Clinical and radiobiological advantages of single-dose stereotactic light-ion radiation therapy for large intracranial arteriovenous malformations

Technical note

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Object. Radiation treatment of large arteriovenous malformations (AVMs) remains difficult and not very effective, even though seemingly promising methods such as staged volume treatments have been proposed by some radiation treatment centers. In symptomatic patients harboring large intracranial AVMs not amenable to embolization or resection, single-session high-dose stereotactic radiation therapy is a viable option, and the special characteristics of high-ionization-density light-ion beams offer several treatment advantages over photon and proton beams. These advantages include a more favorable depth-dose distribution in tissue, an almost negligible lateral scatter of the beam, a sharper penumbra, a steep dose falloff beyond the Bragg peak, and a higher probability of vascular response due to high ionization density and associated induction of endothelial cell proliferation and/or apoptosis. Carbon ions were recently shown to be an effective treatment for skull-base tumors. Bearing that in mind, the authors postulate that the unique physical and biological characteristics of light-ion beams should convey considerable clinical advantages in the treatment of large AVMs. In the present meta-analysis the authors present a comparison between light-ion beam therapy and more conventional modalities of radiation treatment with respect to these lesions.

Methods. Dose-volume histograms and data on peripheral radiation doses for treatment of large AVMs were collected from various radiation treatment centers. Dose-response parameters were then derived by applying a maximum likelihood fitting of a binomial model to these data. The present binomial model was needed because the effective number of crucial blood vessels in AVMs (the number of vessels that must be obliterated to effect a cure, such as large fistulous nidus vessels) is low, making the Poisson model less suitable. In this study the authors also focused on radiobiological differences between various radiation treatments.

Results. Light-ion Bragg-peak dose delivery has the precision required for treating very large AVMs as well as for delivering extremely sharp, focused beams to irregular lesions. Stereotactic light-ion radiosurgery resulted in better angiographically defined obliteration rates, less white-matter necrosis, lower complication rates, and more favorable clinical outcomes. In addition, in patients treated by He ion beams, a sharper dose-response gradient was observed, probably due to a more homogeneous radiosensitivity of the AVM nidus to light-ion beam radiation than that seen when low-ionization-density radiation modalities, such as photons and protons, are used.

Conclusions. Bragg-peak radiosurgery can be recommended for most large and irregular AVMs and for the treatment of lesions located in front of or adjacent to sensitive and functionally important brain structures. The unique physical and biological characteristics of light-ion beams are of considerable advantage for the treatment of AVMs: the densely ionizing beams of light ions create a better dose and biological effect distribution than conventional radiation modalities such as photons and protons. Using light ions, greater flexibility can be achieved while avoiding healthy critical structures such as diencephalic and brainstem nuclei and tracts. Treatment with the light ion He or Li is more suitable for AVMs ≤ 10 cm in diameter, whereas treatment with the light ion Li, Be, or C may be more appropriate for larger AVMs. A binomial model based on the effective number of crucial vessels in the AVM may be used quite well to predict AVM obliteration probabilities for both small and large AVMs when therapies involving either photons or light ions are used. (DOI: 10.3171/2007.10.17205)

Key Words • arteriovenous malformation • stereotactic ion beam therapy • radiosurgery

Abbreviations used in this paper: AVM = arteriovenous malformation; D50 = radiation dose at which the response probability is 50%; FSU = functional subunit; γ = maximum normalized value of the dose-response gradient; GKS = Gamma Knife surgery; LET = linear energy transfer; LINAC = linear accelerator; RBE = relative biological effectiveness.

Intracranial AVMs are congenital vascular lesions that affect 0.01–0.5% of the general population; their diagnosis generally occurs in patients younger than 40 years.12 Symptoms are often subtle until complications occur. In many cases, AVM symptoms are related to hemorrhage from the abnormal vessels comprising
the AVM, which are often fragile and lack the supportive structure of normal arteries and veins. The risk of bleeding associated with AVMs is 2–4% per year, and ~50% of patients harboring these malformations present with hemorrhage. Symptoms may also occur due to lack of blood flow to some areas of the brain (ischemia), compression or distortion of brain tissue by large hemorrhages, or abnormal brain development in the area of the malformation. Although AVMs are present at birth, symptoms such as seizures, headache, and visual and mental disturbances may occur at any time. The combined morbidity—mortality rate after an initial AVM rupture has been recorded to be as high as 50–80%.

