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Research Article

Clinical Outcomes of Acoustic Neuromas Patients Treated with Single Fraction Vs Multi-Fraction Radiosurgery

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Abstract

Purpose: Patients with acoustic neuromas have several treatment options including close observation if hearing loss is mild or absent and other cranial nerve deficits are not present. The best radiosurgery fractionation regimen for expected control rates as well as acceptable treatment risks in this patient population has not been well studied. This article describes two patient groups treated at a single institution with two leading radiosurgery platforms. We stratify patients to a single fraction or multi-fraction regimen based on presenting symptoms and reports on the two patient population outcomes.

Methods and Materials: Between 2007 and 2013, 49 patients with Acoustic Neuromas (ANs) received fractionated stereotactic radiosurgery (Group A) and 30 patients with ANs received single fraction radiosurgery (Group B). Median f/u for Group A was 39 months and for Group B 18 months. The average fraction number in Group A was 3 and in Group B 1. The mean dose for Group A was 18Gy and for Group B 12.5 Gy. The mean tumor volume and prescription isodose for Group A was 2.4 cc's and 73%, respectively and group B 1.8 cc's and 50%, respectively. The fraction regimen chosen was not based on tumor volume. Instead, patients who presented with symptoms other than mild hearing loss were encouraged to proceed with the fractionated regimen.

Results: For Group A patients who received fractionated radiosurgery, tumor control was observed in 92% (48/52). Thirty-three of the 52 patients were either deaf before treatment or did not obtain post treatment audiograms. Sixty-eight percent (13/19) had decline in hearing to a non-functional level in the treatment ear. Thirty-two percent (6/19) patients had stable hearing post treatment. Post treatment, 22% of the patients noted the new onset of headaches, 11% imbalance, 4% tinnitus, 6% facial spasms, 2% facial weakness and 7% facial numbness.

For Group B patients who received single fraction radiosurgery, tumor control rate was 90% (27/30). Fifty-seven percent of patients (17/30) were either deaf before treatment of did not obtain post treatment audiograms. Seventy-seven percent (10/13) patients had decline in hearing to a non-functional level in the treatment ear. Twenty-three percent (3/13) had stable hearing after treatment. Post treatment, 3% of the patients noted the new onset of headaches, 7% imbalance, 10% tinnitus, 3% facial spasm, 3% facial weakness and 0% facial numbness.

Conclusion: Considering the principles of radiobiology, our algorithm postulated that if a patient had progressing cranial nerve deficit(s) at presentation, the underlying cranial nerve injury could be less affected by a SRS fractionated regimen than a single fraction treatment. Tumor controls rates and hearing outcomes in our 2 patient treatment populations were similar. The benefits if any of a multi-fractionated stereotactic treatment regimen in the treatment of an acoustic neuroma were not able to be determined in this study when compared to a single fraction regimen.

Keywords: Acoustic Schwannoma; Acoustic Neuroma; Control Rates; Complications; Cyber Knife; Gamma Knife; Multi Fraction; Stereotactic Radiosurgery; Single Fraction

Introduction

Acoustic Neuromas are benign tumors arising from the vestibular or 8th cranial nerve. Aside from hearing loss, large tumors which cause significant or sudden worsening cranial nerve deficits from mass effect on the 7th or 8th nerve or brainstem compression are best treated with surgery [1,2]. Control rates and complications with surgery are well documented [3-6]. Tumors under 3 cm which cause few if any cranial nerve deficits have been treated with radiosurgery over 3 decades with comparable results and toxicities to surgery. Although most of this experience has been with Gamma Knife delivered in a single fraction, varying fractionation schemes using linear accelerator based techniques are being used with reportedly similar results [7-9]. Nevertheless, few direct comparisons have been made between varying radiation schemes which take into account the number of fractions, prescription dose and prescription isodose. The principles of radiobiology stress the benefits of adjacent and embedded normal tissue sub lethal repair with increasing fractionation regimens [10]. Hence, it would be expected that in cases where definite cranial nerve deficits are present, multi-fraction SRS dose delivery may have a benefit, particular for hearing preservation where the mean cochlear dose must be taken into consideration [11,12]. The purpose of this study is to evaluate outcomes including AN control rates and hearing preservation as well as side effects between two leading Radiosurgery platforms and different fractionation schemes.

