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PREDICTED DOSE–VOLUME ISOEFFECT CURVES FOR STEREOTACTIC RADIOSURGERY WITH THE ^{60}Co GAMMA UNIT

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Abstract

Mathematical models were developed to predict tolerance of brain tissue to stereotactic radiosurgery. The use of these formulas for predicting symptomatic brain necrosis from stereotactic radiosurgery with the ^{60}Co gamma unit is discussed. Predicted dose–response curves for different collimator sizes were calculated. Dose–volume isoeffect curves for a 3% risk of brain necrosis from a single fraction radiosurgery were then derived. Dose–volume isoeffect curves for combinations of fractionated whole brain irradiation with radiosurgery boosts were also calculated. The predicted dose–volume isoeffect curves provide useful tolerance guidelines for the practice of stereotactic radiosurgery.

Key words: Stereotactic radiosurgery, brain radiation tolerance linear quadratic, ^{60}Co gamma unit.

Stereotactic radiosurgery has developed into an invaluable technique for irradiating small unresectable targets in the brain with relative sparing of normal tissue. The development of the ^{60}Co gamma unit or 'gamma knife' (1) as well as charged particle treatment techniques and later development of techniques based on linear accelerators have resulted in stereotactic radiosurgery being practiced in many centres throughout the world (2–19). Impressive results with the gamma unit have been reported in the treatment of small, unresectable arteriovenous malformations and tumours such as acoustic neurinomas, craniopharyngiomas, pinealomas and pituitary tumours (15, 16, 20–23).

Single-fraction doses greater than 10 Gy used in radiosurgery are outside the usual practice of radiation oncology, since conventional radiation treatments usually employ relatively large radiation fields and are fractioned over one to seven weeks. While the majority of conventional radiation treatments employ doses of 1.6–4.0 Gy per fraction, most gamma knife treatments have been given with single-fraction doses of 16–25 Gy to the target volume with maximum doses as much as twice these values. Even higher doses have been used for functional radiosurgery with 3 × 5 or 3 × 7 mm collimators for conditions such as intractable pain where doses greater than 150 Gy are required to intentionally produce sharply demarcated necrotic lesions in normal brain (24).

The development of dose guidelines for treating different conditions with stereotactic radiosurgery is a complex task due to several factors. First of all, tumours and arteriovenous malformations vary in size, shape, and are located in different parts of the brain. The treatment isodose volumes used to enclose these tumours or malformations encroach on varied but small volumes of normal brain tissue. Treatment is administered with inhomogeneous radiation dose distributions using different collimator sizes and one or more isocenters. This all makes the representation of the biological effect of the radiation more difficult. Kjellberg et al. (7) have published an estimated 1% dose-volume isoeffect line for radiation necrosis from proton beam irradiation. This has been used by some groups as a starting point for selecting treatment doses for linear accelerator stereotactic radiosurgery (17).

The integrated logistic formula was specifically developed to predict complications from stereotactic radiosurgery with the gamma unit (25). The tolerance predictions of the exponential and linear quadratic versions of the integrated logistic formula have been used at the University of Pittsburgh to provide guidelines for

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prescribing treatment doses using the newly developed 18 mm diameter collimators on the Pittsburgh gamma unit, for treatment with multiple isocentres, and for stereotactic radiosurgery combined with fractionated, large field (whole brain) radiotherapy.

Material and Methods

Treatment planning for the gamma unit at the Presbyterian-University Hospital of the University of Pittsburgh is performed on a MicroVax II computer using specially developed software which adds measured single beam data from the direction of each of the 201 different 1-mm cobalt-60 sources. In-phantom film and LiF thermoluminescent dosimetry studies at both the University of Pittsburgh and in Sheffield, England showed good agreement between computer generated dose profiles and measured isodose distributions (11, 19, 26).

Risk calculations were based upon dose–volume histogram data from computer treatment plans. A 16 cm spherical tissue phantom was used to approximate the size of an average skull with the centre of the sphere selected as the treatment isocenter.

