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Stereotactic Radiosurgery for Vestibular Schwannomas: Tumor Control Probability Analyses and Recommended Reporting Standards

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JS: None
GD: None
JK: Varian Medical Systems – Grant; ClearSight RT Products – partial ownership
LM: None
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Abstract

Purpose—We sought to investigate the tumor control probability (TCP) of vestibular schwannomas (VS) following single-fraction stereotactic radiosurgery (SRS) or hypofractionated SRS over 2–5 fractions (fSRS).

Materials and Methods—Studies (PubMed Indexed from 1993 – 2017) were eligible for data extraction if they contained dosimetric details of SRS/fSRS correlated with local tumor control. The rate of tumor control at 5 years (or at 3 years if 5-year data were not available) were collated. Poisson modeling estimated the TCP per equivalent dose in 2 Gy per fraction (EQD2) and in 1, 3, and 5 fractions.

Results—Data were extracted from 35 publications containing a total of 5162 patients. TCP modeling was limited by the absence of analyzable data of <11 Gy in a single-fraction, variability in definition of ‘tumor control’ and by lack of significant increase in TCP for doses greater than 12 Gy. Using LQ-based dose conversion, the 3- to 5-year TCP was estimated at 95% at an EQD2 of 25 Gy, corresponding to 1-, 3- and 5-fraction doses of 13.8 Gy, 19.2 Gy and 21.5 Gy, respectively. Single-fraction doses of 10 Gy, 11 Gy, 12 Gy, and 13 Gy predicted a TCP of 85.0%, 88.4%, 91.2% and 93.5%, respectively. For fSRS, 18 Gy in 3 fractions (EQD2 of 23.0 Gy) and 25 Gy in 5 fractions (EQD2 of 30.2 Gy) corresponded to TCP of 93.6% and 97.2%. Overall, the quality of dosimetric reporting was poor; recommended reporting guidelines are presented.

Conclusions—With current typical SRS doses of 12 Gy in 1 fraction, 18 Gy in 3 fractions, and 25 Gy in 5 fractions, 3- to 5-year TCP exceeds 91%. To improve pooled data analyses to optimize

treatment outcomes for patients with vestibular schwannoma, future reports of SRS should include complete dosimetric details with well-defined tumor control and toxicity endpoints.

Summary:

To determine the tumor control probability (TCP) of vestibular schwannomas following 1–5 fraction stereotactic radiosurgery (SRS and fSRS), a systematic review extracted data from 35 studies consisting of 5162 patients. Summary models suggest a TCP of 91% for 12 Gy in 1 fraction, 94% for 18 Gy in 3 fractions, and 97% for 25 Gy in 5 fractions. Recommended reporting standards for future manuscripts are presented, as the quality of the published dosimetric data was poor.

Keywords

Vestibular Schwannoma; Acoustic Neuroma; Stereotactic Radiosurgery; (TCP) Tumor Control Probability; Reporting Standards; HyTEC; Dose

1. CLINICAL SIGNIFICANCE

Vestibular schwannomas (VS) (commonly referred to as acoustic neuromas) are benign tumors originating from the Schwann cells of the myelin sheath of the vestibular portion of the vestibulocochlear nerve (cranial nerve VIII). Approximately 20 patients are diagnosed per million people, with the incidence rising in recent decades due to more incidentally discovered VS (1–3). Over 90% of VS are sporadic, unilateral tumors at diagnosis, with bilateral tumors associated with neurofibromatosis type 2 (NF2)(2). Common symptoms from VS include gait imbalance and vertigo as well as hearing loss and tinnitus due to compression of the cochlear branch of cranial nerve VIII. Facial numbness or pain, from compression of cranial nerve V, occur less frequently. Although the facial nerve (cranial nerve VII) is immediately adjacent to the tumor within the internal auditory canal, facial weakness or hemi-facial spasm are rarely seen at initial presentation. One must consider these tumors' location relative to the critical structures of the cranial nerves (V, VII, VIII), cochlea, and brainstem when making treatment decisions.

Management options include observation with serial imaging and audiometry, surgery, conventionally fractionated or hypofractionated radiotherapy, or stereotactic radiosurgery (SRS). Although some VS may not progress if observed over time, hearing loss can occur in the absence of tumor growth(4). The median growth rate is typically 2 mm per year(5), although it is poorly understood how size and growth rate affect the progression and severity of symptoms. For example, hearing loss can be the presenting symptom for very small tumors, while other VS can become quite large before being diagnosed. Hydrocephalus from brainstem compression can occur from large tumors that exert mass effect and compression on the ventricles.

Historically, prior to the advent of neurosurgical techniques in the late 19th century, these tumors were life threatening. Resection, which made these tumors curable, was primarily carried out with the oncologic principle of gross total resection, often at the expense of neurologic function(6). SRS and conventionally fractionated irradiation emerged

as alternative therapies, with the treatment intent being tumor control while minimizing treatment-related morbidity such as hearing loss and facial palsy. The high local control rates seen in reports from the late 1980s to 1990s of SRS for VS(7) have changed the treatment paradigm for these tumors. Today, even in patients who undergo resection, subtotal removal is acceptable with the availability of radiotherapy for salvage.

