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BIOLOGIC BASIS OF RADIATION THERAPY

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The process of cell killing by x-rays and gamma rays, also called photons, begins with the production of ionizations in tissue. In the process of ionization, the oncoming photon interacts with a tissue atom and results in ejection of an electron, leaving a positively charged atom.[11] The electron, which has a defined range in the tissue, may damage DNA and render cells reproductively dead. The electron may produce chemical damage directly in the DNA molecule, but the majority of DNA damage is produced by high-energy free radicals created in the proximity of the DNA molecule by the interaction of the electron with water, an abundant intracellular compound (Fig. 1).

Cell killing by radiation essentially follows exponential kinetics. This means that for any given dose of radiation the same fraction of cells in the population will be killed. Thus, in representing radiation killing of cells graphically, with surviving fraction plotted as a function of radiation dose, the log of the surviving fraction is basically a linear function of dose except at very low doses (Fig. 2). This concept is an oversimplification of the actual response of a cell population to radiation but suffices for this discussion.

The goal of radiation therapy is to administer a sufficiently high radiation dose to the tumor to reduce the surviving fraction of clonogenic tumor cells to zero. An important component of this plan is the administration of the dose as accurately as possible, i.e., treatment planning. Treatment planning is discussed in detail in another article in this volume as well as in other sources.[30, 32] In theory, the dose to eradicate all tumor clonogens could be administered to any tumor as-

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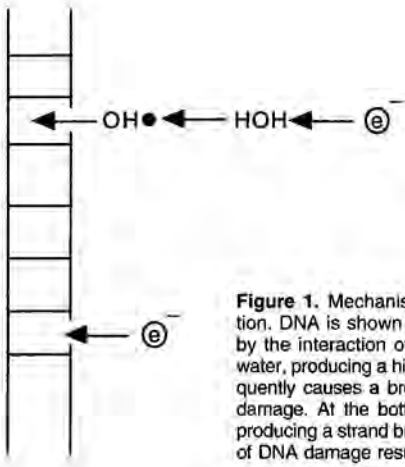

Figure 1. Mechanisms of DNA damage resulting from irradiation. DNA is shown as a ladder. At the top, an electron created by the interaction of a photon with a tissue atom interacts with water, producing a high-energy hydroxyl radical (OH•) which subsequently causes a break in DNA. This is the indirect type of DNA damage. At the bottom, an electron interacts directly with DNA, producing a strand break. With x-rays and gamma rays the majority of DNA damage results from the indirect mechanism.

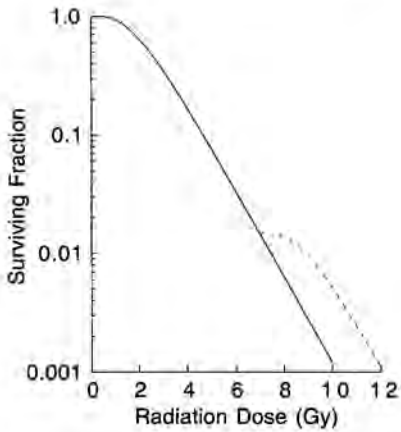

Figure 2. A typical radiation cell survival curve. A given dose of radiation essentially kills a fixed proportion of cells; this is exponential kinetics. Thus, when surviving fraction is plotted against radiation dose, with surviving fraction on a logarithmic scale, the curve depicting survival is straight, except for the low dose region where there is a shoulder in the survival curve. In the low dose region, the efficiency of killing increases with the dose because of accumulation of sublethal injury. As the dose increases, sublethal injury accumulation is saturated and any additional dose results in equivalent killing. It has been shown that sublethal injury is repairable. Thus, if a second dose of radiation is given after sublethal injury has been repaired, the shoulder reappears on the survival curve. In this figure, a dose of 7.0 Gy would reduce the surviving fraction to slightly greater than 0.01. If sufficient time was allowed for sublethal injury to be repaired before another dose of radiation was given, the shoulder region would reappear on the survival curve. This is illustrated by the dashed cell survival curve beginning at a dose of 7.0 Gy. Thus, fractionation of the radiation dose increases the total dose necessary to reach an isoeffect.