Integrated logistic formula

The derivation of the integrated logistic formula is discussed elsewhere (25). A generalized version of the integrated logistic formula is shown below:

$$1 - P = \prod_i \{[NTD_2 d(i)/NTD_2 D_{50}(r)]^{k(r)} + 1\}^{-v(i)/V(r)} \quad [1]$$

were $1 - P$ is the total probability that no brain necrosis occurs anywhere in the brain. This probability is the product of the probabilities of necrosis which could be described by any number of separate dose–response functions. Each dose–response function is described by different parameters for $D_{50}(r)$, $k(r)$ and a reference volume $V(r)$. The volume increment with any segment that has received a normalized total dose of $NTD_2 d(i)$ is represented by $v(i)$.

Normalized tolerance dose, NTD, is a convenient generalized way of representing the biological effect of a course of radiation. NTD is defined at the total dose of radiation administered at a specified reference dose per fraction (indicated by the subscript 2, for 2 Gy per fraction) 5 fractions per week which is predicted to have a biological effect equivalent to the course of radiation received by the patient according to the dose fractionation formula under consideration (25, 27–30). For a simple exponential formula such as Normalized Standard, Neuret, or variable exponent TDF, the NTD value is equal to the value of the variable exponent TDF multiplied by a different normalization constant (29, 31–32). Similarly any NTD value based upon the linear quadratic factor (LQF) is equal to the LQF formula multiplied by a different normalization constant (29, 31). The exponential version of the integrated logistic formula used values for NTD that are calculated based upon the Neuret formula and the linear quadrantic version is based on the LQF formula and uses an alpha/beta ratio of 3.3.

$$NTD_2(\text{Neuret}) = \sum_i 0.5206 n_i d_i^{2.00} (t_i/n_i)^{-0.12} \quad [2]$$

$$NTD_2(\text{LQF}) = \sum_i n_i (0.1887\, d_i^2 + 0.6226\, d_i)(t_i/n_i)^{-0.12} \quad [3]$$

Since separate dose–response functions for different parts of the human brain and for different target cell populations of functional subunits have not been well categorized it is reasonable to use the following simplified version of the integrated logistic formula; below a dose of 100 Gy:

$$1 - P = \prod_i \{[NTD_2 d_{(i)}/72.19]^k + 1\}^{-v(i)/1136} \quad [4]$$

An average whole brain volume of 1 136 cm^3 is used in the above equation (tables of average brain weights or volumes are available classified according to age, sex, and race) (33). The choice of values for $NTD_2 D_{50}$ and k has been previously discussed (25). An average value for $NTD_2 D_{50}$ of 72.19 Gy is used in the above equation. The acceptable range of values of k appears to be between 11–20 (25, 31, 34, 35). In order to normalize the risk of radiation necrosis of 3% for gamma knife radiosurgery to 25 Gy with a 14 mm diameter collimator, values of $k = 12.2$ and $P = 0.04$ should be used with the exponential and $k = 18.5$, $P = 0.02$ with the linear quadratic version of the integrated logistic formula.

One can switch from using NTD_2 values to actual doses when the exponential model is used for calculating necrosis probabilities for single fraction radiosurgery, by rearranging the equation and substituting the single fraction equivalent to the NTD_2 of 72.19 Gy which is 12.02 Gy. This simplifies the expression to the following:

$$1 - P = \prod_i \{[d_{(i)}/12.02]^{24.4} + 1\}^{-v(i)/1136} \quad [5]$$

Since the target volume contains tumor or arteriovenous malformation instead of brain tissue, it was assumed that the target volume would not contribute to the risk of necrosis and should be excluded from the risk calculations. Since treatment isodose volumes rarely match target volumes exactly, only the inner 60% of the treatment isodose volume was excluded from all risk calculations to represent an average target volume treated for each collimator size.