Stereotactic Radiosurgery Delivery Systems

Multiple commercial products are available which are designed to delivery SRS. For each device, intra-cranial SRS delivery requires either fiducials reference markers including the bony anatomy of the skull or a skull based frame and an algorithm to align a collimated external radiation source to a tumor with 1 mm or less accuracy. Multiple crossing or intersecting beams allow for a sharp dose fall-off outside the target and a build-up of dose within the tissue being irradiated. This steep dose gradient allows for higher therapeutic doses than can be delivered that with conventional radiation techniques and greater sparing of adjacent normal tissues. Gamma Knife uses a fixation frame and multiple fixed cobalt sources which are aligned to intersect at a given intra-cranial point usually in a single fraction. CyberKnife uses a compact linear accelerator attached to an industrial robot. Since the CyberKnife is non-frame based, single or multiple fractions can be used and treatment can be delivered to a target anywhere in the body.

Method and Materials

Between 2007 and 2013, a total of 2340 patients were treated at the Swedish Radiosurgery Center in Seattle Washington. Our Center houses both a Gamma Knife and a CyberKnife which are located side by side in the department and share a common shielded wall. The treating physician team was the same regardless of the treatment platform used. The center has three dedicated 4 physicians, 3 nurses and 2 technologists to operate the accelerator. Of the patients receiving SRS during this 82-month period, 79 patients had an acoustic neuroma. Before making a treatment decision, all patients were seen by a Neurosurgeon or Otolaryngologist and Radiation Oncologist. All patients treated with SRS were offered surgery or radiosurgery. If the patient had useful hearing at the time of the initial consultation for SRS, a hearing test was pre-formed pre and post treatment or until useful hearing was on longer measurable.

Patient who presented with cranial nerve symptoms other than stable or mild hearing loss were encouraged to consider fractionated stereotactic surgery rather than single fraction treatment. We hoped to exploit the radiobiology advantage of fractionation and possibly mitigate or reduced the risk of worsening cranial nerve deficits than what had been previously reported with single fraction SRS. Patients who were deaf or had no ipsilateral useful hearing as their only deficit were equally divided between both fractionation regimens. Group A patients received fractionated SRS with the Cyberknife. Group B Patients were treated with a single fraction using the Gamma Knife. Table one records the baseline patient and tumor characteristic s of the two groups (Table 1).

Of the 52 patients treated in Group A, 35 tumors were radiographically intracanalicular in location and 17 were extracanalicular. We defined extracanalicular as a tumor located within the cerebellopontine angle cistern with or without extension radiographic extension into the auditory canal. The average tumor diameter was 1.7 cm (range: 0.6-5.4 cm). The mean patient age was 53 and the male to female ratio 26:23. The follow up time for this group ranged from 3 to 82 months with a mean of 38 months. Fractionated radiosurgery was the primary treatment in 34 patients. One patient had NF2 with bilateral tumors but only the right side was treated. Fourteen surgeries had previously been performed in 12 patients and 6 patients had prior radiation. At baseline, 4 patients had normal hearing, 35 limited and 13 patients had no useful hearing. The most common presenting symptoms were Tinnitus and imbalance (20 and 21 patients respectively). Other presenting symptoms for Group A patients from greatest to least frequency were facial numbness, facial weakness, dizziness, facial spasm, headaches and nausea see (Table 2).

	Group A (multi-fraction)	Group B (single fraction)
Patient s (n)	49	30
Male: Female	26:23:00	15:15
Age	53 mean (range: 26-92)	61 mean (range 45-83)
Tumor diameter (cm)	1.7 mean (range: 0.6 -5.4)	1.5 mean (range: 0.6-3.1)
Tumor volume (cm3)	2.4 mean (range: 0.1-34.1)	1.8 mean (range: 0.3-7.2)
Tumor site (RT: LT)	22:27	17:13
Intra-canalicular	12 (E 37)	16 (E 14)
Primary treatment	34	22
Prior surgery	14 (12 patients)	9 (8 patients)
Prior radiation	5	0
NF2 (n)	1	0
Follow up (months)	38 mean (range: 3-82)	18 mean (range: 4-33)

Table 1: Patient and Tumor Characteristics.

	Group A (multi-fraction)	Group B (single fraction)
Hearing normal/ limited/deaf	4:34:10	3:19:08
Facial weakness	5 (E 3, IAC 2)	5 (E3, IAC 2)
Facial numbness	7 (E6, IAC 1)	5 (E3, IAC 3))
Facial Paralyses	0	1 (IAC 1)
Facial spasms	3 (E 2, IAC 2)	0
Imbalance	21 (E 17, IAC 4)	10 (E6, IAC 4)
Dizziness	5 (E 4, IAC 1)	7 (E5, IAC 2)
Headaches	3 (E 3)	0
Tinnitis	20(E 14, IAC 6)	7 (E5, IAC 2)
Nausea/vomiting	0	1 (IAC 1)

Table 2: Acoustic neuroma symptoms at presentation.