Initial reports of SRS for VS noted excellent short-term local control rates of up to 98%. However, low rates of useful hearing preservation (20–50%) and unfavorable preservation of facial nerve (34–86%) and trigeminal nerve (41–85%) function were seen at these higher doses of 16–25 Gy(2). Today, doses of SRS have been successfully lowered (typically 12–13 Gy in a single fraction, 18 Gy in 3 fractions, or 25–30 Gy in 5 fractions) to reduce cranial nerve toxicity risks while maintaining similar rates of local control.

A key question is whether the dose of SRS can be further lowered in order to maximize hearing preservation and neurologic morbidity, while not compromising the expected excellent tumor control probability (TCP) rates. This paper is part of the High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic (HyTEC) effort of the American Association of Physicists in Medicine (AAPM) Working Group on Biological Effects of Hypofractionated Radiotherapy/SBRT (WGSBRT). The objective of the HyTEC Project is to summarize the published dose/volume/outcome data related to tumor control probability in order to help guide clinical practice. Herein, we systematically review the available literature addressing the association between tumor- and dosimetric-based metrics, and tumor control outcomes for patients treated with SRS for VS.

2. ENDPOINTS

A major challenge in defining tumor control in patients with VS is that the typical endpoint of stability or regression in tumor size is unreliable. Following SRS, these tumors characteristically develop diminished central contrast enhancement associated with an increased size of the tumor. Transient enlargement, which occurs in up to 74%(8,9), typically 6 to 18 months after SRS, should not be mistaken for failure of tumor control, as the tumor may stabilize in size (and be larger than prior to SRS) or regress(10). Continued, sustained growth, however, equates to tumor progression.

Another measure of tumor progression is the need for subsequent salvage surgery or radiotherapy due to tumor growth or for relief of tumor-associated symptoms. This measure of control relies on the clinical judgment of the treating physicians in distinguishing post-SRS tumor swelling from tumor growth. However, this endpoint may overestimate control if true biologic growth of tumor is scored as post-SRS swelling, or underestimate control if a biologically controlled tumor (i.e., one that would not grow) required resection for worsening symptoms.

For the present TCP analysis, we did not specifically characterize the differences in how tumor control was defined in each reviewed manuscript, acknowledging that the definition of ‘control’ may vary from one report to another.

3. CHALLENGES DEFINING VOLUMES

The 8th cranial nerve arises from the brainstem and enters the internal auditory canal (IAC). VS can be confined entirely within the IAC, be mostly outside the IAC with protrusion into the cerebellopontine angle (CPA), or extend from the IAC to the CPA. The CPA component can be adjacent to, abut, or compress the brainstem. These tumors are readily discerned on post-contrast magnetic resonance images (MRI) and computed tomography (CT) images. The cerebrospinal fluid (CSF) surrounding the tumor and brainstem is often best seen with a steady-state gradient echo sequence that provides thin, high-resolution T2-weighted images with insensitivity to CSF flow artifacts, which aids in tumor and normal structure delineation. A T1 post-contrast volumetric sequence aids in target delineation. The post-contrast T1 and high-resolution T2-weighted images should be fused to thin slice planning CT scans.

Only 71% of reviewed manuscripts reported complete definitions of the contoured volumes, including GTV and if any PTV margin was used (see Table 1). In general, histologic extension beyond the gross tumor is not expected, therefore the GTV is the same as the CTV. Only 29% of manuscripts reported the use of a PTV margin of 1 or 2 mm; therefore, for most data, GTV was assumed to be the same as PTV.

4. REVIEW OF OUTCOMES DATA

Papers published from 1993 to 2013 were identified in PubMed (search criteria shown in supplemental table 1). SRS was defined per the AANS/CNS/ASTRO consensus report(11) as 1 to 5 fractions. We term treatments performed in 1 fraction as ‘SRS’, with 2 to 5 fractions considered hypo-fractionated SRS (fSRS). Patients receiving more than 5 fractions (fractionated stereotactic radiotherapy (fSRT)) were not included in this review. We also excluded studies that grouped other benign tumors (e.g., meningioma) with VS. Reports which included SRS/fSRS dosimetry and tumor control information suitable for TCP analyses were selected, as noted below. For series with multiple publications, the most recent update of their experience was included, unless the earlier reports included higher dose regimens or other subgroup analyses useful for TCP modeling. Although other systematic reviews(12,13) on SRS for VS had been published subsequent to our data extraction, they emphasized local control outcomes, but not dosimetric correlates of local control, nor TCP modeling.

The local control rates associated with dose and fractionation from the literature are shown in Supplemental Table 2, and the range of reported data characteristics are summarized in Table 1. These rates are also shown graphically in Figure 1a. The x-axis gives conversion scales based on the linear-quadratic (LQ) model with $\alpha/\beta=12.4$ Gy (see Section 6 for further explanation) in order to facilitate comparison of different fractionation schedules. Three- to 5-year tumor control rates were greater than >90–95% for 89% of the reviewed studies, with only 4, typically smaller, studies with control rates of 80–90%. The last column of Supplemental Table 2 describes the definition of tumor control used in each reviewed paper. Only 46% of papers provided Kaplan-Meier estimates of tumor control; when absent, tumor control was considered to be the crude incidence of control at the median follow-up time.

Few reports have follow-up beyond 10 years, highlighting the need for longer-term data to confirm the durability of tumor control after SRS for VS.

