tumor extension and hearing loss\(^5\). The median intracanalicular tumor volume was 126.9 mm\(^3\) for those with hearing preservation compared to 166.6 mm\(^3\) in the group with hearing loss (p=0.0061). The odds ratio for hearing loss for patients with intracanalicular tumor volume >100 mm\(^3\) was 3.5 compared to those with lesser volumes. Mean maximum dose to the intracanalicular tumor was not significantly different between those with or without hearing loss. Integrated dose, however, was 2.14 mJ for hearing preservation patients compared to 3.45 mJ for hearing loss patients (p=0.0005). Dose to the brainstem cochlear nucleus was the only significant predictor of hearing loss according to Paek et al\(^6\). In a series of 25 patients treated to 12 Gy, the mean maximum dose to the cochlear nucleus was 9.4 Gy. Patients with hearing loss received 11.1 Gy to the nucleus compared to 6.9 Gy for those with hearing preservation (p=0.03).

**STEREOTACTIC RADIOTHERAPY FOR ACOUSTIC NEUROMAS**

SRT refers to focal irradiation of a stereotactically acquired target but with dose delivered in more than a single treatment. SRT combines the physical dose localization advantages inherent in SRS with the biologic advantages to normal tissue of dose fractionation\(^2\). Normal tissue typically demonstrates an increase in radiation tolerance as the size of the daily dose decreases and this radiobiologic axiom is most pronounced in the central nervous system. SRT is typically delivered by a linear...
accelerator and treatment planning aims for highly conformal and homogeneous dose distributions. In general, SRT is used for tumors > 3 cm or those with Hasegawa Type D lesions not amenable to surgical decompression. AT UCLA and elsewhere, SRT has become the treatment of choice for patients with useful hearing, regardless of tumor size.\textsuperscript{16,87,98}

Objections to SRT involve the isocentricity of linear accelerators and the accuracy of patient repositioning. Isocenter deviations of current accelerators dedicated to stereotactic irradiation are 0.06-0.17 mm.\textsuperscript{29} Repeated set up is accurate and reproducible, whether confirmed by portal films, CT or the depth helmet method.\textsuperscript{27,82,94} Robar et al documented inter-fraction translational standard deviations of 0.42 mm anterior-posterior, 0.47 mm medial-lateral and 1.36 mm superior-inferior using a commercially available thermoplastic face mask system.\textsuperscript{82} Solberg et al demonstrated a mean three-dimensional displacement from baseline of 0.468 mm (range 0.169-1.438 mm) in a study of 30 patients repeatedly fitted with a Gill-Thomas-Cosman frame.\textsuperscript{94}

There is no Level I evidence supporting SRT as an alternative to microsurgery. In a retrospective chart comparison of microsurgery, observation and SRT, Lin et al reported significant loss of useful hearing in all three groups.\textsuperscript{55} Rates of useful hearing retention were 16%, 9% and 43%, respectively. Only 16 patients were included in the SRT group and it is unclear whether MRI-based planning was used. The rationale for SRT can be inferred from results of conventional radiotherapy. Maire et al reported a series of 46 tumors receiving 51 Gy from 1986-2004.\textsuperscript{57} Median tumor size was 3.1 cm and the treatment plan included 0.8-1 cm margin of normal tissue. After an 80 month follow-up, the 5- and 15-year actuarial local control rates were 86%.

There are no randomized trials comparing SRS and SRT. Andrews et al, prospectively compared 50 Gy SRT with 12 Gy SRS in a series of 122 patients.\textsuperscript{2} Local control rate for sporadic tumors was 97% with SRT and 98% with SRS. For those with NF-2, local control rate was 67% with SRT and 80% after SRS (p=0.66). There were no differences in preservation of cranial nerve V/VII function. The rate of preserving Gardner-Robertson grade I-II hearing was 33% with SRS and 81% with SRT (p=0.023). The rates of preserving grade I hearing were 40% and 90%, respectively (p=0.034). The superiority of SRT may be due to the unexpectedly poor result of SRS.

