Biological Aspects of Conformal Therapy

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Both conformal and intensity-modulated radiation therapy have great potential to further increase tumor control rates and decrease morbidity. A homogeneous escalation of 'biological' dose within a tumor should increase the likelihood of local cure, especially within the mid-range (e.g. 15% to 80%) of tumor control rates, and conversely, a lower control rate should follow a homogeneously reduced dose. However, when the dose to critical normal tissues is tightly contrained, the dose distributions within the treatment volume may necessarily be heterogeneous, and the effect on tumor control probability will depend upon the magnitude of over- or underdosage, and on the proportions of the tumor clonogen population receiving higher or lower than the nominal dose. Dose-volume histograms provide a measure of heterogeneity of dose within the planned treatment volume, but tumor control probability is also influenced by other variables, e.g. inherent tumor clonogen radiosensitivity and growth rates during a course of treatment, α/β ratios, oxygenation and clonogen density throughout the target volume. Heterogeneity in these factors introduces heterogeneity in tumor responses and a less steep change in tumor control probability with change in dose, reducing the gains or losses that would be predicted to result from heterogeneity of dose. Similarly, modeling the effect of inhomogeneous dose distributions on estimates of probability of complications in normal tissues is hindered by uncertainty of estimates for α/β ratios, especially for late-responding tissues, and lack of data on volume effects. Although the effects of dose inhomogeneity cannot be presented with sufficiently reliable quantitation to be directly applicable to dose prescriptions in radiation therapy, the *relative* influences of heterogeneities in dose and volume can be modeled to provide a framework for clinical decision-making. The magnitude of a dose reduction is the major determinant of decline in tumor control probability. A large dose reduction to even a small volume of tumor can profoundly decrease tumor control probability. Conversely, the most rapid improvement in tumor control probability occurs the closer to 100% the amount of tumor exposed to an increased dose. Escalation of dose is of little value unless it is distributed through most of the tumor: even very large increases in dose to small volumes are of little benefit.

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Improvements in technology which permit 3-D planning and treatment and the creation of heterogeneous dose distributions within and adjacent to the planned treatment volume using intensity-modulated beams has made unprecedented demands on our knowledge of oncology and radiation biology. Sophisticated algorithms for optimizing dose distributions to maximize the therapeutic differential between the responses of tumors and normal tissues have been developed based on an interplay of physics, biology and oncology (1–9). In this paper I revisit some biological questions with a view to illustrating the need for more accurate understanding and quantitation of the biology and radiation responses of tumors and normal tissues.

HETEROGENEITY IN BIOLOGICAL DOSE PER FRACTION

Planned heterogeneity of physical dose distribution is a characteristic capability of conformal radiation therapy, especially when combined with intensity modulation. The associated heterogeneity in 'biological' dose always exceeds that in physical dose because the response of both normal and malignant tissues is a non-linear function of dose; that is, the change in biological effect is always amplified by the curved shape of the cellular dose-survival response regardless of whether the actual physical dose is greater or less than the reference dose. The extent of the discrepancy between physical and 'biological' doses is greater in slowly-proliferating tissues, and probably also slowly proliferating tumors, than in the more proliferative, earlier-responding normal and malignant tissues because the dose-response curve is curvier for late, than early-responding tissues (10–26), as discussed later. Thus, not only does the change in biological effect of dose not precisely match the change in physical dose, but there is no universal modification factor which can be applied to all tissues to convert physical dose distributions into biological dose distributions. However, if the relative curvature of the dose-response curve for the tissue in question were known, the

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changed biological effectiveness of a heterogeneous dose per fraction, or of a new fractionation regimen, could be quantified in terms of a linear quadratic description of the survival curve (25).

The non-linearity of cellular dose responses can be quantified by the α/β ratio where α and β are coefficients of radiosensitivity for single hit (linear) and accumulative interactive (quadratic) injury, respectively. A relatively high value for the α/β ratio implies a near linear response, especially at the low doses of clinical interest, whereas low values of α/β are reflected in a curvy survival curve and a large change in biological effect with change in dose per fraction. Relatively high α/β values, and the associated more linear initial dose response, with little change in response with change in dose per fraction, are characteristic of acutely responding normal tissues, and at least the more highly proliferative tumors such as squamous carcinomas of head and neck (18, 23). Late-responding normal tissues, and probably also less-proliferative tumors such as prostate cancer (14, 16) or some melanomas (13), exhibit larger changes in response with change in dose per fraction, that is, they have low α/β ratios.