Within the last decade, there have been significant developments in the management of intracranial AVMs. The 3 main AVM treatment protocols currently in use include microsurgical removal, endovascular embolization, and radiotherapy. Each treatment modality is indicated for specific patients, and management strategies may include a single or combined method. Treatment efficacy, a critical outcome parameter, can be defined as the fraction of patients in whom angiographic studies show permanent obliteration of the lesion. For each treatment, efficacy depends on various factors that influence the obliteration and complication rates.

In treatment modalities such as endovascular embolization and microsurgery, the skill and dexterity of the operating neurosurgeon are paramount to success. In radiation therapy, success is not contingent on the expertise of the neurosurgeon. Instead, other factors predominate and reproducibility of results allows us to define the important parameters for treatment success and fewer complications, as well as to compare various types of radiation therapy methods more precisely.

The aim of this article is to compare different types of radiation—photons, protons, and light ions—for stereotactic radiosurgery of AVMs and to evaluate the possible benefits of high LET Bragg-peak radiosurgery.

Potentials and Properties of Ion Beams in the Treatment of Large AVMs

Light ions are nuclei of low-atomic-weight atoms that are fully stripped of their electrons. Light ions have atomic numbers between 2 and 6 (He, Li, Be, and C ions; the B ion is excluded because of its toxicity) and display significantly elevated ionization densities at the Bragg peak (Appendix A). In matter the energy deposition of light ions increases with penetration depth and reaches a maximum at the Bragg peak, just before the end of the penetration range. This behavior is due to the probability of high ionization when the speed of the ion coincides with that of the molecular electron clouds, resulting in charge interaction and increased ionization density. Within the therapeutically relevant energy range (up to several hundred mega-electron volts per atomic mass unit), the ionization density factor specified by the LET is dominated by electron collisions and is well described by the Bethe–Bloch formula.

Specially designed cyclotrons and synchrotrons are able to produce monoenergetic beams of charged particles with tissue penetration ranging up to 20 cm and farther, which is enough for stereotactic radiation therapy. The width of the Bragg peak can be spread out in the direction of such a beam by either interposing variable-thickness absorbers in the beam path or delivering a series of beams of reduced energies and intensities (Fig. 1).

For clinical application with stereotactic delivery, the lateral scattering of the beam may be as important as the longitudinal dose falloff. Comparative studies have produced evidence showing that the lateral scattering of protons exceeds that of photons for ranges > 10–15 cm. For light ions such as He and C, the lateral deflection is very small, with a penumbra one-half or less than that associated with protons. This is one major advantage that light-ion beam therapy has over photon and proton beam radiation therapies, especially when used for intracranial AVMs. Other major advantages light-ion treatment has over proton therapy include reduced range straggling and increased LET, which not only sharpen the Bragg peak but also increase the possibility that an elevated LET is accurately deposited only within the target volume. Because of possible uncertainties in particle range, treatment planning may need to be verified by imaging studies, such as PET or CT, to ensure that the beam stops directly in front of critical structures. How close the beam can pass by critical structures is determined by the ion beam optics collimator system and by lateral multiple scattering and longitudinal straggling. Lars Leksell tried first to use proton beams when irradiating small lesions in the brain. The multiple scatter and lateral penumbra were not good enough, however, so he designed the Gamma Knife instead. The lateral penumbra associated with light ions such as Li and C ions, is ~2–3 times sharper than that associated with protons, and thus a clear-cut advantage is obtained, particularly when narrow beams are used. Also the minimum target dose for an ion beam can be ~90% of the maximum dose, which is much higher than that delivered by the Gamma Knife or electron accelerators. In addition to the dose-distribution advantage, light-
Stereotactic light-ion radiation therapy for large AVMs

ion beams have an increased RBE, which is due to an increase in ionization density within the individual tracks of the ions, where complex double-strand DNA breaks become clustered and, therefore, more difficult to repair. Because the RBE is an important determinant for equivalent doses in light-ion beam radiation therapy, corrections for the equivalent dose have to be made by considering variations in the RBE. In the case of protons, on the other hand, RBE variation does not play a major role because the RBE is ~ 1.1.

In many studies the RBE in spread-out Bragg peaks of the He ion is considered to be 1.3; this is an estimation of the true mean RBE, which depends on cell line, LET, particle energy, ion atomic number, and cellular repair processes. For efficient vessel obliteration, Li and Be ions are probably ideal because they both have a high RBE in the Bragg peak and practically none elsewhere, saving normal tissue responses.