suming that the magnitude of that dose was known. However, in practice, a dose sufficient to kill all tumor clonogens cannot always be given because of the radiation response of adjacent normal tissue. Normal tissue in the radiation field is said to be "dose limiting" with respect to the maximum dose that can be safely administered to the patient. Therefore, rather than attempting to tailor the administered dose to any given tumor, one normally administers the maximally tolerated dose, as determined by the type and volume of normal tissue that is in the irradiated volume, with the hope of permanently controlling some fraction of tumors. The ultimate effects of the maximally tolerated radiation dose on tumor and normal tissue are determined by the biologic response of tumor and normal tissue to the given dose (biologic considerations) and the manner in which the radiation is given (i.e., time-dose considerations).

BIOLOGIC CONSIDERATIONS

Tumor clonogen number affects the probability of the tumor being controlled by radiation therapy. The greater the number of clonogens the more radiation is required for their complete eradication (see Fig. 2). Tumor clonogen number is related to tumor volume; larger tumors will almost certainly require a greater dose to be controlled than will small tumors. Many studies have been published regarding response of human tumors to irradiation when tumor volume has been a significant predictor of response. Fewer studies exist of the effect of tumor volume in veterinary medicine, but some reports of its negative effect on tumor control are available.[16, 26, 27] Not only do large tumors require a higher radiation dose for control, they are more difficult to treat from planning and implementation standpoints and the probability of normal tissue complications is also greater when larger volumes are irradiated.[38] The negative influence of tumor volume on tumor control probability and normal tissue complications makes important the treatment of tumors as early in their natural history as possible.

The *inherent cellular radiosensitivity* of tumor cells is not uniform between tumor types, or even within patients with the same type of tumor.[5, 9] Some tumors considered empirically to be radiosensitive, such as lymphomas, are characterized in some patients by very radioresistant tumor clonogens, whereas some tumors considered empirically to be radioresistant, such as fibrosarcomas, are characterized by radiosensitive tumor clonogens. Thus, tumor type cannot be used as a predictor of response, and the probability of local control in an individual patient should not be predicted because of the histologic diagnosis of a tumor type when overall response in a population has been poor. Great interest exists in predicting the response of individual tumors to irradiation based on quantification of response of a sample of that tumor to irradiation in vitro,[20] i.e., assessment of inherent cellular radiosensitivity. Many studies are underway in which tumor cell radiosensitivity is being

quantified and compared to tumor response. At this time the strength of the relationship between inherent cellular radiosensitivity and tumor control is uncertain, but strong correlations between these parameters have not been identified.[35]

Cells in tumors and in normal tissue are capable of repairing some component of radiation damage. Damage that can be repaired is referred to as sublethal damage. The accumulation of sublethal damage is responsible for the "shoulder" region present on the radiation cell survival curve (see Fig. 2). Once accumulation of sublethal damage is saturated, the kinetics of cell killing become more nearly exponential, (i.e., steeper slope). After a dose of radiation, some of the sublethal damage is repaired. If the interval between radiation doses is long enough, the shoulder reappears on the survival curve (see Fig. 2). Increasing the repair capacity of normal tissue or decreasing the repair capacity of tumor has been theorized to improve the likelihood of tumor control after irradiation. However, no successful strategies of repair modulation exist that have resulted in therapeutic gain.