The “Total Dose” in the supplemental table refers to the median physical dose prescribed to cover the gross tumor volume (GTV). This limited view of the literature was necessary because many papers do not report even summary dose distribution metrics such as the prescription isodose line or the conformity index (14) (ratio of the prescribed dose volume to the GTV or, when defined, the PTV). Of note, at the time of the initial literature search in 2013, only 1 paper contained outcomes data for a prescription dose lower than the equivalent of 12 Gy in 1 fraction. To broaden the range of doses analyzed, subsequent publications were included only if they contained lower dose data (e.g., 11 Gy in 1 fraction(15,16) or 20 Gy in 5 fractions(17)). Our literature review found no data for less than the equivalent of 11 Gy in 1 fraction with tumor control outcomes, hence any modeling below this dose is extrapolation with a large range of potential error.

5. FACTORS AFFECTING OUTCOMES

There is considerable heterogeneity in the reviewed datasets in target delineation, dose prescription, and the definition of tumor control as reported across the studies. Publications that follow the reporting standards suggested in Section 10 and Table 3 of this report will help clinicians to better understand the effect of such factors on outcome and to account for them in designing future treatments.

Although target volume may be one of the significant factors affecting TCP, there were not enough data to partition the TCP modeling by tumor volume. Additionally, as NF2-related tumors have worse TCP outcomes(18), approximately 75% at 5-years(19), they were excluded from analysis. Other factors unrelated to SRS plan dosimetry were considered (see Section 7), but not factored into TCP modeling, as reports were not consistent as to their correlation with TCP. These include tumor growth prior to SRS(20), tumor size(21) and prior surgical resection.

6. MATHEMATICAL/BIOLOGICAL MODELS

6a. Modeling Limitations Due to Available Data

The modeling of TCP for VS faced several limitations. First is the incomplete reporting of key radiosurgical indices (see Table 1). Only 26% of the reports provided conformity indices, and no report provided detailed dosimetry such as Dxx and Vxx (i.e., minimum dose (D) to the hottest xx% of the tumor volume or the minimum percent or absolute volume (V) of tumor receiving at least xx% of the prescription dose). As no paper had complete reporting of tumor dosimetry, the prescription dose was assumed to be the minimum dose delivered to the gross tumor *and* the sole determinant of TCP. Thus, there was no consideration of PTV margins nor target dose heterogeneity; this latter assumption is supported by prospective data that suggest no difference in brain metastasis TCP with homogeneous vs. heterogeneous plans(22).

Second, the control rate with observation alone (e.g., TCP at 0 Gy) is difficult to characterize(23) which led to problematic fitting issues. In our modelling, we estimated that untreated VS had a rate of tumor stability (i.e., no progression in size) of 30%(24). While series have noted measurable growth in over 95% of untreated patients by 10 years of follow-up(25), the duration of follow-up post-SRS/fSRS being considered in this review is only 3–5 years, so a lower rate of regrowth (i.e. < 95%) at 0 Gy should be considered. However, many patients are not referred for SRS/fSRS unless they have evidence of tumor progression on serial imaging, and these patients likely would have been expected to experience continued tumor progression if untreated. We assumed what we believe is a conservative non-progression rate of 30% (i.e. a lower rate perhaps could be justified and would have increased the apparent utility of SRS/fSRS). Thus, we modeled this assumption by adding the point (0 Gy, 0.3 TCP) to the dataset, but did not force the curve to go through this point during the fitting process by using the median sample size as a weighting factor. For comparison, Supplemental Figure 1 and Supplemental Table 3 is the result of a similar exercise but assuming that TCP at 0Gy (TCP (0)) is 0%.

Third, as noted in Section 4, there are very little TCP data in the single-fraction range of 0 to <11 Gy; this leads to the wide confidence bands presented in the Figures. The dashed portions of the curves in Figures 1b, 2 and Supplemental Figure 1 are based on extrapolations in the models.

Finally, as noted in Section 4, the literature reports tumor control at various time points. For modeling, we used the reported TCP at 5-years if it was available; if not we used the 3-year rate. Studies that reported neither 3- nor 5-year TCP rates were not included in our models. The studies we included are shown in Supplemental Table 2.

6b. Other Modeling Considerations

As with other hypofractionated treatments, the α/β ratio for VS is not known. Therefore, we included α/β as a free third parameter in all TCP modelling. Many investigators have questioned the validity of the Linear-Quadratic (LQ) model at high single fraction doses. The LQ model, despite its well-known deficiencies at high fraction doses, has the fewest assumptions, is widely used in the literature, is easily calculated in the clinic and has been the de facto approach in other HyTEC papers and many published studies. However, for completeness and to inform the reader about the differences that might result from using potentially more accurate models of biological effects at the higher doses used in VS regimens, we also applied a version of the Linear-Quadratic-Linear (LQ-L) model(26). The LQ-L model is gaining use among the different alternatives for high dose per fraction modeling because it is thought to better describe cell survival curves at high fraction doses and is relatively easy to implement. In our TCP models for VS, we investigated both of these models.

6c: TCP models

Tumor control data were extracted at the 3-year time point in 21 (60%) manuscripts, with 5-year data extracted for the remaining 14 (40%) of papers. If both the 3- and 5-year data were provided, the lower value at 5-years was used in the graphic summary and for modelling.

In the studies that report both 3- and 5-year TCP data, these values were similar (typically within 0–3%), thus the pooling for TCP data through this interval range is reasonable and termed 3–5 year TCP.

Ultimately, we extracted data for tumor control data from 35 publications (see Supplemental Table 2) containing a total of 5162 patients. Since the most common prescriptions range from 12–13 Gy in 1 fraction, 18–21 Gy in 3 fractions or 25 Gy in 5 fractions, a radiobiological model is needed to allow quantitative comparison of the efficacy of the different regimens.