The most readily understood way for the clinician to adjust the biological dose to account for a change in size of dose fractions (or for heterogeneities in dose distribution) is to calculate the dose to which it would be equivalent if given in 2 Gy fractions ($LQED_2$) (22, 25). The dose modification factor to equate a new regimen with a standard 2 Gy per fraction regimen is $D_{new}/D_2 = \alpha/\beta + 2/\alpha/\beta + d_{new}$, where D_{new} and D_2 are total doses in dose fractions of d_{new} and 2 Gy, respectively, and the α/β ratio measures the ratio of the coefficients of linear and quadratic radiosensitivity, and is variable from tissue to tissue. Late-responding normal tissues such as spinal cord, optic nerve, brain and other cranial and peripheral nerves have lower α/β values than acutely responding tissues and are the most responsive to change in size of dose fractions, and, therefore, also to heterogeneity of dose distribution within the irradiated volume. The α/β ratio for spinal cord is probably less than 2 Gy (26), fibrovasculature in the range of 4 to 5 Gy, whereas for epithelial tissues it may range between about 7 and 15 Gy (10, 22). The large fractionation response characteristic of tissues with low α/β ratios is a double-edged sword: while the injury from large doses per fraction is increased disproportionately to the increase in physical dose, the rate of fall-off in biological dose in the penumbra, e.g. of conformal treatment dose distributions, is also steeper than for physical dose.

Data on tumor fractionation responses are most numerous for squamous carcinomas of head and neck. They exhibit high α/β ratios (18, 23) and so, for them, heterogeneity of biological dose is not very different from heterogeneity of physical dose distribution. However, some other tumors, notably those with an indolent proliferation profile (27), probably have low α/β ratios, and their response will be more sensitive to heterogeneities in dose distribution. There is suggestive evidence for low α/β ratios for prostate cancer (14, 16), and the same could be true for other slowly-proliferative tumors such as chordomas, chondrosarcomas, meningiomas, acoustic neuromas, etc. These slowly proliferative tumors, which are commonly already treated with conformal therapy for other reasons, may incur added biological damage from the higher physical doses per fraction within the tumor made possible by the heterogeneity of doses achievable with conformal and/or intensity-modulated therapy.

The differences in α/β ratios for normal tissues and tumors provide opportunities to amplify the therapeutic ratio through judicious choice of dose per fraction, which is not only defined by the prescribed tumor dose per fraction but also by the isodose line at which it is prescribed and by heterogeneities introduced by intensity-modulated dose delivery. For example, in treating prostate cancer, a higher prescribed dose per fraction, or a similarly lower percentage chosen for the prescribed isodose contour, may be advantageous if the α/β value for the tumor is low relative to the value for rectal mucosa. (The potential disadvantage is that the muscle of the urethral sphincter and trigone of the bladder, which probably also are characterized by a low α/β ratio, may also manifest greater injury many years after therapy if they receive the full dose per fraction and maximum total dose.) Conversely, if a squamous carcinoma had invaded close to optic nerve, brain stem or spinal cord, the therapeutic differential would be maximized by ensuring that the dose per fraction to the critical normal tissue is kept as low as logistically possible, and, at least, not increased above standard levels. Thus, either hyperfractionation or hypofractionation may provide a favorable therapeutic index, depending upon the relative values of α/β for tumor and critical normal tissues. Only when the α/β ratios of the tumor and normal tissues are similar would there be no added biological benefit (or loss) from exploiting the fractionation effect using planned heterogeneity of physical dose. Although we now understand these principles, we do not have sufficiently precise values for α/β for most tissues, and for even fewer tumors, to be confident in making large changes in dose per fraction.

Regardless of the fractionation effect, there may be other advantages or disadvantages of a heterogeneous dose distribution, and the associated variation in total dose, within the geometry of normal and malignant tissues (28).

OVERALL DURATION OF THERAPY

a. Accelerated growth in macroscopic (primary) tumor

The adverse effect on local control from regrowth of surviving tumor clonogens during the latter part of a course of treatment has been quantified for many human tumors (10, 12, 15, 17, 18, 23, 29–37). This potential for

regenerative 'escape' by surviving tumor clonogens can be reduced by increasing the intensity of treatment, i.e. by accelerating the rate of dose accumulation or by adding other cytotoxic agents, e.g. chemotherapy (35).