Tumor cells may become hypoxic because of diffusion limitations of oxygen (diffusion-limited hypoxia)[28] or because of transient fluctuations in perfusion (perfusion-limited hypoxia).[3] The practical significance of this hypoxia is that cells at decreased oxygen tensions are radioresistant,[22] possibly by a factor as great as 2.0 to 3.0. Radioresistance stemming from hypoxia is related to the repairability of lesions in DNA under oxic and hypoxic conditions. Under oxic conditions, oxygen is capable of reacting with the lesion in DNA with "fixation" of damage; under hypoxic conditions repair enzymes may repair the DNA lesion before it is altered by oxygen and rendered irreparable.[11] Oxygen may have other adverse effects on tumor response. For example, oxygen modifies the therapeutic effectiveness of a number of chemotherapeutic drugs,[13a, 24a, 24b] and may play a role in upregulating production of substances such as endothelial growth factor that may promote tumor growth.[4a, 24c] Poor oxygenation may also select for oncogenically transformed cells that have lost their apoptotic potential.[10a]

Hypoxic cells are generally limited to neoplastic tissue. Thus, tumors have the potential to be more resistant than normal tissue and may regulate their environment to promote their growth—definitely a disadvantageous situation. Hypoxic cells are more likely to survive a radiation dose than are oxic cells; therefore the fraction of viable tumor cells that are hypoxic might be expected to increase with time during irradiation. Typically, the fraction of hypoxic cells does not increase with time during irradiation but either stays the same or decreases. This phenomenon is called reoxygenation and implies that the hypoxic cell population might be self-limiting during a course of irradiation.[13, 33] Reoxygenation may occur because of greater availability of oxygen as a result of decreased utilization by cells killed by radiation. Also, as oxic cells adjacent to capillaries die and are removed, hypoxic cells might become positioned near a capillary and thus exposed to higher oxygen concentrations. If reoxygenation were complete hypoxic cells would not

be problematic, but if reoxygenation were ineffective hypoxic cells might limit the response of solid tumors to irradiation.

Few data are available on the extent of reoxygenation during irradiation of tumors in animals or people, but hypoxia probably persists throughout irradiation in some patients.[14, 31] For example, reoxygenation was assessed in eight canine tumors using enzyme-linked immunosorbent assay (ELISA) quantification of a hypoxia marker. Tumor oxygen concentration after 15 Gy remained essentially unchanged in six dogs, increased in one dog, and decreased in one dog.[31] Assuming reoxygenation in solid tumors is incomplete, at least in some patients, various strategies have been implemented to overcome the hypoxia problem. These have included treatment of patients under hyperbaric oxygen conditions[6] and the use of modalities such as agents that selectively kill hypoxic cells,[40] hypoxic cell radiosensitizing agents,[18] hyperthermia,[10] and intravenous oxygen-carrying compounds.[8] All of these interventions, the roles of which remain incompletely determined, have been implemented without a way to predetermine if tumor hypoxia is present or to monitor the response of hypoxia during treatment. Recently, various methods to measure tumor oxygenation have been developed. These include oxygen electrodes,[34] quantification of agents that bind to hypoxic cells,[4, 14, 23, 24, 31] and assays of DNA damage.[17] Therefore, important information pertaining to the significance of tumor hypoxia is likely to be forthcoming in the future.

Tumors are obviously proliferating, and their *proliferation rate* may have bearing on the probability of control after irradiation. The rate of tumor growth depends on the fraction of tumor cells that are proliferating, the cell-cycle time of the proliferating tumor cells, and the cell-loss factor.[11] These three factors differ from tumor to tumor, and may vary within the same tumor over time. The existence of tumor proliferation suggests that gaps or breaks in a fractionated course of irradiation should be avoided because tumor proliferation will occur during the break. In the past, gaps have been planned into a course of fractionated radiation therapy for human tumors to allow for recovery from some of the acute normal tissue effects. Tumor control is diminished, presumably because of proliferation of tumor clonogens, when such gaps are present.[19]

Some data also support the hypothesis that tumor proliferation kinetics are altered by fractionated irradiation, with the tumor undergoing more rapid proliferation as a consequence of treatment,[37] but this view is not universally held.[7] Apparent accelerated repopulation has been suggested to begin approximately 4 weeks after the initiation of irradiation.[25] With regard to use of daily 2.0 Gy fractions, during the latter part of a fractionated radiation therapy protocol, 60 cGy of a daily radiation dose may simply offset the apparent increased proliferation rate characteristic of some tumors.[12, 25] Therefore, until the extent that tumor proliferation affects local control is known, both breaks in treatment and prolongation of treatment should be avoided. Measurement of tumor proliferation has been advocated as a means to identify those

patients in which more rapid administration of the radiation dose than one fraction per day might be beneficial.[2] Prospective studies of the effect of tumor proliferation on radiation response have been undertaken, but whether tumor proliferation rate is a significant predictor of response is not yet known.[1]