Clinical Experience

The most detailed reports about charged-particle radiation therapy of AVMs are about the use of proton and He ion beams. Detailed reports on light-ion radiation therapy of AVMs have been produced by the University of California at Berkeley–Stanford University collaborative program. Researchers in that program published clinical and radiological follow-up results in 86 patients with symptomatic, but surgically inaccessible, cerebral AVMs that were treated with stereotactic He ion Bragg-peak radiation. In almost half of these patients (44%) the AVM was located in the brainstem, corpus callosum, thalamus, or basal ganglia; in most of the remaining patients, a large AVM was located in a critical region of the cerebrum—a sensory, motor, language, or visual area of the cortex. One-quarter of the AVMs were > 25 cm³.

Although some investigators have suggested that stereotactic proton beam radiation therapy may be ineffective for treating AVMs > 3 cm, others state that it is Bragg-peak radiation therapy that has the required precision to treat very large and irregular AVMs (Fig. 2).

Posttreatment Morphological Findings

Posttreatment pathological examinations show regions of vascular constriction apparently due to abnormal proliferation of surviving endothelial cells. Denudation of the surface of blood vessels leads to thrombus formation and vascular necrosis. In general, veins are less susceptible to radiation than arteries.

Schneider et al. observed endothelial proliferation; hyaline and calcium deposits in AVM vessel walls, which were associated with partial or complete thrombosis of some AVM vessels; and necrosis of vessels and adjacent brain tissue. Blood vessels within AVMs undergo progressive changes leading to narrowing or obliteration of their lumina. Changes after irradiation include endothelial cell damage, which is followed by progressive thickening of the intimal layer, caused by proliferation of smooth-muscle cells that elaborate an extracellular matrix including type IV collagen, and finally, cellular transformation and hyaline degeneration. The histopathological findings and the relative number of degenerated vessels significantly change temporally and spatially during the follow-up period.

This sequence of pathological changes in AVMs after radiosurgery is essentially similar to the response-to-injury model for atherosclerosis. Conventional fractionated radiotherapy, which has not been effective in treating AVMs, has been unable to produce similar effective histological changes.

Various Radiosurgical Modalities for Treatment of Large AVMs

One difficulty in comparing obliteration probabilities in different clinical trials as a function of AVM size and radiation dose within a particular patient population is the study methodology that is followed. When comparing angiographic outcomes only, a meaningful interpretation and comparison of obliteration and complication rates can only be assured when there is sufficient follow-up time and clear reporting of clinical outcomes in all patients in all series.

Many researchers have established the efficacy of radiation treatment of AVMs < 14 cm³ (equivalent diameter 3.0 cm) when the Gamma Knife, LINAC, or light-ion beam delivery is used. Nidus obliteration rates of 65–96%, determined using angiography, have been reported, with associated complication rates below 10%. In an extensive retrospective study of patients treated with GKS, Karlsson and colleagues angiographically confirmed an AVM obliteration rate of 80% after 2 years of follow-up. In another study of patients treated with charged-particle Bragg-peak radiosurgery, total AVM obliteration was iden-
tified in 92% of patients and partial obliteration in 4% after 3 years of follow-up.26

The GKS study conducted by Karlsson et al.20 had a sufficient number of AVMs (945) to demonstrate the importance of minimum dose within subgroups stratified by AVM volume. The low obliteration rates observed for large AVMs are partly due to the low radiation doses with which they are generally treated—at a peripheral dose < 10 Gy only 40% obliteration is achieved. This should be expected on radiobiological grounds, given that variations between peripheral and maximal doses are large due to the physics of Gamma Knife dose distribution.4 It is important to know that for greater dose inhomogeneities, the minimum target dose is more closely related to the effective dose, and this is the reason that minimum dose plays a key role in many photon studies.3

A 67% obliteration rate has been reported for small AVMs treated by LINAC-based stereotactic radiosurgery.32,38,47 Limited data on the radiosurgical obliteration rate of large AVMs exist; however, many studies have shown lower rates of total obliteration for larger AVMs than for smaller ones. In a 3-year follow-up study of AVMs treated by LINAC radiosurgery, Miyawaki et al.32 demonstrated an obliteration rate of 67% for small AVMs (< 4 cm³) and a rate of 38% for larger ones (> 4 cm³). Colombo et al.6 found an obliteration rate of only 33% for AVMs > 2.5 cm in diameter. Similar studies have been reported by other researchers, as shown in Table 1.