TCP for the studies shown in Figure 1a together with the assumed 30% local control for untreated tumors was modeled using the Poisson model and the LQ model for dose conversion and using the maximum likelihood estimation method(27) to determine its parameters:

$$TCP = \exp\left(-ln2\exp\left(2\gamma_{50}/ln2\left(1 - EQD2_{\alpha/\beta}/EQD2_{\alpha/\beta,50}\right)\right)\right) \quad (1)$$

where the two parameters $EQD2_{\alpha/\beta,50}$, and $\gamma 50$ describe the bio-corrected dose to 2 Gy per fraction and normalized slope at the point of 50% probability of control, respectively. As previously noted, α/β is the third parameter that is determined in the fitting of Equation 1 to the data from the chosen studies. The equation describing TCP is the same for both the LQ and LQ-L models, but the biological correction which converts the physical dose to an equivalent dose in 2 Gy fractions, $EQD2_{\alpha/\beta}$, is calculated differently depending on the cellular response model used. For the LQ model, conversion from n fractions of physical dose per fraction d to $EQD2_{\alpha/\beta}$ is given by

$$EQD2_{\alpha/\beta} = BED/(1 + 2/(\alpha/\beta)) \quad (2a)$$

$$BED = nd(1 + d/(\alpha/\beta)) \quad (2b)$$

where BED is the biologically effective dose. At high fraction doses, the quadratic term dominates the behavior of BED in the LQ-model.

For the bipartite LQ-L model, we used the approximations of reference 26 and $EQD2_{\alpha/\beta}$ was given by(26):

$$EQD2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}} \quad (3a)$$

$$BED = \begin{cases} nd + \frac{nd^2}{\frac{\alpha}{\beta}}, \ if \ d < d_T \\ nd_T + \frac{nd_T^2}{\frac{\alpha}{\beta}} + \frac{\gamma}{\alpha}n(d - d_T), \ if \ d \geq d_T \end{cases} \quad (3b)$$

Such that,

$$d_T = 2\frac{\alpha}{\beta} \tag{3c}$$

$$\frac{\gamma}{\alpha} = 1 + \frac{2d_T}{\frac{\alpha}{\beta}} \tag{3d}$$

where BED is the biologically effective dose, γ is log cell kill per Gy, and d_T is the transition dose into the linear portion of the survival curve at high doses; based on a crude approximation developed in reference 26, γ/α=5. Note that if $d < d_T$ the LQ-L model is the same as the traditional LQ model, but at high single fraction doses, BED in the LQ-L model increases linearly, a behavior observed in some cell survival studies.

The value of α/β that emerges from fitting the data to Equation 1 depends on which cellular response model is applied. The LQ model yielded a larger value for α/β than the LQ-L. This is similar to the observation of Brown et al.(28) in discussing fits of the two models to cell survival curves.

For the VS TCP data modeled here, though both models were statistically significant, the LQ-L yielded a marginally better fit and tighter confidence intervals. However, both models are currently in use for hypofractionation and sufficient data at lower doses are needed to decide between models. The fit quality was assessed with chi square goodness-of-fit statistics. Confidence intervals were calculated with the Agresti-Coull method, and confidence intervals were estimated using profile likelihoods, all at a nominal 95% confidence level. Both fits were statistically significant ($p < 0.0001$) as measured by the chi square goodness-of-fit statistic, and the dotted lines represent 95% confidence bands with their ranges shown in the legends of Figure 1b (LQ Model with TCP(0)=30%), Figure 2 (LQ-L Model with TCP(0)=30%) and Supplemental Figure 1 (LQ model with TCP(0)=0%).

In the case of LQ (Figure 1b), α/β = 12.4 Gy (95% CI: 9.0–19.3), compared with α/β = 2.97 Gy (95% CI: 1.72–4.27)) using the LQ-L model (Figure 2) and hence d_T = 5.94 Gy in this case. Note the discrepancy between LQ and LQ-L estimate of $\frac{\alpha}{\beta}$ in this case, where LQ tends to overestimate the radiation response as mentioned earlier(28) while the LQ-L provided a more consistent estimate with radiobiological intuition. For LQ, the $EQD2_{50}$ was 3.48 (95% CI: 3.15–4.08), $\gamma 50$ was 0.15 (95% CI: 0.12–0.17), and EQD2 of 13, 19, 25, 33 Gy yielded a predicted TCP of 80%, 90%, 95% and 98%, respectively. In the case of LQ-L, $EQD2_{50}$ was 5.15 Gy (95% CI: 4.67–5.87), $\gamma 50$ was 0.16 (95% CI: 0.13 – 0.18), and EQD2 of 18, 26, 35, 45 Gy yielded a predicted TCP of 80%, 90%, 95% and 98%, respectively. The physical doses predicted to give these TCP levels by both the LQ and the LQ-L cellular response models are shown in Table 2.

Using the LQ model, single-fraction doses of 10 Gy, 11 Gy, 12 Gy, and 13 Gy predicted a TCP of 85.0%, 88.4%, 91.2% and 93.5%, respectively. For fSRS, 18 Gy in 3 fractions (EQD2 of 23.0 Gy) and 25 Gy in 5 fractions (EQD2 of 30.2 Gy) corresponded to TCP of

93.6% and 97.2%, respectively. Using the LQ-L model, single-fraction doses of 10 Gy, 11 Gy, 12 Gy, and 13 Gy predicted a TCP of 89.7%, 93.1%, 95.6% and 97.33%, respectively. For fSRS, 18 Gy in 3 fractions (EQD2 of 32.5 Gy) and 25 Gy in 5 fractions (EQD2 of 40.1 Gy) corresponded to TCP of 94.0% and 96.9%, respectively.