Little is known regarding the rate of proliferation of animal tumors, or the effect of proliferation on outcome. In one study, proliferation was assessed in cats with squamous cell carcinoma of the nasal plane and progression-free survival was poorer in patients with tumors judged to be faster growing.[27] In that study, radiation was given in three fractions per week, which provided considerable opportunity for tumor proliferation during treatment. Thus, in animals, the effect of proliferation when daily fractions are used and when proliferation may be expected to have less of an effect is unknown. Also, most time-dose schema used for treatment of animal tumors have been characterized by relatively short overall treatment times of approximately 3 to 4 weeks. Thus, accelerated repopulation may not be as significant in animal tumors as in human tumors, for which treatment times are typically 6 to 7 weeks and accelerated repopulation has been estimated to begin 4 weeks after the start of radiation therapy. Nevertheless, the kinetics of canine solid tumors are not known and every effort should be made to deliver the prescribed treatment without gaps and in as short a time as possible.

TIME-DOSE CONSIDERATIONS

Radiation is administered to cancer patients in a series of treatments called fractions. Therapeutic radiation is not typically given in a single large dose for two reasons.[29] First, decreased oxygen tension (hypoxia) is a characteristic of the tumor microenvironment that renders cells resistant to the killing effects of ionizing radiation. Thus, with a radioresistant subpopulation of cells the killing efficiency of the administered dose decreases after oxic cells are killed, thereby rendering the tumor more radioresistant than adjacent normal tissue. Second, some normal tissues are more sensitive to large radiation doses than is the tumor. Thus, administering large single doses would preferentially damage these normal tissues. For these two reasons the radiation dose is fractionated and administered over a period of time.

The exact manner in which the radiation dose is fractionated has great impact on whether the tumor is controlled. For many years administering radiation treatments on a Monday, Wednesday, Friday schedule was commonplace in veterinary medicine, with relatively large doses of radiation (e.g., 4.0 to 5.0 Gy) given at each treatment. This schedule became popular because it was convenient for the animal owner and because of concern about the effects of more frequent anesthesia on the patient. We now know that treating only three days per week is not optimum; reasons for this statement will be discussed shortly. Many combinations of dose-per-fraction, timing of fractions, and total dose can

be administered. The effect of each of these variables on expected outcome is discussed.

The size of the radiation *dose-per-fraction* can have a dramatic effect on the probability of normal tissue complications, thereby limiting the total dose that can be administered. For example, if complications are increased by using large radiation doses-per-fraction, the probability of complications prevents a tumoricidal dose from being administered. This has been discussed previously.[29] Clinical observations from treatment of human tumors with radiation provided evidence that large doses per fraction are preferentially damaging to slowly proliferating normal tissues such as connective tissue, nervous tissue, and muscle.[21] This is in comparison to rapidly proliferating tissues such as skin, gut, and tumors in which response is less a function of the size of radiation dose-per-fraction. This difference between slowly proliferating and rapidly proliferating tissues in response to size of dose-per-fraction suggests that the basic cell survival kinetics for slowly proliferating tissues are different from the survival response of more rapidly proliferating tissues. If the survival curve for late responding normal tissues was "curvier" than the curve for acutely responding tissues and tumors, the former would be preferentially damaged by large radiation doses (Fig. 3). To fully understand this difference in survival kinetics, a specific model of radiation cell killing must be considered. The model describing curves of the general shape of those in Figure 3 is