Results

The dose–response functions for brain necrosis predicted by the exponential version of the integrated logistic

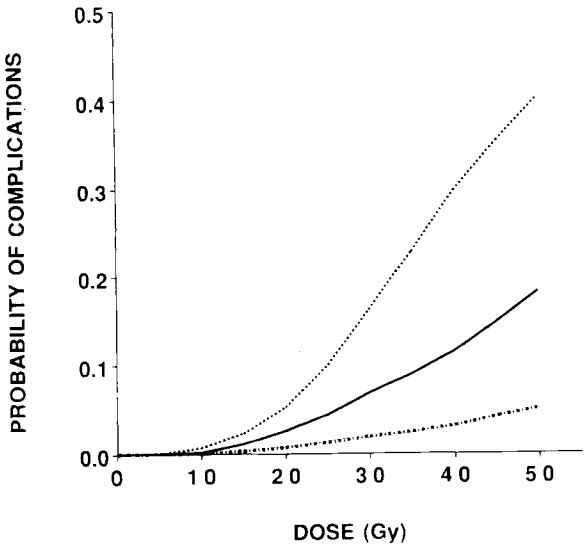

Fig. 1. Dose–response curves for brain necrosis predicted by the exponential version of the integrated logistic formula for single fraction stereotactic radiosurgery with the gamma unit using 8, 14 and 18 mm diameter fields. Doses represented are the minimum dose (Gy) to the treatment volume at the 50% isodose.

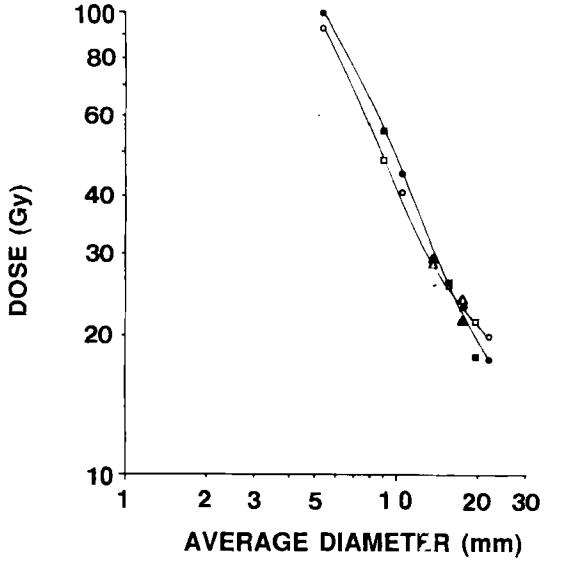

Fig. 2. Dose–volume isoeffect curves for a 3% risk of brain necrosis from a single-fraction gamma knife radiosurgery predicted by the linear quadratic and exponential versions of the integrated logistic formula. Dose is represented by the minimum dose (Gy) to the treatment volume used. The circles, squares and triangles represent doses prescribed to the 50%, 65% and 80% isodose volumes respectively for a single isocenter radiosurgery with either 4, 8, 14 or 18 mm diameter fields. The average diameter refers to the average diameter (mm) of the treatment isodose volume (50%, 65% or 80%).

formula are shown in Fig. 1 for the 8, 14, and 18 mm collimators. The doses shown refer to the minimum dose prescribed to the treatment volume at the 50% isodose.

Fig. 2 shows dose–volume isoeffect curves for a 3% risk of brain necrosis predicted by both the exponential and

