Radiation therapy evolved as a treatment for cancer because it permitted tumor eradication with preservation of function of normal tissues. The concept of delivering therapeutic radiation in multiple small-dose fractions rather than as a large single exposure evolved early in the history of radiation therapy. It was based initially on two rationales for maximizing a differential between responses of dose-limiting normal tissues and the tumor. Regaud (1) observed that irradiation of the testes of experimental animals with a series of daily low-energy X-rays available at that time was assumed to follow by a Ph.D. degree from the University of London where he worked with Dr. Gray. After spending two years as a visiting research scientist at the National Cancer Institute, working with Dr. Mortimer Elkind, he became an associate professor of radiotherapy at the University of Texas M.D. Anderson Cancer Center. In 1971, he became a professor of radiotherapy at M.D. Anderson, and then, in 1980, he moved to UCLA, where he became a professor in the Department of Radiation Oncology.

After a two-year stint as professor and director of the Institute of Oncology at the Prince of Wales Hospital, University of New South Wales, Sydney, Australia from 1989 to 1991, Dr. Withers returned to UCLA where he is currently professor and chair of the Department of Radiation Oncology.

Dr. Withers has received numerous honors in recognition of his scientific achievements, including the Polish Academy of Science Conference: Developmental Biology and Cancer, June 9-10, 1998, Bethesda, MD. This investigation was supported by U.S.P.H.S. Grant CA-31612 awarded by the National Cancer Institute, Department of Health and Human Services.

Received 11/11/98; accepted 1/27/99.

1 Presented at the "General Motors Cancer Research Foundation Twentieth Annual Scientific Conference: Developmental Biology and Cancer," June 9-10, 1998, Bethesda, MD. This investigation was supported by U.S.P.H.S. Grant CA-31612 awarded by the National Cancer Institute, Department of Health and Human Services.

2 To whom requests for reprints should be addressed.

In summary, Dr. Withers' research has provided the basis for modern radiation therapy concepts worldwide. I am very proud today to introduce such a distinguished scientist, and I look forward to Dr. Withers' talk titled "Biology of Dose Fractionation in Radiation Oncology."

Lorraine J. Gudas
Cornell University Medical College
New York, NY

Historical Development of Dose Fractionation

Radiation therapy evolved as a treatment for cancer because it permitted tumor eradication with preservation of function of normal tissues. The concept of delivering therapeutic radiation in multiple small-dose fractions rather than as a large single exposure evolved early in the history of radiation therapy. It was based initially on two rationales for maximizing a differential between responses of dose-limiting normal tissues and the tumor. Regaud (1) observed that irradiation of the testes of experimental animals with a series of daily doses resulted in infertility without desquamation of the skin of the scrotum, a differential that could not be achieved with single exposures. Because skin was the dose-limiting normal tissue with the low-energy X-rays available at that time and the testis was assumed to be a reasonable surrogate for the proliferative behavior of a tumor, radiation treatments were spread over several days. It was also observed early on that X-rays were more damaging to mitotic than to interphase cells, mitosis and interphase being the only two phases of the division cycle identified at the time. On this basis, Schwarz (2) reasoned that treatment with six fractions rather than one would increase the chances of irradiating tumor cells in mitosis.

After these biology-based beginnings, dose fractionation evolved by empirical clinical experimentation until, by the 1960s, standard practice in curative radiation therapy had evolved to a variety of schemes ranging in length from 3 to 8 weeks. Doses in short regimens were limited by the severity of acute responses in normal tissues such as mucosae. Higher doses could be given in regimens lasting 6–8 weeks because the severity of acute responses was modulated by regeneration of surviving cells within those tissues during the course of treatment, but ultimately, the dose was limited by the tolerance of late-responding normal tissues (which did not regenerate during treatment).
The advent in 1956 of cell cloning techniques in vitro (3, 4) and, subsequently, in vivo (Refs. 5-9 and Fig. 1) and the development of other quantitative assays of normal tissue (10) and tumor responses (11-13) marked the beginning of a new era of scientific investigation of the biology of radiation therapy. The processes that predominate in determining fractionation responses were identified as the “four R’s” (14): repair of sublethal injury, regeneration (repopulation) by surviving cells, redistribution within the division cycle between dose fractions, and, in tumors, reoxygenation of cells that become hypoxic through inadequate blood perfusion. Although reoxygenation and

Fig. 1. Examples of in situ clonal regeneration in normal tissues, which permitted quantitation of radiosensitivity and fractionation responses. Macrocolonies in skin (A) and jejunal mucosa (B), microcolonies in the epithelium of jejunum (C), colon (D), testis (E), and renal tubule (F) are shown.
jejunal crypt cell survival after a T-ray dose of 11 Gy (Fig. 2).

In four phases of the division cycle. The ratio of the effective slopes for 11-Gy tractions depicted.