Local control rates following SRT equal those of SRS (Table 3). Hearing function in these series is frequently evaluated using subjective criteria. Use of subjective ratings of hearing function rather than audiometric analysis may underestimate hearing decrement and overestimate the clinical impact of SRT. Cox et al, however, demonstrated a significant correlation between subjective and objective scoring of speech intelligibility.\textsuperscript{18}

The largest SRT experiences have been reported from Germany and Japan. Combs et al treated 106 patients with tumors ≤4 cm.\textsuperscript{16} Treatment planning involved CT-MRI fusion, MMLC field shaping, single isocenter and a 1-2 mm margin of normal

### Table 3 - Outcome Following Linear Accelerator SRT for Acoustic Neuromas

<table>
<thead>
<tr>
<th>Series</th>
<th># Pts.</th>
<th>Dose (Gy)</th>
<th>Follow-up (mos)</th>
<th>Local Control (%)</th>
<th>Imaging Response (%)</th>
<th>Retention of Useful Hearing (%)</th>
<th>VII Injury* (%)</th>
<th>V Injury* (%)</th>
</tr>
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<tbody>
<tr>
<td>Lederman, 1997</td>
<td>38</td>
<td>20</td>
<td>18</td>
<td>100</td>
<td>69</td>
<td>-</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Kalapurakal, 1999</td>
<td>19</td>
<td>30-36</td>
<td>54</td>
<td>100</td>
<td>53</td>
<td>-</td>
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<td>0</td>
</tr>
<tr>
<td>Andrews, 2000</td>
<td>56</td>
<td>50</td>
<td>29</td>
<td>97</td>
<td>-</td>
<td>81</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Meijer, 2003</td>
<td>80</td>
<td>20-25</td>
<td>33</td>
<td>94</td>
<td>-</td>
<td>61</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Sawamura, 2003</td>
<td>101</td>
<td>40-50</td>
<td>45</td>
<td>91</td>
<td>-</td>
<td>71.7</td>
<td>5</td>
<td>18</td>
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<tr>
<td>Selch, 2003</td>
<td>48</td>
<td>54</td>
<td>36</td>
<td>100</td>
<td>27</td>
<td>92.5</td>
<td>2.2</td>
<td>2.1</td>
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<tr>
<td>Combs, 2005</td>
<td>106</td>
<td>51</td>
<td>48.5</td>
<td>95</td>
<td>47</td>
<td>64</td>
<td>2.3</td>
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<td>Chan, 2005</td>
<td>70</td>
<td>54</td>
<td>45</td>
<td>98</td>
<td>53</td>
<td>84</td>
<td>1</td>
<td>4</td>
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<tr>
<td>Thomas, 2007</td>
<td>34</td>
<td>45</td>
<td>36.5</td>
<td>96</td>
<td>-</td>
<td>56</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Koh, 2007</td>
<td>60</td>
<td>50</td>
<td>32</td>
<td>93</td>
<td>-</td>
<td>77</td>
<td>0</td>
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</table>

* Any degree of injury, transient or permanent.
tissue added to the target volume in all patients. The median dose at isocenter was 57.6 Gy and the 90% isodose line encompassed the tumor plus the added margin. After a median 48.5 month follow-up, actuarial 3- and 5-year local control rates were 94% and 93%, respectively. Tumor size and presence of neurofibromatosis did not influence local control rate. Useful hearing was defined subjectively as ability to communicate without visual aids. Useful hearing was preserved in 98% of sporadic tumors compared to 64% for those with neurofibromatosis (p=0.0006). The rates of irreversible injury to cranial nerves V and VII were 3.4% and 2.3%, respectively. Sawamura et al treated 101 patients with unilateral, sporadic tumors ≤4 cm66. Median SRT dose was 48.6 Gy and local failure was defined as >2 mm enlargement and need for surgical intervention. After a median 45 month follow-up, local control rate was 91.4%. Tumor size had no significant influence on local control. Useful hearing, analyzed audiometrically, was retained in 71.7%. Transient dysfunction of cranial nerve V and VII occurred in 14% and 4%, respectively. Permanent dysfunction occurred in 4% and 0.9%, respectively. Communicating hydrocephalus requiring shunt placement occurred in 11% of patients. Mean tumor diameter in those with hydrocephalus was 25 mm compared to 18 mm in those free of this complication (p=0.0011).