In a study of AVMs > 4 cm³ that were treated with charged-particle Bragg-peak radiosurgery and observed for 2 years afterward, Steinberg48 found on angiography that total AVM obliteration occurred in 87% of lesions. This rate is much higher than those associated with other radiation treatment modalities. For AVMs > 4–5 cm³, obliteration rates have been reported to be 20–35% for proton therapy, 41–59% for GKS, and 38–51% for LINAC radiation treatment (Table 1).

In an comparative study of a variety of charged particles (He, C, and protons) and photons (Gamma Knife and LINAC systems), dose-volume histograms were calculated and a noticeable difference was observed between charged particle and photon modalities.26 The dose distributions of charged particles were more favorable than those of photons. Differences in conformation to the AVM between charged-particle and photon-beam treatments increased with the increasing size of the target volume. The dose distributions of the various charged particles were roughly comparable to each other, although the lateral penumbra was sharper when He and C ions were used.

In the series reported by Steinberg et al.,48 angiography demonstrated that after charged-particle Bragg-peak radiosurgery, the obliteration rate for AVMs > 25 cm³ improved from 39 to 70% between the 2nd and 3rd years of follow-up.

In another clinical trial involving LINAC radiosurgery, the obliteration rate for AVMs > 25 cm³ improved from 39 to 70% between the 2nd and 3rd years of follow-up.

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**TABLE 1: Obliteration rates after 3 years of follow-up as a function of treatment volume at various centers**

<table>
<thead>
<tr>
<th>Authors &amp; Year of Publication (institution)</th>
<th>Treatment Modality</th>
<th>AVM Volume</th>
<th>Minimum Dose (Gy)</th>
<th>Complete Obliteration Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kjellberg et al., 1983 (Massachusetts General Hospital)</td>
<td>proton beam</td>
<td>7–50-mm beam diameter</td>
<td>10–100 (entire series)</td>
<td>15/74 (20)</td>
</tr>
<tr>
<td>Steinberg et al., 1991 (Lawrence Berkeley Laboratory)</td>
<td>light-ion beam (He ion)</td>
<td>&gt;4 cm³</td>
<td>7.7–34.6 (GyE) (entire series)</td>
<td>26/30 (87)</td>
</tr>
<tr>
<td>Flickinger et al., 1996 (University of Pittsburgh)</td>
<td>Gamma Knife</td>
<td>&gt;5.5 cm³</td>
<td>12–25 (entire series)</td>
<td>20/49 (41)</td>
</tr>
<tr>
<td>Karlsson, 1996 (Karolinska Institute)</td>
<td>Gamma Knife</td>
<td>&gt;2 cm³</td>
<td>10–28</td>
<td>186/394 (47)</td>
</tr>
<tr>
<td>Ellis et al., 1998 (University of Florida)</td>
<td>LINAC</td>
<td>&gt;4 cm³</td>
<td>10–20</td>
<td>42/73 (58)</td>
</tr>
<tr>
<td>Miyawaki et al., 1999 (University of California, San Francisco)</td>
<td>LINAC</td>
<td>&gt;4 cm³</td>
<td>10–20</td>
<td>16/42 (38)</td>
</tr>
<tr>
<td>Mavroidis et al., 2002 (Tenon Hospital, Paris)</td>
<td>LINAC</td>
<td>&gt;5 cm³</td>
<td>16–33 (entire series)</td>
<td>19/37 (51)</td>
</tr>
<tr>
<td>Shin et al., 2002, 2004 (University of Tokyo Hospital)</td>
<td>Gamma Knife</td>
<td>&gt;2–3.3 cm (mean diameter)</td>
<td>17–28</td>
<td>11/19 (58)</td>
</tr>
<tr>
<td>Silander et al., 2004 (University Hospital, Uppsala)</td>
<td>proton beam</td>
<td>&gt;5 cm³</td>
<td>11–18</td>
<td>7/26 (27)</td>
</tr>
</tbody>
</table>

* No. of AVMs obliterated/total no. of AVMs (%).
† See Fig. 3.
Stereotactic light-ion radiation therapy for large AVMs

Miyawaki et al.\textsuperscript{32} reported serious complications in 80% of patients treated with doses > 16 Gy and target volumes > 14 cm\textsuperscript{3}. Other authors preferred doses < 16 Gy for AVMs > 14 cm\textsuperscript{3} to reduce the risk of complications, accepting lower rates for obliteration. As mentioned by Friedman et al.\textsuperscript{14} a reduction in the margin dose to < 16 Gy would cause the probability of total obliteration to decrease 50% for a single procedure, whereas if the dose administered to the margin of every AVM could be ~ 25 Gy, a 3-year total obliteration rate of > 95% could be achieved.