Of the 30 patients treated in Group B, 16 were intracanalicular and 14 tumors were extracanalicular in location. The average tumor diameter was 1.5 cm (range: 0.6-3.1 cm). The mean patient age was 61 and male to female was equal. The mean follow up time was 18 months (range 4-33 months). Single fraction radiosurgery was the primary treatment in 22 patients. No patients had NF2. Nine surgeries had been previously performed in 8 patients. No patient had had prior radiation. At baseline 3 patients had normal hearing, 19 limited and 8 patients were deaf. The most common presenting symptom for this group was imbalance, tinnitus and dizziness (10, 7 and 7 patients respectively). Other presenting symptoms for Group B patients from greatest to least frequency were facial weakness, facial numbness, facial paralysis and nausea (Table 2).

For treatment, Group A patients were treated in an aquablast head immobilization mask. Group B patients were placed in a Leksell Stereotactic frame. A planning non-contrast head CT was obtained prior to treatment for both groups and fused to an MRI. Our MRI treatment planning protocol for Gamma Knife and CyberKnife was the same. The MRI was obtained with contrast. The slice thickness was 1mm and the images covered the entire lesion and surrounding critical structures. In the majority of cases a T2 weighted sequence was added to better visualize the cranial nerves and the cochlea. Stereotactic images were transferred via a fiberoptic Ethernet to the appropriate planning station for each machine. Treatment planning was performed on axial MR imaging with coronal and sagittal reconstruction. All targets including the Schwannoma, cochlea and brainstem were contoured and reviewed by the physician team consisting of a Radiation Oncologist, Neurosurgeon or Otolaryngologist as well as medical physicist. The treatment parameters for both groups are shown in (Table 3). Forty-four of the 49 patients treated with CyberKnife (Group A) received the total prescribed dose of 18Gy in 3 fractions (6Gyx3 fractions). All Gamma Knife patients (Group B) were treated in a single fraction with 26 of 30 receiving 12.5 Gy. The mean tumor volume for Group A was 2.4 cc's (range: 0.1-34.1 cc's) and group B 1.8 cc's (range: 0.27-7.2 cc's). The mean prescription isodose was 73% (Range: 59-85%) for Group A. All patients in Group B were treated to the 50% isodose line. The cochlear mean and max dose for Group A was 9.8 Gy and 15.5 Gy divided over 3 fractions in 90% or 44/49 patients and for Group B was 4.9 Gy and 10.1Gy, respectively, delivered in a single fraction.

Most patients were given a steroid taper over 1-week post treatment starting with 8 mg BID. Radiographic tumor response was determined by serial contrast enhanced MRI requested at 6 months, 12 months then annually. All patients were instructed to obtain audio logical testing annually around the time of their follow up scan (Tables 4,5).

	Group A (multi-fraction)	Group B (single fraction)
Tumor volume (cm3)	2.4 mean (range: 0.1-34.1)	1.8 mean (range: 0.3-7.2)
Prescription isodose	73% mean (range: 59-85%)	50% (range: 45-65%)
Dose (Gy)	19 mean (range: 13-27.5)	12.5 (range: 12.5-14)

Fraction size	3 mean (range: 1-5)	1
Conformity index (CI)	1.2 mean (range: 1.1-1.7)	
Cochlear dose average Gy	9.8 mean (range: 0.3-18.1)	4.9 mean (range: 2.5-13.0)
Cochlear dose maximum Gy	15.5 mean (range: 0.6-20.7)	10.1 mean (range: 0.7-20.1)

Table 3: Acoustic neuroma treatment parameters.

	Group A (multi-fraction)	**Group B (single fraction)**
Local tumor control	n=49-4, 2 died, 2 LTF	n=30-1, 1 LTF
	34 stable or decr, 3 incr, 12 LTF	26 Stable or decr, 3 incr, 1LTF
	34/37=92% control	26/29=90% control
Hearing status	0 improved	1 improved
	22 stable	13 stable
	13 decreased	7 decreased
	10 deaf - no change	8 deaf - no change
1TBD/Unk	Group A: 22/45-10-1 or 65% no change in hearing	Group B: 14/29-8 or 67% no change in hearing

Table 4: Treatment results.