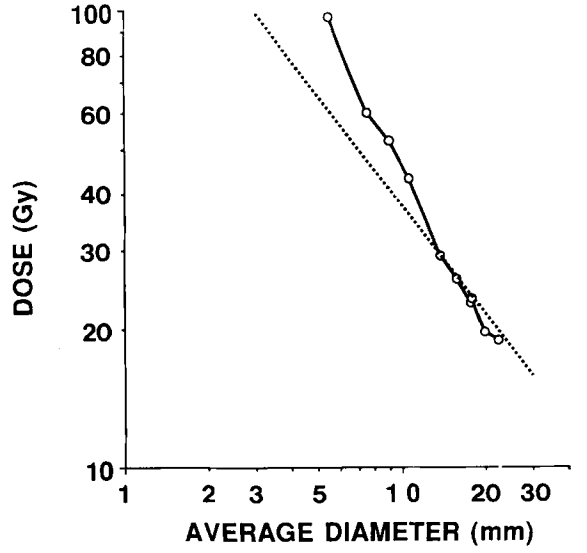

Fig. 3. A 3% dose–volume isoeffect curve for brain necrosis from single-fraction gamma knife radiosurgery averaged from predictions by the linear quadratic (LQ) and exponential (Ex) versions of the integrated logistic formula. Doses are represented by the minimum dose (Gy) to the treatment volume at the 50% isodose (○), 65% isodose (□) or 80% isodose (△). The average diameter (mm) is that of the treatment isodose volume treated (50%, 65%, or 85%). For comparison, the 1% isoeffect line for brain necrosis from proton beam irradiation described by Kjellberg et al. (7) is included.

linear quadratic versions of the integrated logistic formula. Individual calculations were made for single isocentres for treatment doses prescribed to the 50%, 65% and 80% isodoses. The 'average' treatment volume diameter indicated in Fig. 2 is defined as the diameter of a sphere with a volume equivalent to the treatment isodose volume used. For an ellipsoidal shape, the average treatment volume diameter is equal to the cube root of the product of the diameters through the major and two minor axes. As can be seen in Fig. 2, there is little or no deviation from either of the dose–volume isoeffect curves due to differences in the tolerance dose predictions caused by the effects of treating to either the 50%, 65% or 80% isodoses. For treatment volume diameters less than 16 mm, the linear quadratic version of the integrated logistic formula gives a more conservative tolerance dose prediction and for diameters above 17 mm, the exponential version is more conservative. Averaging the tolerance dose predictions from both versions of the integrated logistic formula, as shown in Fig. 3, provides a single isoeffect curve that provides reasonable dose–volume guidelines for the practice of stereotactic radiosurgery with the Leksell gamma unit. The 1% isoeffect line for brain necrosis from proton beam irradiation reported by Kjellberg et al. (7) is compared to the dose–volume isoeffect curves predicted for gamma knife radiosurgery by the integrated logistic formula in Fig. 3. The slope of the integrated logistic

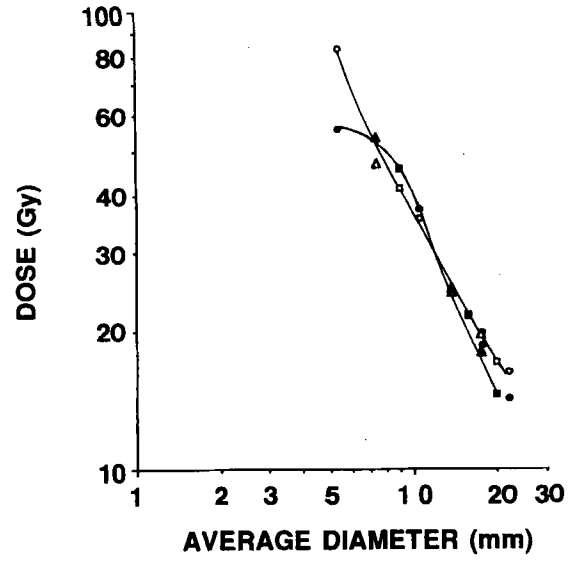

Fig. 4. Dose–volume isoeffect curves predicted by the linear quadratic and exponential versions of the integrated logistic formula for a 3% risk of brain necrosis from 30 Gy of whole brain irradiation to midplane administered in 12 fractions, 5 fractions per week followed by a single fraction gamma knife radiosurgery. Radiosurgery doses represented are those prescribed (in Gy) to treatment volumes consisting of either the 50% isodose (○), 65% isodose (□) or 80% isodose (△). The average diameter refers to the average diameter (mm) of the treatment isodose volume.