Chan et al reported the largest United States experience12. Seventy patients were treated with 54 Gy. After a median 45 month follow-up, 3- and 5-year actuarial local control rates were 100% and 98%, respectively. Several patients required surgical intervention for reasons not associated with tumor growth and respective 3- and 5-year rates of freedom from any neurological intervention were 95% and 89%. Tumor volume was predictive of need for intervention. For tumors <8 cc, the rates of freedom from surgical intervention were 100% and 97%. For those with larger lesions the respective rates were 74% and 47% (p=0.0001). Three and 5-year rates of preserving useful hearing, defined subjectively, were 84%. Tumor volume, neurofibromatosis and prior surgery did not affect the rate of preservation. Actuarial 5-year rate of freedom from facial weakness was 99%. Freedom from new or progressive trigeminal dysfunction was 96%. Cranial nerve injury in this series was unrelated to neurofibromatosis, tumor volume and prior surgery. At UCLA, 48 patients with sporadic tumors were treated with 54 Gy over six weeks87. Thirty-two patients had no imaging evidence of tumor growth prior to SRT. A median 2 mm margin and MM LC field shaping were used in all patients. Local relapse was defined as sustained increase in tumor >2 mm. After a median 36 month follow-up, the 5-year actuarial rate of local control was 100%. Subjectively defined useful hearing was preserved in 91%. Actuarial rates of preserving pre-treatment level of cranial nerve V and VII function were 96% and 97%, respectively. Cranial nerve V and VII injuries were seen only in those patients with prior neurosurgical intervention.

The most efficacious dose-time regimen for acoustic neuromas has not been established. In the literature, the reported rates of useful hearing retention after the various hypofractionated approaches (ie, 3-6 fractions) are inferior to the best results of conventionally fractionated SRT (ie, 25-30 fractions). Several authors admit abandoning 6-Gy fractions due to acute morbidity or exacerbation of ataxia13,30. Acute hearing loss has been reported following 21 Gy in three fractions13,30. Williams et al non-randomly compared 25 Gy in five fractions versus 30 Gy in 10 fractions in a series of 125 patients104. After a median follow-up of 1.8 years, the rate of useful hearing preservation was 71% in the five fraction regimen compared to 100% in the 10 fraction course (p=0.39). Although these results suggest 10 fractions are sufficient, only 14 patients were treated with this regimen compared to 111 in the shorter course. Only three patients in the 10-fraction regimen were followed >12 months. The statistical similarity of hearing preservation rates following SRS and hypofractionated SRT reported by Meijer et al above implies hypofractionation does not sufficiently exploit the biologic advantage of dose fractionation for preservation of eighth cranial nerve function. For all these reasons, an SRT course of 50.4 Gy in 28 fractions has become the standard of care at UCLA10.

The low rate of morbidity in SRT series associated with the low rate of improvement in established cranial neuropathy provides strong incentive for irradiating all patients at initial diagnosis of acoustic neuroma. Some have objected to treating patients who do not have documented evidence of tumor growth since this may overestimate the impact of SRT. Bedavanija and colleagues, however, reported that acoustic neuromas >18 mm demonstrated proliferative activity based on immunohistochemical staining for Ki-67 and proliferating nuclear cell antigen7. Tumors capable of proliferation were more common in patients <50 years of age. In the UCLA series, median patient age was 49 years and median tumor size was 23 mm.

An observation-first policy may expose patients to an unwarranted risk of hearing loss. According to Charabi et al, candidacy for hearing-preserving microsurgery was lost in three-quarters of observed patients due to tumor growth14. Shirato et al, by contrast, documented significant reduction in tumor growth rate following SRT90. Mean growth rate was -0.75 mm/year after SRT compared to 3.87 mm/year in an observation group (p<0.0001). Mean annual rate of hearing loss decreased significantly after SRT. Prior to irradiation, hearing loss was 18.6 dB/year44. Following SRT, hearing loss in the second and third years of follow-up were 6.2 and 5.1 dB, respectively (p=0.025 and 0.018). Andrews et al, in their non-random comparison of SRS and SRT, reported that retention of useful hearing was significantly more likely following SRT for patients rated Garner Robertson Class I compared to those who had already declined to Class II. In view of the continual hea-
ring loss accompanying observation, these findings encourage earlier rather than later intervention with SRT for those with newly diagnosed acoustic neuromas10,21.

**IMAGING CHANGES FOLLOWING SRT**

Imaging studies demonstrate a biphasic pattern of change mimicking findings after SRS (Figure 3). Andrews et al demonstrated an equal incidence, degree and time course of developing central tumor non-enhancement and eventual recovery of enhancement on serial CT scans following either SRS or SRT1. In the UCLA experience, loss of central tumor enhancement occurred in 67% a median of six months after SRT. Return of enhancement was recorded after another six month interval (Figure 3). Transient tumor enlargement ≤2 mm was noted in 25% of patients in the UCLA series. Transient enlargement was associated with simultaneous loss of tumor enhancement in 80% of this subgroup.