If a steep gradient in dose distribution permits a higher tumor dose per fraction than is possible with standard therapy (through exclusion of critical normal tissues from the high dose treatment volume), then the dose intensity to the tumor can be selectively increased. For example, if a complex beam arrangement, with or without intensity modulation, produces steep dose gradients, it may be possible to include the tumor within, say, the 80% isodose line, in which case the dose per fraction within the tumor is increased by a factor ranging up to 1.25 (100/80). If a dose of 70 Gy in 7 weeks were prescribed to encompass all the tumor at the 80% isodose, the total dose within the tumor would range between 70 Gy and 87.5 Gy, in an overall time of only 7 weeks, an acceleration of up to 25% in dose intensity. Obviously, this heterogeneity can be further increased by prescribing to the 50% isodose line, depending upon the steepness of the dose-gradient and clinical judgement regarding tumor control and complication probabilities. (Note also that the biological dose intensity within the treatment volume would be further increased by the 'double trouble' of both higher total dose and larger dose per fraction, the extent of the gain being greater the lower the α/β ratio for the tumor). The potential gain from this type of dose escalation depends upon the dose-volume distribution and is discussed in more detail later.

b. Subclinical disease

The techniques underlying conformal therapy (3-D imaging and planning and multiple treatment beams) and intensity modulation not only permit the dose to be 'tailored' to the detectable tumor volume, but also gradients in dose per fraction can be generated to deliver lower total doses to potential sites of subclinical spread. For example, by appropriately tailoring the dose distribution, 70 Gy in 2 Gy fractions could be delivered to the main tumor mass while delivering 50 Gy in 1.4 Gy fractions to volumes at risk for harboring subclinical tumor deposits. Such a prescription in which the different total doses are delivered in a constant number of heterogeneously-distributed dose fractions is technically elegant but has the biological disadvantage of protracting the overall duration of treatment of subclinical disease, e.g. from 50 Gy in 5 weeks to 50 Gy in 7 weeks.

The relative decrease in control of subclinical disease from protraction of treatment is greater than predicted from growth rates of primary tumors (38) or from what is known about accelerated regrowth of surviving clonogens late in a course of radiation therapy for primary tumors (37). Analysis of the results of elective preoperative pelvic irradiation for carcinoma of the rectum suggests that clonogenic cells in unperturbed microscopic deposits double as quickly as every 4 days (39). This rapid growth is an inherent characteristic of microscopic foci, occurring from the outset of treatment, without the lag period which characterizes the response of larger tumors to injury. Rapid growth also occurs in early brain metastases from small cell carcinoma of the lung (40), and in residual tumor cells after surgery for cancers of the head and neck (41). This pattern of rapid growth of tiny metastatic deposits is also consistent with what would be predicted from back-extrapolation to microscopic tumor dimensions of Gompertzian growth curves for macroscopic tumors (42).

In summary, when subclinical metastases are a factor in treatment planning, they should be treated quickly. Unless it is possible to treat subclinical disease with about 2 Gy/day, with the dose to the primary tumor escalated safely to higher doses, e.g. 3 Gy/day, the use of conformal and/or intensity-modulated therapy may be limited to only the 'boost' phase of treatment of the main tumor volume, or to treatment not requiring irradiation of subclinical locoregional metastases.

VOLUME EFFECTS

a. Geographic underdosage beyond margins of treatment volume

Tight conformation of the prescribed dose to the margins of the detectable tumor introduces an increased risk of geographic underdosage. Complete geographic miss is a disaster, regardless of how few clonogenic cells are missed. However, a complete miss is difficult to achieve, as illustrated by the centripetal spread of isodose lines on both standard and conformal treatment plans, and geographic underdosage is a more usual problem. The consequence of geographic underdosage depends upon how many tumor clonogens are relatively underdosed, and the magnitude of the underdosage.

In considering inhomogeneous dose distributions, a single tumor can be considered to be a conglomeration of a large number of subvolumes (or tumorlets). If, for example, each tumor were considered to be 100 subvolumes then, instead of equating a 90% probability of cure with an average of 1 surviving clonogen among 10 tumors (0.1 clonogenic cell per tumor), it can be equated with 1 surviving cell among 1000 subvolumes, or, 0.001 cells per subvolume. In treatment planning using inhomogeneous dose distributions, the dose to each of a large number of subvolumes can be estimated and the overall patterns of dose distribution presented as a dose-volume histogram. The relative survival of cells per subvolume can then be used to calculate relative probabilities of eradicating all clonogenic cells from the whole tumor.

To quantify how the steep dose gradients and inhomogeneities (introduced by tightly conformal fields and by

modulation of dose intensity) can modify the result from that achieved using a homogeneously distributed dose, it is necessary to consider variability in the volume under- or overdosed and the magnitude of the under- or overdosage, as well as the baseline efficacy of homogeneous irradiation. It also demands knowledge of the rate at which a change in dose changes the probability of cure, itself a reflection of many other variables, such as clonogenic cell number and density, cellular radiosensitivity, reoxygenation and regeneration kinetics, etc. (4–6, 9, 12, 19, 20, 43–45).