Recently, investigators at the University of Pittsburgh presented their results for staged-volume radiosurgical treatment of large AVMs.\textsuperscript{26} They described 21 patients who underwent this procedure with sufficient follow-up, 33% of whom had confirmed complete AVM obliteration. The likelihood of obliteration of large AVMs was also improved when LINAC-based fractionated stereotactic radiotherapy delivered a dose of 42 Gy in 7-Gy fractions.\textsuperscript{22}

Figure 3 shows a compilation of the dose-response curves at some radiation treatment centers. In this paper we have used a rough estimate of 1.3 for the RBE of the spread-out He ion beam. In fact, however, the RBE value is tissue specific and is a function of the LET and particle energy; thus the equivalent dose and the D\textsubscript{0} may be calculated more precisely when more data are available. Although the best model is one with 3D dose-volume histogram data,\textsuperscript{31} the use of a scalar quantity such as the minimum dose to quantify AVM obliteration may simplify the analysis. Relying on the concept of a limited effective number of crucial vessels (number of vessels that must be obliterated to effect a cure), we used the binomial model to predict the probability of AVM obliteration for all centers (Appendix B).

The response curves in Fig. 3 demonstrate large differences in AVM radiosensitivity among the various radiation treatment centers; this could be due to differences in reporting principles, patient selection, different radiation modalities, prior embolization, and the accuracy of the AVM nidus definition, as well as different AVM structures and vessel sizes. It should be noted that clinicians at all centers tried to use dose values that would keep complication rates as low as possible.

For light ions (data from Lawrence Berkeley Laboratory), a high γ value (γ = 0.8) and a small increase in the D\textsubscript{50} (D\textsubscript{50} = 16.9) were observed. The biological variance in tumor sensitivity was shown to be inversely related to the normalized dose-response gradient, γ.\textsuperscript{2} This means that the γ value is higher for a patient population in which there is homogeneous AVM radiosensitivity than it is for a patient group in which there are inter-patient variations or inhomogeneous intra-AVM radiosensitivity. One major advantage of ion beam radiation lies in the fact that variabilities in intra- and inter-target cell radiosensitivity have less of an effect (than for other radiation modalities) and that one can consider the target more homogeneous with respect to radiosensitivity,\textsuperscript{31} resulting in steeper dose-response relations as seen in Fig. 3.

**Effective Number of Crucial Vessels and the Binomial Model**

The notion that, for the purposes of a mathematical model, an AVM can be considered to be similar to a tumor and, therefore, the Poisson statistic (which is defined for N >> 1 and P << 1 in which N = number of events and P = probability of each event) can be used to evaluate characteristics of AVMs is inappropriate. If one focuses on treatment of the AVM volume, the number of FSUs in the AVM is the effective number of crucial vessels in the AVM, that is, the number of vessels that must be obliterated to effect a cure (that is, total AVM obliteration). In the case of an AVM, this number is not large enough for the Poisson model, and thus the binomial statistic should be used. If all crucial vessels inside an AVM could be occluded by radiation’s effect on the vascular endothelium, the result would be total obliteration of the AVM. Although larger AVMs have a lower chance for obliteration this is not always the case. In a plexiform angioarchitecture with a simple network of compact or loose arteriovenous shunts, the number of crucial vessels may be lower than in a more radioresistant AVM of the same size that has a greater number of arteriovenous fistulas.

Arteriovenous malformations are currently believed to be hemodynamically compartmentalized, with each compartment containing its own feeding arteries and draining veins. The number of compartments in an AVM is proportional to its size. An AVM < 3 cm in diameter is likely to have only 1 compartment, and an AVM > 4 cm in diameter typically has at least 3 compartments with a corresponding higher number of crucial vessels. According to this theory, the number of large and dilated vessels should be greater in large AVMs than in small ones.