	Group A (multi-fraction)	B (single fraction)
	n=49, 2 died, 2 LTF	n=30, 1 LTF
Facial spasm	4 (E 2, IAC 2)	1 (E1)
Headaches	10 (E 7, IAC 3)	1 (E1)
Tinnitis	2 (E 2)	3 (E2, IAC 1)
Facial numbness	3 (E 3)	0
Nausea/ vomiting	3 (E 2, IAC 1)	0
Imbalance	5 (E 2, IAC 3)	2 (E1, IAC 1)
Facial Paralyses	0	1 (IAC 1)
Facial weakness	1 (E1)	1 (E1)

Table 5: Treatment toxicity (new symptoms).

Results

Median f/u for Group A was 39 months (range: 3-82 months) and for Group B 18 months (range 4-33 months). Forty-five patients in Group A were available for evaluation. Two patients have died of non-CNS causes. Two patients were lost to follow. The tumor was stable or decreased in size on follow up MRI in 92% of the patients treated. There was no post-treatment change in hearing in 22 patients or 65%. Ten patients in Group A were deaf at the initiation of treatment and 13 patients level of hearing was decreased. The most common treatment toxicity in Group A was headaches which was observed in 10/45 or 22% of the patients. Other cranial nerve toxicity included imbalance in 5/45 or 11%, tinnitus in 2/49 or 4%, facial spasms in 3/49 or 6%, facial weakness in 1/49 or 2% and facial numbness in 3/45 or 7%.

Twenty-nine patients in Group B were available for evaluation. One patient was lost to follow up. The tumor was stable or decreased in size on follow up MRI in 90% of the patients treated. There was no post-treatment change in hearing in 14 patients or 67%. Eight patients in Group B were deaf prior to treatment and in 19 patients the level of hearing was decreased. The most common treatment toxicity in Group B was Tinnitis which was observed in 3/29 or 10% of the patients. Other treatment related toxicity included imbalance in 2/29 or 7%. Headaches, facial spasm, facial paralysis and facial weakness all had a post treatment incidence of 1/29 or 3%.

Discussion

Compared to single fraction radiosurgery, it has been proposed that multi-fractions SRS for AN's should provide equivalent tumor dose escalation but better potential sparing of the auditory complex and facial nerve function [13]. Fractionation radiosurgery uses the most beneficial features of both conventional radiation and SRS. These benefits include high dose to the tumor while sparing surrounding normal tissue [14-18]. The risk to auditory, trigeminal and facial function in single fraction radiosurgery has been shown to be proportional to the dose and length of nerve irradiated [19]. Therefore, the risk of injury after SRS delivered in a single fraction increases exponentially with the tumor volume, since the length of the underlying cranial nerves treated increases as well. The therapeutic gain is defined as the ratio of the tumor Biology Effective Dose (BED) for a fractionated versus single dose regimen. The therapeutic gain increases with the number of fractions. Thus SRS fractionated regimens are postulated to better maintain cranial nerves and brainstem function regardless of nerve length within the treated tumor given equivalent dose regimens.

When a multi-fractionated regimen is used, the total dose is larger than that given with a single fraction treatment to achieve the same magnitude of tumor cell killing and tumor control. If these doses are radio biologically equivalent, the normal tissue kill will be reduced with the multi-fraction treatment. For the functioning cranial nerves, fractionation is hypothesized to result in increased cranial nerve preservation for this level of tumor killing [20].

Many authors have speculated about the cause of diminished hearing, worsening imbalance, ipsilateral facial weakness and sensory changes in some acoustic neuroma patients post treatment.

Reason given for these deficits have included higher doses with single fraction treatment regimens, increased length of nerves irradiated in large tumor as well as radiation damage to the cochlea and vasculature or both. In our series the tumor size for both groups was small and did not appear to be a factor in complications observed. Definitely the reported risks of post treatment side effects have decreased with lowered total dose regardless of the radiation schemes. When higher treatment doses were used, we previously reported on a subset of patients with tumors in the internal auditory canal who were especially vulnerable for complication [21]. Between 14-63% of tumors treated experience transient tumor enlargement from 6 months to over 1-year post treatment [22-26]. Post treatment tumor swelling against the canal walls can conceivably cause significant compression of the underlying nerves and vasculature. In our current series which used a lower total dose for the single fraction and multi-fraction treatment regimen compared to earlier SRS studies, neurological symptoms post radiation treatments where not influenced by tumor location within or outside the canal. The benefits if any of a multi-fractionated stereotactic treatment regimen in the treatment of an acoustic neuroma were not able to be determined in this study when compared to a single fraction treatment.

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