The ultimate rate of tumor regression after SRT does not equal that reported for SRS. Defining regression as any sustained decrease in tumor size on follow-up MRI, Chan et al reported actuarial 3- and 5-year regression rates of 36% and 62%12. Tumor regression occurred at a median of 22 months but response as late as 74 months was recorded. In the UCLA experience, 27% of tumors demonstrated sustained decrease in size by 1-14 mm (median 2 mm) after SRT7. The onset of tumor regression varied from 6-24 months (median 6). In only two patients (4%), however, was the magnitude of regression in the largest tumor dimension >50% of the pre-treatment value.

**PRESERVING HEARING WITH SRT**

Despite fractionation of a conformal and homogeneous dose, temporal bone structures remain at risk for treatment-associated injury. Damage to the Organ of Corti may be responsible for hearing loss following SRT. In a chinchilla model, Bohne et al demonstrated a significant relationship between loss of inner and outer hair cells and increasing dose of fractionated irradiation over the range 40-90 Gy11. The relevance of cochlear dose in the setting of SRT was evaluated by Thomas et al98. The authors treated 34 patients with Gardner-Robertson grade I-II hearing to 45 Gy. The 5-year rate of useful hearing preservation was 54%. Dose to the cochlea was significantly different between the deteriorated and preserved groups for all cochlear dose parameters evaluated: V90%, V80%, V50%, maximum dose and minimum dose. As an example, the overall median cochlear V90% value was 73.3%. Loss in speech receptor threshold was 25 dB for those at or above the median V90% compared to 10 dB for those below the median (p=0.038). The median V90% values were 86.8% and 30.6% (p=0.043) for the deteriorated and preserved hearing patients, respectively. Dose to the cochlear nucleus was not related to hearing preservation or loss.

It is vital that those planning SRT recognize the cochlea as an organ of risk. Modern planning systems can optimize dosimetry for acoustic neuroma resulting in both local control and hearing preservation. Thomas et al retrospectively replanned five cases in which the V90% exceeded the median value for the entire group. Replanning techniques included static conformal beams, dynamic arcs and IMRT. There was a statistically significant decrease in the cochlear V90%, V80% and conformity index for each approach compared to the original plan. No single technique was superior in all replanned cases.

**RISK OF SECOND MALIGNANCY WITH STEREOTACTIC IRRADIATION**

Stereotactic irradiation imparts a finite risk of transformation of an acoustic neuroma to a malignant peripheral nerve sheath tumor or induction of a de novo glioma28,57. There are case reports of each of these types of second malignancy following SRS for acoustic neuromas5,42,89,90. Shamisa et al emphasized...
the risk of second malignancy due to normal tissue exposure in the dose falloff region. After reconstruction of dosimetry for an acoustic neuroma receiving 17 Gy, the investigators documented a glioblastoma arising in an area of the ipsilateral temporal lobe receiving 4 Gy. Patients with neurofibromatosis may be at particular risk for sarcoma induction. Although oncogenesis is an undeniable possibility with SRS/SRT, the absolute risk appears low. Rowe et al reported a cohort study of 4877 patients, including 856 sporadic acoustic neuromas, treated from 1985-2004 with the Sheffield gamma-knife. The series represented 29,916 patient-years of follow-up. There was no significant increase in the observed:expected incidence ratio of new central nervous system or non-central nervous system malignancies. The relative risk of any second malignancy was 0.83 and the risk for central nervous system 0.4. Despite the impressive patient-years of follow-up reported by Rowe et al, the mean follow-up for the entire group was six years and only 364 patients were followed >15 years. The reported latency from exposure to second malignancy must be respected but should not represent a contraindication to stereotactic irradiation for properly selected patients.

CONCLUSIONS

In little over 50 years, SRS and SRT have been accepted as effective alternatives to microsurgery for the treatment of acoustic neuromas. Stereotactic irradiation produces a high rate of tumor control coupled with a gratifying possibility of preserving useful hearing. Evolution in treatment technique and improvements in delivery systems have reduced morbidity, particularly with respect to cranial neuropathies. Prolonged follow-up is mandatory to confirm whether the encouraging 5- and 10-year control rates are tantamount to cure. The specter of second malignancy must be respected but should not represent a contraindication to stereotactic irradiation for properly selected patients.

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