In Fig. 1 it is shown how the 90% probability of tumor control from a homogeneous dose is reduced by various degrees of underdosage to various proportions of the clonogenic tumor cell population in a tumor. Several assumptions were made in constructing Fig. 1. Tumor clonogens were assumed to be evenly distributed throughout the treatment volume and to have equal radiosensitivity. Variations in dose are expressed in units of D_{10}, the dose required to reduce cell survival by a factor of 10, that is, one decade on a semilogarithmic plot. Cell survival curves from in vitro and in vivo experiments indicate that a 10-fold reduction in cell survival requires about 7 Gy in a 2 Gy per fraction regimen. Therefore a dose of 70 Gy would reduce survival to 10^{-10}, to an average of one surviving clonogen per tumor in a series of tumors each containing 10^{10} cells: based on Poisson random statistics, 37% of such tumors would have no surviving clonogens, translating to a tumor control probability of 37% from the dose of 70 Gy. If it were possible to select a series of tumors, each containing 10^{10} cells homogeneous in all relevant determinants of radiocurability (e.g. intrinsic cellular radiosensitivity, oxygenation, growth kinetics, etc.), then the threshold-sigmoid curve for tumor control probability (TCP) would rise very steeply at doses just below and above 70 Gy. For example, an increment of 7 Gy ($1 \times D_{10}$) would increase tumor control from, say, 20% to 85%, an increase of about 9% per Gy.

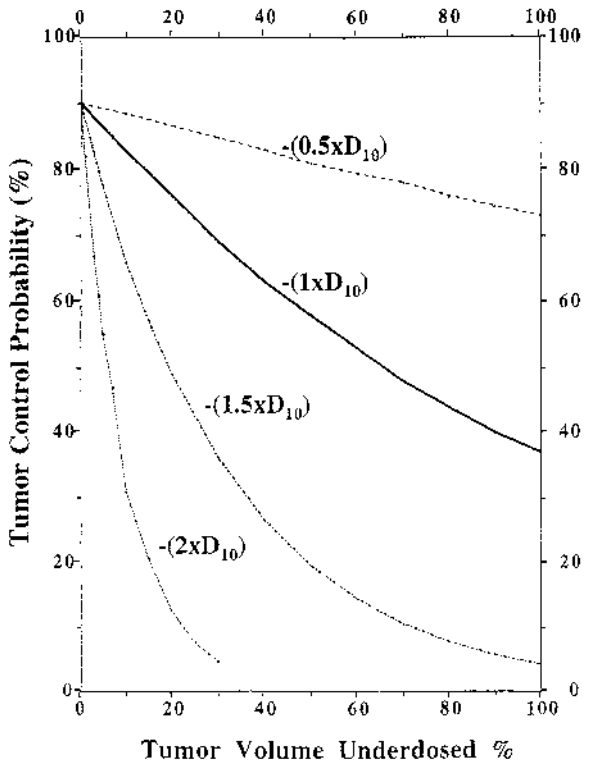

Fig. 1. Plots to illustrate how geographic underdosage can affect tumor control probability (TCP) relative to an anticipated 90% control rate if the tumor were irradiated homogeneously. The four curves are for doses lower than the prescribed dose by $0.5\times$, $1.0\times$, $1.5\times$ or $2\times$ the value of the effective D_{10}. D_{10} is the dose required to reduce cell survival by an average of one decade, to 10%. In a heterogeneous group of tumors, its 'effective' value, based on analysis of TCP curves, ranges from 11 Gy to at least 20 Gy for a regimen of 2 Gy fractions. For large single radiosurgery doses, its value may be of the order of 2.5–3.0 Gy. Besides the actual value for D_{10}, the volume of the tumor in which the dose is low, and the magnitude of the dose reduction are the most important factors determining outcome from a heterogeneous dose distribution. Note that the abscissa is volume, which is a power function of diameter. Equivalent uniform doses (EUD's) can be determined from the dose-volume values for the intersection of the various curves with a horizontal line at any specified value of TCP in Figs. 1, 2 and 3.

However, in retrospective analyses of clinical results, TCP curves are much shallower and usually show a rise of less than 3% per Gy (4–6, 9, 12, 19, 20, 43, 45) implying an 'effective' D_{10} of about 20 Gy compared with 7 Gy for the 'average' D_{10} for tumor cells assayed in vitro. The reason for the relatively shallow slope of most TCP curves is the heterogeneity within a series of human tumors in the factors determining radiocurability, as well as in dose inhomogeneities (3–9, 43–45). The better a population of patients can be stratified to account for the causes of treatment failure, the steeper the TCP curves for each stratum and the lower the estimated value for D_{10}. For purposes of modeling the effect of inhomogeneities in dose it is useful to use a generic value for D_{10}, rather than to specify a fixed value between 7 and 20 Gy.