7. SPECIAL SITUATIONS

The TCP for VS among patients with neurofibromatosis (NF2) is lower than that for sporadic VS(18); i.e., approximately 75% at 5-years in a systematic review(19). Because of the lower TCP and concern for a potentially greater risk of malignant transformation from radiation(29), NF2 patients are usually offered resection for VS and less commonly treated with SRS. We excluded studies of TCP for VS that were specific to NF2 patients. When a study included patients with NF2, we excluded their data. Similarly, we attempted to exclude data in patients with progression following prior surgical resection. We also did not specifically analyze repeat SRS for treatment failure following SRS, an uncommon scenario given the relatively high TCP. TCP of VS in the pediatric population (uncommon outside of NF2 patients) was also not analyzed. One should not apply the results of our modeling to types of patients not included in the models; we again wish to emphasize the uncertainties in the extrapolated data in the dose range less than 11 Gy in a single fraction, as highlighted in sections 8 and the figure and table captions.

8. DOSE/VOLUME OUTCOMES SUMMARY

For single-fraction radiosurgery, a minimum dose of 12 to 13 Gy ($EQD2_{12.4}$: 20.3 – 22.9 Gy) covering the VS is associated with a TCP of over 90% (figure 1, Table 2) and is thus likely reasonable in most cases. A single fraction dose equivalent lower than 12 Gy is expected to have lower TCP, consistent with the series reporting 5-year tumor control of 91% in 420 patients with 11 Gy(15) and 91% for 20 Gy in 5 fractions(17). Although a few series included patients treated with tumor marginal doses of 10 Gy(30–32) ($EQD2_{12.4}$= 15.6 Gy), the local control data in the subsets of patients treated to low doses were not separately reported and thus not analyzable for modeling. There are very few reported patients treated to <10 Gy to reliably know the resultant TCP, and the model-based extrapolations to these doses are most uncertain.

For fSRS, a marginal dose of 18 Gy in 3 fractions ($EQD2_{12.4}$ = 23.0) or 25 Gy in 5 fractions ($EQD2_{12.4}$ =30.2 Gy) is associated with a very high TCP and is likely reasonable in most cases. However, there are fewer studies(33,34) investigating such an approach compared to single-fraction SRS, and the reported results vary greatly depending upon which definition of ‘treatment failure’ is used (see section 5).

We did not analyze outcomes for treatment in more than 5 fractions. Of note, a large pooled analysis of 451 patients treated with SRS (n=169) or fractionated stereotactic radiotherapy (n=291) found 10 year local control of 94%, with no difference (p=0.4) between a median of 13 Gy in 1 fraction or 54 Gy in 30 fractions, concluding SRS and fractionated stereotactic radiotherapy to be ‘equally effective’(35). Similarly, no differences

were seen in Normal Tissue Complication Probability (NTCP) endpoints such as hearing preservation, and trigeminal and facial nerve toxicity.

9. FUTURE STUDIES

Given a TCP in excess of 90% with tumor margin doses equivalent to a single fraction of 12 Gy, one may consider de-escalating the prescribed marginal dose, either to a portion or the entirety of the tumor, in prospective studies. The rationale for lower doses would be to reduce normal tissue complication probability. While the risks of facial (1.5%(36)) and trigeminal nerve (1.6%(37)) toxicity are low with 12 Gy equivalent dose, progressive hearing loss (which occurs in at least 25–40%(38)) remains an issue in these patients(38).

Currently, for most radiosurgical centers, the first priority in treatment planning is tumor coverage in order to maximize local control. However, given the high local control rates and data supporting that lower cochlear dose may correlate with hearing preservation(39–41), consideration is being given to first prioritizing cochlear dose, allowing relative under coverage of the tumor closest to the cochlea, while maintaining a full 12 – 13 Gy to the majority of the tumor. However, some data find no correlation between cochlear dose and hearing outcomes(42). The rationale for this concept is supported by surgical data where residual tumor following a sub-total resection (perhaps analogous to tumor under-dosed by SRS) may not grow with observation(43).

The nature of hearing loss after SRS for VS is multifactorial. Besides normal age-related decline, hearing loss is likely influenced by compression from the tumor on vessels and nerves, as well as from irradiation of the nerves, vessels, cochlea and brainstem. An area of uncertainty to explore is the role of hypofractionation to minimize NTCP while maintaining or improving TCP. Despite the many factors associated with hearing loss in patients with VS, a modifiable factor which may improve hearing is a lower SRS dose. Given concerns for TCP, such data should ideally be obtained on a prospective protocol. Understanding the interplay between NTCP and TCP in these patients is a challenge but also opens the door for future investigations.

10. REPORTING STANDARDS FOR OUTCOMES

As noted above, the key limitation in extracting information for TCP analysis for SRS for VS is the low quality in reporting dosimetric data associated with statistically valid, well-defined definitions of tumor control. Although VS consensus reporting guidelines exist(44) for describing aspects such as tumor size, location, and TCP and NTCP outcomes following surgical resection, their proposed section on radiotherapy is not applicable for TCP analysis following SRS. To help interpret future data, we recommend detailed reporting of dosimetric variables common to SRS/fSRS. We recommend that future publications expand on previous reporting recommendations(45) as shown in Table 3, either in the primary manuscript or as supplemental data.