$$S.F. = e^{-(\alpha d + \beta d^2)}$$

where S.F. is surviving fraction, α and β are constants, and d is radiation dose. The model is referred to as the linear quadratic model of cell killing and reflects two mechanisms of cell killing—a linear or single-hit component (the αd term), and a quadratic or multiple-event component (the βd^2 term). The single-hit component implies that one interaction of an electron, or free radical, with DNA results in an irreparable lethal lesion. The multiple-event component implies that two reparable events occur within the same vicinity in the DNA molecule and interact before repair occurs to produce an irreparable lethal event. The curvier nature of the survival response for late responding normal tissues (see Fig. 3) denotes accumulation of sublethal (or multiple-event) radiation injury, just as the shoulder region did in the previously described curve (see Fig. 2). The relative straightness of the curve for acutely responding normal tissues and tumors suggests that at low doses most lethality in these populations results from single lethal events, the α component of killing, whereas the curvier nature of the survival response for late-responding normal tissues suggests that at low doses most lethality in this population results from the interaction of multiple sublethal events, the β component of killing. Therefore, the relative amount of single-event versus multiple-event killing determines the overall shape of the survival curve and the sensitivity of the tissue to fractionation.

The relative amount of single-event versus multiple-event killing can be expressed by the α/β ratio (Fig. 4). The α/β ratio is essentially a

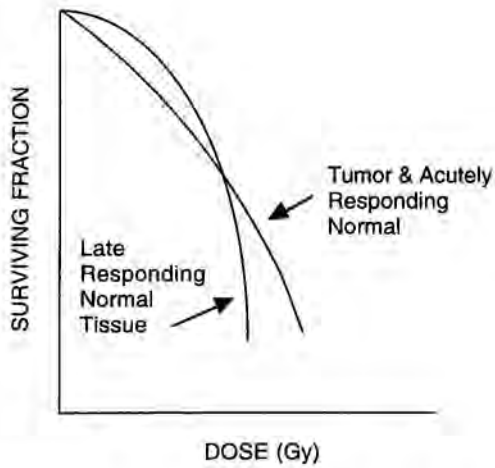

Figure 3. Hypothetical cell survival curves illustrating shape differences between the survival curve for acutely responding tissues and tumors versus the survival curve for late responding normal tissues. This shape difference would account for enhanced injury in late responding normal tissues at large doses per fraction.

numeric measure of the sensitivity of the tissue to killing by single-hit events relative to its sensitivity to killing by multiple-hit events. The α/β ratio has been determined experimentally for a variety of tumors and normal tissues.[36] In general, the α/β ratio for tumors and acutely responding normal tissues ranges from 10 to 20, whereas the α/β ratio for late-responding normal tissues tends to be less than 5.0. The practical significance of this is that late-responding normal tissues, which have a curvy survival curve and therefore a large capacity for accumulation and repair of sublethal injury, are preferentially injured by large doses per fraction. Late-responding normal tissues are, therefore, fractionation sensitive (Fig. 5). On the other hand, acutely responding normal tissues and tumors, which have a straighter survival curve, have less capacity for accumulation and repair of sublethal damage and are relatively less sensitive to changes in fraction size (see Fig. 5). Clearly the large doses per fraction that have been commonplace in treatment of animals tumors are preferentially injuring late-responding normal tissues rather than the tumor and use of smaller fractional doses is indicated. Ideally, fraction size in veterinary medicine should be 2.0 Gy or less. Unfortunately, the length of time needed to give an effective total dose using 2.0 Gy fractions in animals is arduous because of the requisite length of hospitalization and expense. But, even a reduction in fraction size from the typical 4.0 or 5.0 Gy fractions to 3.0 Gy fractions results in considerable sparing of late-responding normal tissues. Fractions of 3.0 Gy represent