The curves in Fig. 1 show that the fastest *rate* of decline of TCP is when the volume underdosed is small, e.g. < 10–20%, but the *absolute* decline is mostly influenced by the magnitude of the underdosage. Modest underdosage to small proportions of a tumor does not greatly affect tumor control probability. For example, the uppermost curve in Fig. 1 shows that even if as much as 50% of the tumor were to be underdosed by $0.5 \times D_{10}$, a 90% probability of local control would be reduced by less than 10 percentage points. If only 20% of the tumor were underdosed by $0.5 \times D_{10}$, the predicted decrease in TCP would be about 3 percentage points, which is essentially undetectable in a clinical trial.

The other curves in Fig. 1 quantify the effects of greater inhomogeneities in dose when a homogeneous dose resulted in 90% TCP. For example, a large decrease of $2 \times D_{10}$ to even as little as 5% of the tumor volume would

reduce TCP by 30 percentage points, from 90% to 60%: if this severe underdosage was to 10% of the tumor, the decrement in TCP would be about 60 percentage points. While such a large degree of dose inhomogeneity ($2 \times D_{10}$) would not be anticipated in a standard prescription, significant inhomogeneities, especially to small volumes, are quite likely to occur in tightly conformal therapies applied to mobile tumors.

Fig. 1 shows that the magnitude of the decrement in dose is the major factor reducing tumor control rates. Although the curves in Fig. 1 indicate that the absolute (but not the proportionate) rate of decline in TCP is steepest when only small fractions of the tumor volume are underdosed, this is a negligible factor in practice compared with the effect of drop in dose.

In single-dose radiosurgery, the absolute D_{10} value is much lower than it is for a regimen of 2 Gy fractions. Based on the slopes of single-dose survival curves from experimental animal studies, the D_{10} value for doses ranging from 15 to 25 Gy would be approximately 2.5–3 Gy, rather than the value of 7 Gy estimated for 2 Gy fractions. If metastatic tumor deposits are eliminated by single radiosurgery doses of 18–20 Gy, the single dose D_{10} value could be lower than 3 Gy, because, even if the shoulder in the single-dose survival curve were ignored, 18 Gy would only reduce survival by 18/3 decades $= 10^{-6}$. From Fig. 1, if a single large dose of 18 Gy were prescribed but 10% of the tumor were underdosed by 3 Gy (assumed D_{10} value), the TCP would be reduced by about 8 percentage points: if the same volume were underdosed by 6 Gy ($2 \times D_{10}$), the TCP value would be reduced by 56 percentage points. Even if only 5% of the tumor were underdosed by 6 Gy, the reduction in TCP would be about 30 percentage points. An overall conclusion from a study of Fig. 1 is that at high rates of tumor control (e.g. 90%), both the magnitude of the underdosage and the volume of underdosed tumor are critical determinants of outcome, but the magnitude of the dose reduction is the most powerful determinant of tumor control.

The equivalent uniform dose (EUD) corresponding to any given inhomogeneous dose distribution is the dose which, when distributed uniformly across the target volume, would result in the same number of surviving clonogens, that is, the same probability of tumor control (4). Equivalent uniform doses for any specified level of tumor control probability are defined by the dose and volume represented by the intersection of the various curves with a horizontal line at that level of TCP (Figs. 1–3).

The effect on TCP of a modest degree of dose inhomogeneity ($0.5 \times D_{10}$) as a function of TCP values ranging from 10% to 90% (for homogeneous irradiation) is plotted in Fig. 2. The rate of decline in TCP with the percentage of tumor underdosed is steepest as the percentage of tumor homogeneously irradiated first shifts from 100% to lower levels, but depends to a modest extent on the TCP