Reason for Treatment:

Given that these tumors sometimes do not grow with short-term observation, future manuscripts should clearly report the indications for treatment, including the percentage of patients treated due to: (1) tumor growth on observation (and time to progression since initial diagnosis); (2) worsening of symptoms on observation (as tumor growth may not correlate with worsening of symptoms); (3) new diagnosis with symptoms and/or tumor size warranting treatment; or (4) new incidental (i.e. without symptoms) diagnosis with patient opting for treatment.

Definition of Tumor Control:

As above, determining control of a VS following SRS can be difficult, as post-SRS enlargement on imaging, which can occur for several years, does not equate to local progression of tumor following treatment. We recommend detailed reporting of how 'treatment failure' is defined, ideally by multiple measures such as 1) sustained growth on imaging following a period of swelling, 2) progression of symptoms leading to subsequent treatment, 3) need for subsequent treatment (salvage resection or repeat SRS), 4) the number of patients whose control is uncertain - for instance, there is a small percentage of patients whose tumor is enlarging, but the final disposition (post-SRS swelling vs. true tumor progression) is not yet known.

Statistical Methods:

A major limitation of the reviewed data is the lack of outcome reporting incorporating actuarial, cumulative incidence or Kaplan-Meier methods to account for latency and censored data from the competing risk of intercurrent death, with many papers only reporting crude incidence of local control.

Radiosurgical Dosimetry:

No manuscript reviewed had detailed radiosurgical dosimetry. We recommend complete reporting as in Table 3, in prior SRS reporting guidelines(45,46), and per the International Commission of Radiation Units and Measurements (ICRU) report 91(47), ideally with complete DVHs (Dose Volume Histograms) or a condensation of the information such as an actuarial dose-volume histogram atlas of local control(48) submitted as supplemental material. Potentially, for tumors with treatment failure, dosimetric reporting and statistical analyses of these tumors separate from controlled tumors may provide insight into the minimum dose needed for tumor control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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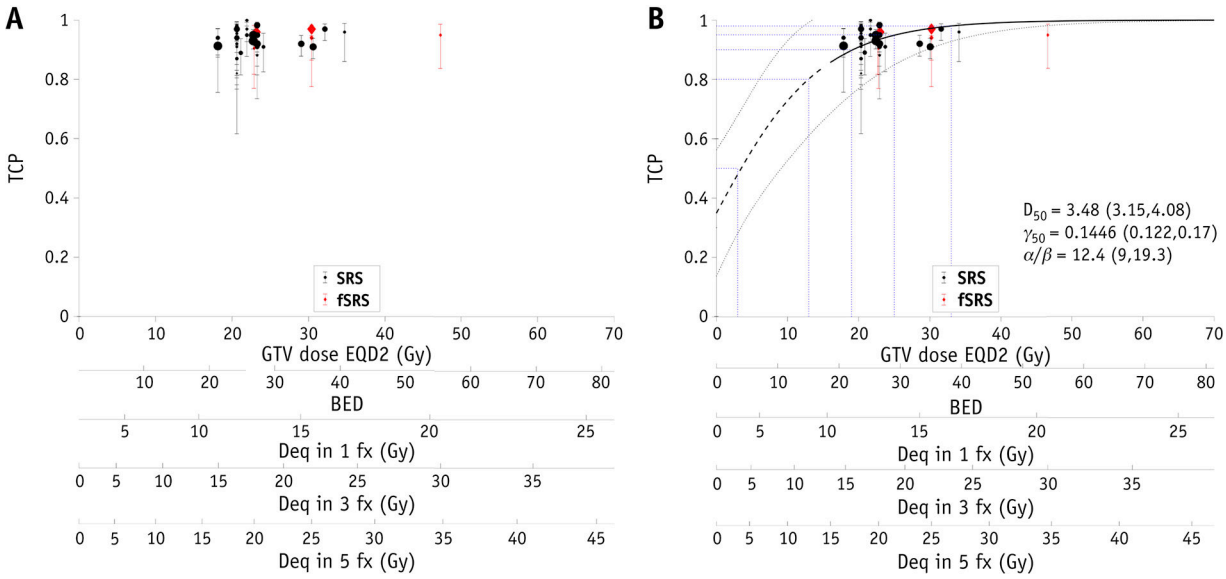

Figure 1.

a: 3–5 year data of Tumor Control Probability

Data for 3–5 year vestibular schwannoma tumor control probability (TCP) following stereotactic radiosurgery (SRS – black dots) and hypo-fractionated SRS (fSRS – red dots) from the literature summarized in Supplemental Table 2. Each study's dot size represents the number of patients in the study and the error bars represent the associated binomial 95% confidence interval. Conversion scales for biologically effective dose (BED), dose equivalent (Deq) in 1 fraction, 3 fractions, and 5 fractions are also provided (with α/β of 12.4 Gy).

b: 3–5 year TCP with LQ Model and TCP(0)=30%

Tumor Control Probability (TCP) plot of vestibular schwannoma control following stereotactic radiosurgery (SRS – black dots) and hypo-fractionated SRS (fSRS – red dots) with a three parameters Poisson model and the observation point of TCP at 0 Gy set to 30% (i.e., the best-fit curve is not forced to go through the zero-dose point). The dotted line represents extrapolation of the curve where no data exist. EQD2 conversion was conducted using the LQ model. Conversion scales for biologically effective dose (BED), dose equivalent (Deq) in 1 fraction, 3 fractions, and 5 fractions are also provided (with α/β of 12.4). Error bars and bands represent 95% confidence levels.