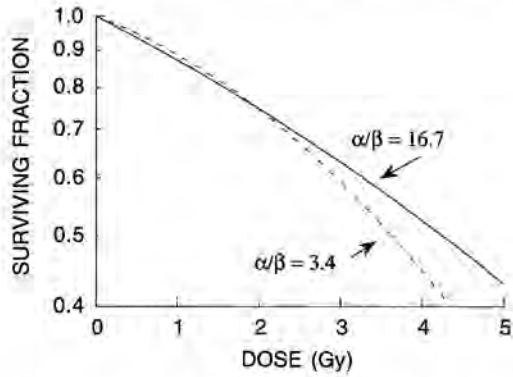

Figure 4. Cell survival curves for two tissues with different α/β ratios. One tissue has a low α/β ratio of 3.4 characteristic of late responding normal tissues. The other has a high α/β ratio of 16.7 characteristic of tumors and acutely responding normal tissues. It is clear that at doses per fraction >2.0 Gy there will be preferential damage to late responding normal tissues versus acutely responding normal tissues and the tumor. This discrepancy in damage becomes greater as the dose per fraction increases. Conversely, decreasing the dose per fraction below 2.0 Gy may preferentially spare late responding normal tissues, allowing a larger biologic dose to be given. Administering radiation therapy in fractions ≤2.0 Gy becomes difficult in animal patients, however, because the number of fractions must increase when very low doses per fraction are used. Nevertheless, this figure clearly shows the deleterious effect of the types of fractional doses (4.0 to 5.0 Gy) that have been used routinely for irradiation of animal tumors.

a reasonable compromise between the ideal of 2.0 Gy or less and large 4.0 or 5.0 Gy fractions.

The effect of *overall treatment time* on tumor response has been discussed above and previously.[29] In veterinary medicine, even though only three fractions were commonly given per week, treatment has historically been given in a shorter overall time than for humans. This has been a consequence of the larger dose fractions and lower total doses used. Accelerated repopulation, therefore, in veterinary radiotherapy may not be as much of a potential problem. However, the large fraction sizes used have the potential to be problematic in terms of normal tissue complications, especially if total doses are escalated in an attempt to improve tumor response. When smaller dose fractions are used, more fractions need to be given to achieve a satisfactory total dose. This requires an increase in the number of fractions. If only three fractions are given per week, overall treatment time increases and the tumor has an opportunity to proliferate on multiple days. This may result in tumor repopulation becoming a limiting factor. Therefore, administering three treatments per week rather than five is difficult to justify. Originally, three weekly fractions were used to minimize the stress of general anesthesia on the patient. However, with newer anesthetic agents, daily anesthesia is readily tolerated. Allowing every-other-

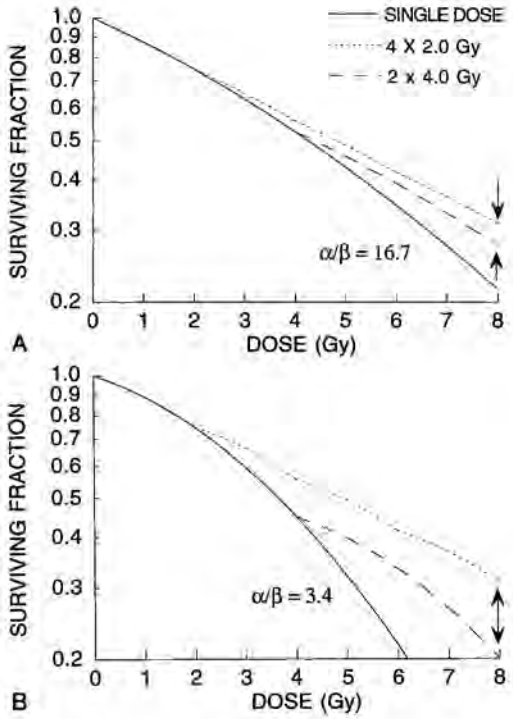

Figure 5. A comparison of the fraction size sensitivity of late responding normal tissues versus tumors and acutely responding normal tissues. In tissues with high α/β ratios (acutely responding normal tissues and tumors), the straight nature of the survival curve resulting from the predominance of single-event killing at low doses renders the tissue relatively insensitive to fraction size. As seen in the panel representing a tissue with an α/β ratio of 16.7 *(A)*, the difference in surviving fraction *(between arrows)* resulting from two doses of 4.0 Gy or four doses of 2.0 Gy is much smaller than the survival difference *(between arrowheads)* resulting from the same two fractionation schemes in a tissue with a low α/β ratio (3.4) characteristic of late responding normal tissues *(B)*.

day gaps in treatment simply provides an opportunity for the tumor to proliferate during treatment and serves no beneficial purpose to the patient or owner.