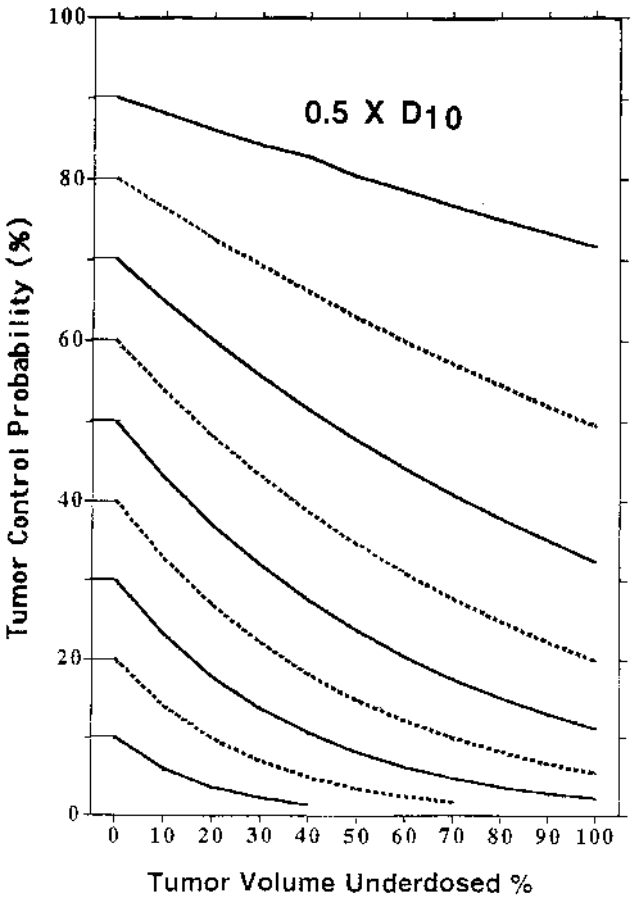

Fig. 2. The rate of decline in TCP as a function of tumor volume underdosed by $0.5 \times D_{10}$. The rate varies with the TCP from homogeneous irradiation and is steepest: a) for low percentages of tumor underdosed, and b) in the midrange of TCP values.

achieved with homogeneous irradiation, being greater in the midrange (e.g. 15–80%) because the dose response for tumor control is sigmoid, being shallower at the low and high extremes of control, and steepest between about 15% and 80% TCP. The curves in Figs. 1 and 2 are based on inclusion of all the tumor clonogens in the treatment volume and an assumption that there was no variation in clonogenic cell density throughout the treatment volume. This may reflect the situation fairly accurately if the gross tumor volume was accurately identified. If, instead of considering the gross tumor volume (GTV), the calculations were based on the planning tumor volume (PTV), and there were lower densities of clonogens in the volume within the PTV, but outside the GTV, and, as most likely, the PTV was the region which was underdosed, then the curves would not show a rapid early decline in TCP with small volumes of underdosage, but, rather, a shallow plateau, followed by a steeper decline as a greater percentage of the PTV was relatively underdosed.

b. Dose escalation within treatment volume

The ability to achieve steep dose gradients allows not only a relatively rapid fall off in dose outside the tumor treatment volume but also permits escalation of doses within the tumor. Obviously, the maximum increase in TCP would accrue from including all the tumor in the escalated dose volume (i.e. a homogeneously increased dose).

The curves in Fig. 3 illustrate how TCP is affected by an inhomogeneous increase in dose within the tumor volume. Dose escalation is not very helpful when TCP is already high, e.g. 90%, but becomes increasingly helpful as the baseline (standard homogeneous dose) control rate becomes lower.

Regardless of the baseline control rate, dose escalation to small volumes is essentially worthless. For example, even when the baseline outcome is as low as TCP = 10%, there is a negligible improvement in TCP from escalating the dose to 30% of the tumor, and, of course, little difference between a small increment or a large increment in dose to these small volumes. For example, a large increment of $2 \times D_{10}$ delivered to 30% of the tumor would only increase TCP from 10% to 19%, a modest effect and negligibly more effective than an increase by only $0.5 \times D_{10}$ to the same 30% of tumor, which would increase TCP from 10% to 16%. In essence, the TCP is mostly determined by the percentage of tumor in which the dose is not escalated. The small gains become even smaller if the baseline TCP level is already high, as illustrated by the shallow slope of all the curves originating at 90%.

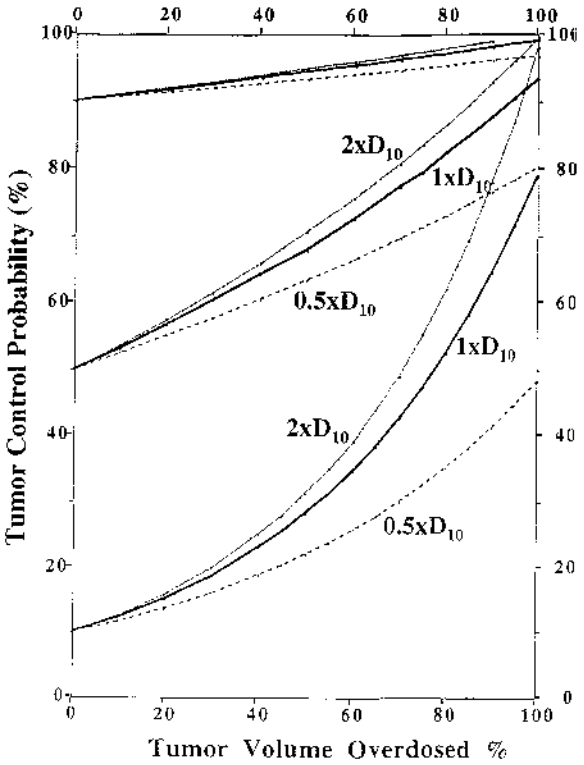

Fig. 3. Plots of the estimated increase in TCP from inhomogeneities in dose distribution within the target volume which yield doses greater by 0.5 ×, 1.0 × or 2.0 × the D_{10} value. The greatest benefits occur when the tumor control rate from the prescribed standard dose is low and when inhomogeneity of dose leads to a large percentage of the tumor receiving a higher dose. Small hot spots add little to tumor control, even when the overall probability of control is low or the dose to the hot spot is high. When tumor control from the prescribed dose is already high (e.g. 90%), there is little change in TCP as a function of either the volume receiving higher doses, or the magnitude of that increase. (Assumptions were similar to those for Fig. 1.)