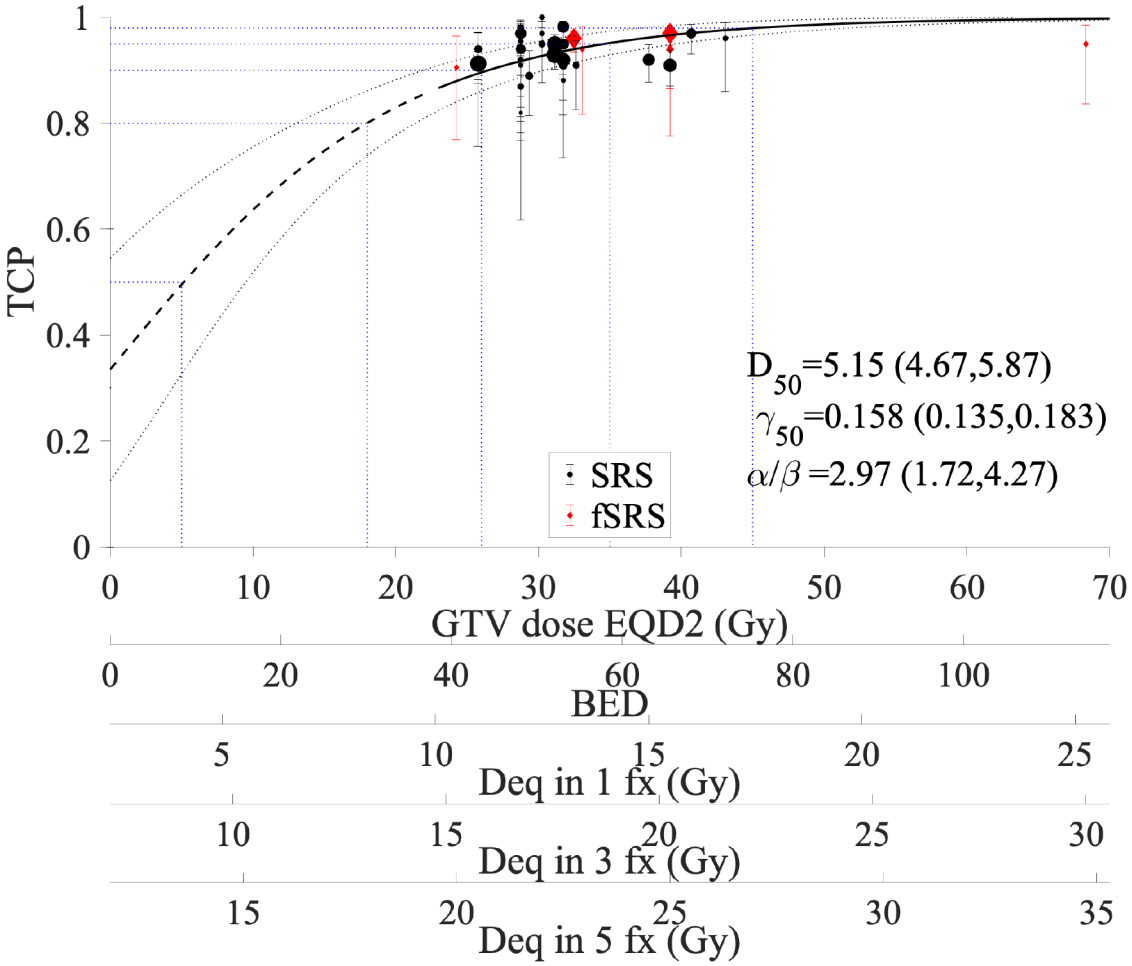

Figure 2: 3–5 year TCP with LQ-L Model and TCP(0)=30%

Tumor Control Probability (TCP) plot of vestibular schwannoma control following stereotactic radiosurgery (SRS – black dots) and hypo-fractionated SRS (fSRS – red dots) with a three parameters Poisson model and the observation point of TCP at 0 Gy set to 30% (i.e., the best-fit curve is not forced to go through the zero-dose point). The dotted line represents extrapolation of the curve where no data exist. EQD2 conversion was conducted using the LQ-L model. Conversion scales for biologically effective dose (BED), dose equivalent (Deq) in 1 fraction, 3 fractions, and 5 fractions are also provided (with a/b of 2.97). Error bars and bands represent 95% confidence levels.