Some consideration should also be given to possible causes of treatment interruption before treatment is started. For example, treatments are rarely given on weekends. Therefore initiation of a treatment course on a Friday should be avoided; it is difficult to justify giving one fraction followed by a gap of 2 days. Interruptions due to forthcoming holiday periods should also be considered. In general, unless the tumor is rapidly growing, temporarily delaying treatment to allow treatment

to begin on a Monday or Tuesday, or to avoid a forthcoming break, is probably less risky than to initiate treatment knowing that a gap will occur.

Unless a sufficient *total dose* is given, what fractional dose or overall treatment time is used makes absolutely no difference.[29] Eradication of the tumor depends on administration of a total dose that has a finite probability of sterilizing all tumor clonogens. Total doses commonly used in veterinary medicine have routinely been in the 40 to 50 Gy range. Direct comparison of these total doses with those historically used in humans is not straightforward because of the difference in fraction sizes (≤2.0 Gy in humans, ≥4.0 Gy in animals) and overall treatment time (>6 weeks in humans, approximately 3 weeks in animals). But, if one accepts the linear-quadratic model of cell killing, comparing various fractionation schemes is possible, within limits, using the following formula:

$$D_{new} = D_{ref} \frac{\left(\frac{\alpha}{\beta} + d_{ref}\right)}{\left(\frac{\alpha}{\beta} + d_{new}\right)}$$

where D_{new} is the total dose being determined for a change in size of dose per fraction to d_{new}, and D_{ref} is the total dose given previously in fraction sizes of d_{ref}, and α/β is a characteristic of the dose response of the tissue (or tumor) in question.[39] For comparative purposes, various dose sequences used in veterinary radiation therapy are compared in Table 1 to two dose sequences used in humans. For acutely responding normal tissues and tumors an estimated α/β value of 15 was used and for late-responding normal tissues an estimated α/β value of 2.0 was used. The estimated α/β values are consistent with experimental data.[36]

Scheme 1 has been commonly used for irradiation of human tumors and because the dose is given in 2.0-Gy fractions, the equivalent doses given in 2.0-Gy fractions to the tumor and late-responding normal tissues are the same as the given dose. A trend in irradiation of human

Table 1. COMPARISON OF FRACTIONATION SCHEMES

Scheme	Fraction Size (Gy)	Given Dose (Gy)	Equivalent Dose in 2.0-Gy Fractions to Acutely Responding Normal Tissue and Tumor (Gy)	Equivalent Dose in 2.0-Gy Fractions to Late Responding Normal Tissue (Gy)
1	2.0	60	60.0	60.0
2	1.8	70	69.2	66.5
3	4.0	48	53.6	72.0
4	5.0	50	59.0	87.5
5	3.0	57	60.4	71.3