However, once the escalated doses can be applied to greater than about 50% of the tumor volume, the gains in TCP increase more steeply, especially when the baseline control rates are low. It is obvious from the upward bending of the curves in Fig. 3 that the same percentage point increase in the volume receiving the higher dose produces an accelerated increase in TCP the closer the higher dose volume approaches 100%. For example, as illustrated by Fig. 3, if a dose which produced a TCP = 10% were increased throughout 50% of the tumor, by a modest $0.5 \times D_{10}$, the TCP would increase by 12 percentage points, but if the volume receiving the same incremental dose were further extended from 50% to 100% of the tumor volume, the TCP would increase by a further 26 percentage points, to 48%. For a larger increment in dose ($1 \times D_{10}$), the comparable increases would be 18% and 50%. Conversely, as is also illustrated in Fig. 1, the absolute rate of decrease in local control rate is greatest when the percentage of tumor exposed to the escalated dose is just beginning to drop from 100% (i.e. from a homogeneously escalated dose), a not uncommon treatment scenario with tightly conformal dose planning, but affected most dramatically by the magnitude of the dose-reduction or escalation (e.g. compare curves for $0.5 \times D_{10}$ and $2 \times D_{10}$, Fig. 1, and the separation of the curves for $0.5 \times D_{10}$ and $2 \times D_{10}$ in Fig. 3).

In summary, the curves in Fig. 3 illustrate that peaks of dose escalation in small volumes of the tumor, regardless of their magnitude, are of little value in any situation, but especially when tumor control rates are already high, as in prostate cancer receiving greater than 80 Gy or meningiomas receiving 50 Gy, whereas, when the percentage of the tumor volume receiving higher doses approaches 100%, even when the doses are only modestly increased, the rate of increase in TCP becomes quite steep, especially when baseline values are low.

GEOMETRY OF TUMOR VOLUMES AND ESCALATION OF DOSE

Volume of a cylinder is a function of the square of the diameter: thus, for example, in a perfectly cylindrical 4 cm diameter tumor, nearly 50% of the tumor volume would lie in the outer 5 mm annulus (between 3.5 cm and 4.0 cm).

This annulus is the most likely to be underdosed when beams are tightly conformed to the tumor with the intent of sparing adjacent normal structures. Although this effect of geometry is accounted for in calculations of dose-volume histograms, it should be considered when defining target volumes on CT images, appreciating also that many tumors are mobile and that there may be errors in set-up and or patient movement which could lead to uncertainties in actual dose distribution especially in the outer annulus.

Many intracranial lesions treated by stereotactic radiosurgery are spherical, and volume is then proportional to the cube of diameter. Thus, for a 1 cm diameter spherical tumor, 50% of the volume lies in the outer 1 mm 'crust', where the potential for geographic underdosage from small inaccuracies in dose localization is greatest. Conversely, because the inner 8 mm diameter core of a 1 cm spherical tumor contains only about 50% of the cells, the gain from a peak of dose within the tumor is limited, and the concept of 'imploding' such a tumor is illogical (Fig. 3). Furthermore, there is not much to gain from prescribing at a 50% isodose line wrapped loosely around the tumor rather than, say, at a 90% line which is tightly conformal, especially when the dose prescribed already yields a high chance of control and patient immobilization is good and tumor movement negligible.

DOSE PRESCRIPTION STRATEGIES

Conformal therapy may be designed to increase tumor control rates, decrease normal tissue sequelae outside the target volume, or both.