Table 1:

Data Characteristics of the Reviewed Manuscripts, Highlighting the Heterogeneity of Reporting

Manuscript Characteristics	Percentage of the 35 Total Manuscripts Reviewed
Indication for treatment stated	51%
-Newly Diagnosed	17%
-Progression on Observation	37%
-Following prior surgery	9%
Volumes clearly defined:	
-GTV	71%
-PTV	29%
Machine:	
-Gamma Knife	80%
-CyberKnife	11%
-Linear Accelerator	17%
Fractionation/Dose:	
−1 fraction. <12 Gy	3%
−1 fraction. 12–13Gy	63%
−1 fraction. >13 Gy	14%
−3 fractions. 18–21 Gy	6%
−5 fractions. 25 Gy	9%
Local Control Reporting:	
Definition of ‘Local recurrence’ stated	100%
Local recurrence defined by:	
-Radiologic progression	66%
-Symptomatic progression	26%
-‘Need for Salvage Treatment’	31%
Reported Statistical Analysis:	
Crude Incidence	74%
Kaplan-Meier estimates	46%
Kaplan Meier Control Curve shown	43%
Dosimetry Details:	
-Prescribed Dose	100%
-Isodose Line	89%
-Dmaximum	91%
-Dminimum	31%
-Conformity Index	26%
-Heterogeneity Index	11%
-Dose Volume Histograms	0%

Table 2:

Model-based 3–5 year Tumor Control Probability (TCP) summary for 1, 3, and 5 fraction SRS, per baseline tumor control at 0 Gy of 30% and based on an alpha/beta ratio of 2.97 Gy with LQ-L model and 12.4 Gy for LQ. Note that there are no TCP data for less than the equivalent of 11 Gy in a single fraction, therefore the model outcomes represent extrapolation at doses below this level with a large range of error.

Data Included in Model per Length of Follow-up	3–5 Year TCP	EQD2 (Gy)	1 fraction SRS equivalent dose (Gy)	3 fraction fSRS equivalent dose (Gy)	5 fraction fSRS equivalent dose (Gy)
LQ model (α/β= 12.4)	98%	33	16.5	23.5	26.8
	95%	25	13.8	19.2	21.5
	90%	19	11.5	15.6	17.3
	80%	13	8.8	11.5	12.6
LQ-L model (α/β = 2.97)	98%	45	17.4	22.2	26.8
	95%	35	14.1	18.8	23.0
	90%	26	11.1	15.7	19.1
	80%	18	8.4	12.5	15.0

Table 3

Model-based 3- to 5-year TCP summary for 1, 3, and 5 fraction SRS, per baseline tumor control at 0 Gy of 30% and based on an alpha/beta ratio of 2.97 Gy with LQ-L model and 12.4 Gy for LQ

Recommended Standards for Future Vestibular Schwannoma Reports	
Component of Report	**Potential Examples to Report**
Study Characteristics	Retrospective, Prospective Single- or Multi-Institution New analysis or an update of a previous report Date range of treated patients
Patient Characteristics	Age Sex Neurofibromatosis Type II (yes/no) Prior treatment
Indication for Treatment	If no prior treatment: Growth on observation (%) Hearing decline on observation (%) Prophylactic treatment at time of initial diagnosis (%) Time from initial diagnosis to SRS If prior surgery: Extent of prior surgical resection (gross-total vs. sub-total) Growth of residual disease following sub-total resection (%) Recurrence of disease following gross-total resection (%) Time from initial diagnosis to surgery Time from surgery to SRS
Treatment Characteristics	SRS device description Linac vs. Cobalt-based Frame-based vs. Frameless Software used for planning Calculation algorithm (e.g., monte carlo, pencil beam, other) Heterogeneity corrections used Use of post-SRS medications (e.g., dexamethasone) Treatment time per fraction If more than 1 fraction, then number of fractions and total number of elapsed days
Contour Definition and Delineation	Imaging modality used (CT and/or MRI with or without contrast) MRI sequences used Definition of the gross target volume (GTV) Definition of PTV (e.g., was a margin added to the GTV and if so, was it a uniform or non-uniform margin) Maximum diameter in three cardinal planes Volume of final target
Radiosurgical Dosimetry	Prescription dose How the prescribed dose is defined (e.g., to isocenter, marginal dose) Prescription isodose line Percent coverage of GTV or PTV at the prescription isodose line Values of coverage (D100%, D95%, D90%, D85%, V100, V95, V90, V85, etc.) Conformity index (CI) Gradient index (GI) Heterogeneity index (HI) Complete DVH values
Statistical Methods	Reporting of missing clinical follow-up or imaging data Values listed as median, range (minimum and maximum), and interquartile ratio Kaplan-Meier analysis (not crude incidence), with complete curves shown (confidence intervals, censor marks, number of patients at risk per time point)
Follow-Up	Type and frequency of clinical and imaging follow-up Length of follow-up
Definition of Local Failure of Tumor	1. Tumor Growth – need to distinguish from the expected post- SRS tumor swelling: a graph of each tumor's relative volume following SRS over time may aid in distinguishing the six possible outcomes: -Tumor is Controlled if: 1. No swelling 2. Swelling followed by shrinkage 3. Swelling followed by stability -Tumor Control is Not Yet Determined if: 4. Tumor continues to increase in size, but the need for salvage treatment has not yet been determined

Recommended Standards for Future Vestibular Schwannoma Reports	
Component of Report	**Potential Examples to Report**
	-Tumor Progression: 5. Stability followed by growth years later 6. Continued growth beyond the expected swelling period 2. Need for subsequent treatment following SRS: Define the reason for salvage treatment (e.g., clinical progression vs. enlargement on imaging vs. both)
Analysis of Local Failures	For those that progressed, complete dosimetric reporting of those failures compared to controlled tumors (Dose, Coverage, Conformity Index, Dminimum, Dxx% and Vxx data) Univariate/Multivariate analysis of factors predictive of outcomes

Abbreviations:
GTV – Gross target volume
PTV – planning target volume
Dxx% - Minimum dose received by xx% of the Target volume
Vxx – Volume of target covered by at least xx% of the prescribed dose