tumors, implemented to increase the total dose and spare late-responding normal tissues, has been to decrease the fractional dose to 1.8 Gy with an increase in total dose from 60.0 to 70.0 Gy. As can be seen, this is equivalent to tumor and late-responding normal tissue doses of 69.2 and 66.5 Gy, respectively, in 2.0-Gy fractions. Schemes 3 and 4 have been used for irradiation of animal tumors. If one assumes that when using 2.0-Gy fractions a total dose of at least 60 Gy is needed in solid tumors to have a significant chance of long-term tumor control,[15] and that doses greater than 70 Gy in late-responding normal tissues should be avoided, schemes 3 and 4 obviously deliver less than a desired total dose to the tumor, but result in overtreatment of late-responding normal tissues. The basis for this differential in equivalent doses relates to the fraction size sensitivity of late-responding normal tissues (high α/β ratio) relative to acutely responding normal tissues and tumors (low α/β ratio) (see Figs. 3 through 5). A reasonable compromise might be use of 3.0-Gy fractions, given daily, to a total dose of approximately 57 Gy. This results in a tumor equivalent dose in 2.0-Gy fractions of approximately 60 Gy, which might be expected to result in significant cell killing in some tumors without high likelihood of serious complications. Scheme 5 results in more cell killing in late-responding normal tissues than does either scheme 1 or 2, but unless fractional doses lower than 3.0 Gy are used administering a biologically greater dose to late-responding normal tissues than to the tumor is unavoidable. Nevertheless, an equivalent dose of approximately 70 Gy given in 2.0-Gy fractions may be tolerable to late-responding normal tissues. Note that the comparisons undertaken in Table 1 do not account for differences in overall treatment time. Schemes 3, 4, and 5 are given in substantially shorter times than are schemes 1 or 2 and clearly the biologic effect of this shorter time would increase the equivalent doses even further, particularly in the tumor that is proliferating.[15] However, this comparison serves to emphasize the relatively low total doses used to date in veterinary radiation therapy and the need to assess higher doses. An important question is whether a modest increase in total dose (Table 1, scheme 5 versus 3 and 4) might be expected to result in significant improvements in tumor control. The answer is yes, based on the sigmoidal shape of radiation dose-response curves (Fig. 6). Much work remains to be done in veterinary radiation therapy to define improved radiation time-dose schemes, but a trend to smaller doses per fraction and larger total doses has a high probability of being beneficial.

SUMMARY

The biologic effects of ionizing radiation are well understood. The limitations of radiation therapy time-dose schemes typically used in veterinary medicine are also well understood. Before expensive and potentially toxic combinations of treatment, such as radiation combined with chemotherapy or radiation combined with hyperthermia, can be

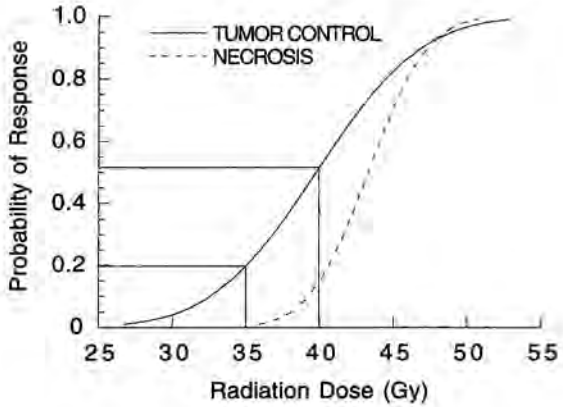

Figure 6. Dose–response curves for tumor control and serious normal tissue complications. The shape of radiation dose–response curves is generally sigmoidal. The practical significance of the sigmoidal shape is that no response is noted until some "threshold" dose is reached; then the probability of a response increases rapidly as additional dose is given. The steepness of the curve results in large changes in response for small changes in dose. In this example, an increase in total dose from 35 to 40 Gy results in an improvement in tumor control from approximately 20% to more than 50%. It is a goal to administer the radiation in such a manner that the dose response curve for complications lies to the right of the curve for the tumor. This is done by selection of dose per fraction, number of fractions, overall time, and total dose. In general, the slope of the dose–response curve for normal tissue will be steeper than the dose–response curve for tumors; this results from greater heterogeneity in the tumor population. As can be seen from the figure, increasing dose for the purpose of increasing tumor control will also increase the probability of complications. The probability of complications will ultimately limit the total dose that can be given no matter what combination of fraction size, fraction number, and total dose is used.

fully understood, the effect of optimizing the manner in which radiation itself is administered must first be defined. This will only occur after a sufficient period of observation after improvement of the radiation time-dose schemes in use today.

Also, when evaluating historic data regarding the response of canine and feline tumors to irradiation, the time-dose scheme used must be considered. Many papers were published based on coarsely fractionated schemes using large doses per fraction and relatively low total doses. Thus, the response rates published must be tempered by the fact that it may be possible to obtain better tumor control rates using smaller doses per fraction and a larger total dose.

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