Assuming that normal tissue sequelae with conventional treatments are acceptable and that the aim of conformal treatment is to increase the rate of tumor control, then the standard dose per fraction could be prescribed to the critical normal tissue, with a higher dose per fraction and total dose to the tumor. This has the advantage of delivering a higher total tumor dose in the same overall treatment duration resulting in an acceleration in dose intensity. Furthermore, the higher dose per fraction yields an increase in the biological dose depending upon the α/β value which characterizes the fractionation response of the tumor. Fortuitously, many tumors currently treated with conformal therapies have relatively indolent proliferation profiles (e.g. prostate cancer, meningiomas, acoustic neuromas, chordomas) and hence may have low α/β ratios. If such were the case, the biological dose would be enhanced and the biological dose intensity further increased to an extent that would depend upon the dose per fraction and α/β value for the tumor. For example, consider an indolent tumor such as prostate cancer and assume its fractionation response is characterized by a low α/β ratio of 2.0 Gy. If, for a dose of 2 Gy to the critical normal tissue, a tumor dose of 2.5 Gy could be achieved by conformal IMRT, the 25% increase in physical dose would be amplified by a further 12.5% to yield a biological dose 40% higher than the dose to the normal tissue. If such a large gradient in biological dose can be achieved (in treating indolent tumors), it may be possible to reduce the total dose and/or dose per fraction with a view to reducing normal tissue sequelae. Since the 'double-bubble' of physical and biological dose amplification is most likely to occur in indolent tumors, the risk of treatment failure through an early onset of tumor repopulation is also less than in more proliferative tumors. [In more proliferative tumors, such as epitheliomas of head and neck, steep dose gradients may permit the prescription of higher doses per fraction to the tumor, thereby accelerating its rate of treatment without a concomitant intensification of dose in adjacent normal tissues, but there is little benefit from a double-bubble because α/β values are characteristically high for these tumors.]

If the normal tissue sequelae from conventional irradiation are too severe, they may be reduced using conformal therapy through a reduction in the volume of normal tissue exposed to high doses. A reduction in total dose may also lead to a concomitant decrease in dose per fraction, with a 'sparing' effect which is greatest in slowly responding tissues with low α/β ratios.

VOLUME EFFECTS IN NORMAL TISSUES

Dose-volume histograms (DVHs) provide more data for predicting tumor control and toxicities than has been available historically. The value of this more detailed description of dose distribution will increase with time as our ability to interpret DVHs increases. Models of dose-volume parameters of tissue response to radiation therapy have been developed based on the concept of functional or structural subunits and whether they are arranged in parallel (e.g. nephrons in the kidney) or in series (e.g. myelinating subunits of nerve tracts) (3, 45, 46). When functional subunits are aligned in series and dependent upon one another to maintain the functional integrity of the organ, then increasing *length* of the irradiated tissue is associated with increased incidence of an adverse event (46). Examples are nerve tracts in the spinal cord and the peritoneal sheath around the small intestine.

A spurious volume effect may occur when large volumes of tissue are irradiated: large volumes involve dose inhomogeneity, with high-dose regions suffering the 'double-trouble' of high doses in proportionately larger dose fractions: the adverse events reflect dose inhomogeneity rather than a true volume effect (22).

Apart from these examples, most volume effects are patho-physiologic changes common to other forms of injury and not specific to irradiation. Radiobiological assumptions about, and biophysical modeling of a volume effect have led to misunderstandings of the many different reasons why the severity of sequelae are often related, in a

reasonable physiological way, to the volume of tissue injured (22). For example, in tubular structures such as esophagus and gut, and for sphincters, the same dose-volume histogram may have different significance, depending upon whether the volume involves a short length of the whole circumference or some of the circumference for a long length (47, 48). This is not, however, specific to radiation injury. Since the subject of normal tissue tolerance as a function of dose-volume histograms is not readily studied in animal experiments, there is a crucial need for meticulous long-term studies in man (8).

CONCLUSIONS

Inhomogeneities in dose within a tumor affect the probability of cure to an extent that is influenced by many factors:

1. Steepness of the TCP curve, which is a function of the effective slope of the dose survival curve for clonogenic tumor cells, which in turn is affected by the intrinsic radiosensitivity of the tumor cell population, and their fractionation response (α/β ratio), the extent of hypoxia, and growth rate of surviving clonogens during treatment, and other less-defined factors.
2. Magnitude of variation of dose within the tumor volume: a large degree of underdose to even a small volume can have grave consequences. In terms of dose-volume histograms, 'notches' in the shoulder may be associated with a rapid rate of decline in TCP values relative to those predicted from homogenous irradiation, especially if the TCP from homogeneous irradiation is high.
3. The density of clonogenic cells in areas of over- or underdosage.
4. Volume of tumor underdosed.
5. Volume of tumor overdosed. The effectiveness of overdosage in controlling tumors increases more rapidly the closer the percentage of tumor overdosed approaches 100%. High doses limited to small percentages (e.g. $< 50\%$ of the tumor) are essentially worthless in improving TCP.
6. The rate of change in TCP as a function of volume under- or overdosed varies with the TCP which would result from a homogeneous dose.

Although we can model these effects in a general way, imprecision in biological and radiobiological parameters limits potential clinical application.

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