A binomial model with N\textsubscript{0} equal to the effective number of crucial vessels in the AVM and D\textsubscript{0} as the in-
trinisc radioresensitivity of the AVM could be used to predict AVM obliteration for small and large AVMs based on the radiobiological characteristics of each single vessel in the AVM. Other features such as pseudoaneurysm formation and the radioresitivity of AVMs\(^{32,33}\) may also be considered.

**Conclusions**

With increasing AVM size, the dose and biological effect delivery need to be augmented for optimal results, that is, successful obliteration with minimal risk of early and late complications (including posttreatment hemorrhage). The majority of complications have occurred in patients harboring large AVMs treated with high radiation doses. Although staged-volume radiosurgery is currently proposed by some radiation treatment centers, management of large AVMs remains difficult and less effective than that of small AVMs.\(^{40}\) Stereotactic light-ion beam radiation therapy has successfully obliterated a number of large AVMs in the past\(^{9,10}\) and recently the C ion beam has been successfully applied to radiation therapy in Japan\(^{19}\) and in Germany.\(^{41}\) Additional ion beam centers are expected to open in the near future.

An analysis of published data from the Lawrence Berkeley Laboratory shows that the response of large AVMs to ion beam radiation therapy can be explained by taking into account the heterogeneous structure of AVMs and the radiobiological aspects of light-ion beams.\(^{3,22}\) Based on a study of the LETs of a variety of therapeutic ion beams (H, He, Li, and C),\(^{19}\) it appears that the light ions He and Li may be more suitable for treating AVMs whose volumes are \(\leq 10\text{ cm}^3\) and the light ions Li, Be, and C may be more appropriate for treating larger AVMs.

In general, a better dose distribution of ion beams and an increased radiosensitivity homogeneity in the target volume is an advantage over other radiation modalities. The unique physical characteristics of light-ion beams are of considerable advantage for the treatment of AVMs. Bragg-peak radiation therapy has been recommended for most large and irregular AVMs and for lesions located in front of or adjacent to sensitive and functionally important brain structures. Therefore, additional investigations on the role of light ions and on intra-AVM variations in the radioresitivity of small and large vessels to charged-particle radiation should be considered for future optimization of stereotactic radiation therapy of large AVMs.

The binomial model is a useful and interesting tool for the prediction of responses to radiation by both small and large AVMs. Radiosurgical simulation of a hypothetical AVM obliteration response has shown the validity of the binomial model (unpublished data) and future investigations are planned.

**Appendix A. Definition of Physical and Biological Terms**

**Bragg Peak.** For a charged particle traveling in matter, a peak occurs in the dose deposited along the particle’s path. This happens shortly before the charged particle loses all its energy and stops.

**Light Ions.** Light ions are nuclei of low-atomic-weight atoms that are fully stripped of their electrons. The atomic numbers of these atoms range between 2 and 6, and these ions (He, Li, Be, and C ions; the B ion is excluded because of its toxicity) display a significantly elevated ionization density at the Bragg peak.

**Linear Energy Transfer (LET).** The LET is a measure of ionization density or the amount of energy transferred to matter per unit distance as an ionizing particle travels through the matter.

**Relative Biological Effectiveness (RBE).** The RBE is a measure of the relative effectiveness of a particular type of radiation (compared to a reference radiation) in producing effects in biological systems.

**Appendix B. Poisson and Binomial Models**

Unlike the binomial model, the Poisson model requires that the number of FSUs be large and that inactivation of individual FSUs consist of independent processes. The dose-response and normalized dose-response gradients as well as the dose producing 50% obliteration (\(D_{50}\)) for these 2 models are shown in the following models.\(^{1,3,27}\)

**Poisson Model:**

\[
P(D) = e^{-\lambda D}D^\lambda/\lambda!
\]

\[\bar{\lambda} = \ln N_0/e, D_{50} = D_0(\epsilon - \ln[\ln2])\]

**Binomial Model:**

\[
P(D) = (1 - e^{-D_0}/N_0)^N_0
\]

\[\bar{\lambda} = \ln N_0(1 - 1/N_0)^{e-1}, D_{50} = -D_0\ln(1 - 1/2^{N_0})\]

where \(N_0\) is the number of FSUs (effective number of crucial vessels) and \(D_0\) is the radiosensitivity parameter.

**Disclaimer**

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