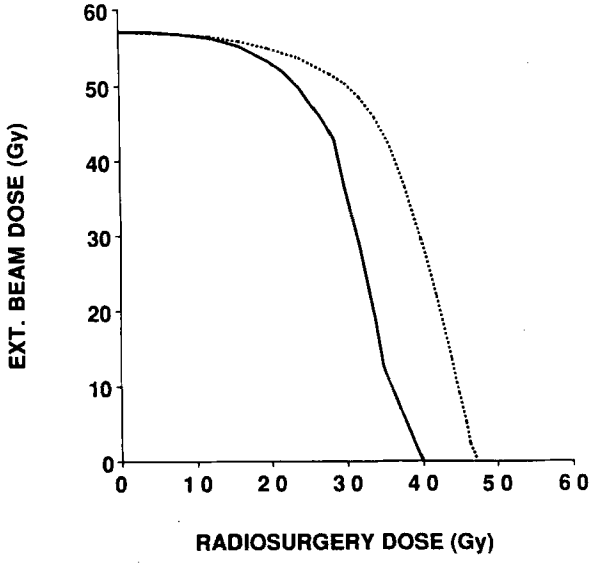

Fig. 5. Combinations of a single fraction, gamma knife radiosurgery using 14 or 18 mm diameter collimators with different total doses of fractionated whole brain irradiation administered at 2 Gy per fraction, 5 fractions per week, which are predicted to have a 3% risk of brain necrosis by the integrated logistic formula. Fractionated whole brain doses are averaged from predictions for both the exponential and linear quadratic versions of the integrated logistic formula.

formula appears to be slightly greater, particularly at small volumes.

A 3% risk dose–volume isoeffect curve for brain necrosis from stereotactic radiosurgery combined with 30 Gy of whole brain irradiation administered in 12 fractions is shown in Fig. 4. Two different 3% risk isoeffect curves for brain necrosis from varied combinations of fractionated whole-brain irradiation and radiosurgery with 14 and 18 mm collimators radiosurgery are shown in Fig. 5. The whole-brain irradiation doses are for treatment at 2 Gy per fraction, 5 fractions per week. Doses for the radiosurgery portion of the combined treatment are specified at the 50% isodose treatment volume.

Discussion

The integrated logistic formula is potentially quite useful for guiding the choice of treatment dose for different collimator or treatment volume sizes, and for combining fractionated large-field irradiation and stereotactic radiosurgery. Since there is only limited data available regarding treatment complications from stereotactic radiosurgery on which to base formulas such as these, the complication probabilities predicted from both versions of this formula cannot be regarded as completely reliable and are no substitute for clinical experience. A thorough analysis of data from careful follow-up of a large number of radiosurgery patients is needed to test when, if ever, the integrated logistic formula can predict complications and to find the most appropriate values of D_{50}, k and V to use. There is a particular need for data regarding the tolerance to radiosurgery in different portions of the brain. If different target cell populations or functional subunits exist with different dose response of functions and can be clearly defined these should be incorporated into appropriate tolerance formulas. Models such as the local stem cell depletion model and functional subunit model could be applied to stereotactic radiosurgery and examined when more clinical data are available to see if they are applicable and can more accurately predict complications (36–39). It is unlikely that cranial nerve tolerance will be the same as the rest of the brain so a simplified integrated logistic formula like eq. 4 or 5 without a separate expression to describe cranial nerve tolerance will not predict cranial nerve complications.

Despite the limitations of the integrated logistic formula, it appears to be the most useful method presently available for predicting complications from stereotactic radiosurgery. Hopefully, it should be quite useful in both guiding the practice of stereotactic radiosurgery and analyzing its results. Ultimately accumulated clinical data on radiation tolerance to these types of treatment will either verify of refute any dose–volume tolerance formulas and if necessary allow them to be appropriately modified.

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