Cultured Chinese hamster V79 cells show an asynchronous distribution throughout the division cycle, their subsequent progression and redistribution into other phases will result in a net average radiosensitization of the surviving cell population. Tumor cells progress through the cycle at highly variable rates and soon revert to asynchrony. Thus, multifraction irradiation of a tumor produces a net radiosensitization relative to a nonproliferative cell population that does not progress (from Go) between dose fractions.

The difference in net radiosensitivities between redistributing "self-sensitizing" proliferative tumor cells and static, relatively radiosensitive target cells in late-responding normal tissues favors the use of multiple small doses to achieve a therapeutic advantage in radiotherapy of cancer (21). Fig. 3 was constructed assuming only two aged subpopulations of tumor cells: one resistant and one sensitive, varying by a factor of only 3 in the effective slopes of their survival curves between 0 and 2 Gy. (This 3-fold difference in radiosensitivity relates to the slope of the survival curves and does not result in a 3-fold difference in cell survival, the survival fractions from 2 Gy being 60 and 30% for resistant and sensitive phase cells, respectively.) The curves trace the factor by which the survival of relatively radioresistant nonproliferating, nonrepopulating (Go) target cells, which remain static in the cycle, exceeds that in a fully redistributing (tumor) cell population composed of mixtures of up to 40% sensitive phase cells, after exposure to three different regimens: a single dose of 20 Gy, 35 fractions of 2 Gy, and 70 fractions of 1.175 Gy. (As discussed below, two fractions of 1.175 Gy produce late injury equivalent to that from one fraction of 2 Gy, based on an α/β ratio of 4 Gy.) The differential between survival of nonproliferative cells in normal tissues and tumor clonogens is dramatic when a single fraction is replaced by a regimen of 35 fractions. The advantage from replacing 35 fractions of 2 Gy with 70 fractions of 1.175 Gy is less but still important when considering total doses above the threshold in a threshold-sigmoid dose response for tumor control (for which small increments in dose are reflected in measurable gains in cure).

Repair Capacity, Isoeffect Curves, and α/β Ratios. When treatment is given in multiple doses, it is necessary to increase the total dose for a constant level of tissue response or tumor control. This increase in total "isoeffect" dose as a function of increasing dose fractionation was originally plotted against overall treatment time (22).

After Puck cloned mammalian cells in vitro (3), it was possible to determine X-ray dose-survival curves. They showed an initial shoulder preceding a logarithmic decline at higher doses. Elkind and Sutton

vascularization are active areas of investigation (15), they will not be considered here.

For reasons to be discussed, the two modifications of standard dose fractionation of the most current clinical interest are the use of smaller dose fractions (hyperfractionation) and the intensification (acceleration) of dose delivery.

Hyperfractionation

Cell Cycle Redistribution. Most cell death after irradiation is linked to disruption of reproductive integrity, although apoptosis also occurs. The rate of expression of injury is related to the proliferative activity of the tissue. Highly proliferative tissues, such as bone marrow, skin, hair, mucous, and seminiferous epithelium, manifest a response within days or weeks, whereas slowly proliferating or nonproliferative structures, such as fibrovasculature, kidney, central nervous system and peripheral nerves, bones, and so on, may not develop detectable changes for months or years. Likewise, regeneration after radiation injury occurs at different rates, being quicker in more proliferative tissues.

Cells vary widely in their radiosensitivity as they progress through the division cycle (16-19). As a consequence, when a population of proliferating cells distributed asynchronously throughout the division cycle is irradiated, the more radiosensitive phases are selectively sterilized, leaving a partially synchronized subpopulation of relatively radioresistant survivors. Cultured Chinese hamster V79 cells show an ~7-fold variation in the effective slope of a survival curve between 0 and 2 Gy, yielding ~80% survival of late S-phase cells and ~20% survival of G2-M cells (18). Such variation is consistent with in vivo data (20) that show as much as a 100-fold phase-related difference in jejunal crypt cell survival after a γ-ray dose of 11 Gy (Fig. 2).

Because cells surviving immediately after a dose of 2 Gy are partially synchronized in relatively resistant phases of the mitotic cycle, their subsequent progression and redistribution into other phases will result in a net average radiosensitization of the surviving cell population. Tumor cells progress through the cycle at highly variable rates and soon revert to asynchrony. Thus, multifraction irradiation of a tumor produces a net radiosensitization relative to a nonproliferative cell population that does not progress (from Go) between dose fractions.

The difference in net radiosensitivities between redistributing “self-sensitizing” proliferative tumor cells and static, relatively radiosensitive target cells in late-responding normal tissues favors the use of multiple small doses to achieve a therapeutic advantage in radiotherapy of cancer (21). Fig. 3 was constructed assuming only two averaged subpopulations of tumor cells: one resistant and one sensitive, varying by a factor of only 3 in the effective slopes of their survival curves between 0 and 2 Gy. (This 3-fold difference in radiosensitivity relates to the slope of the survival curves and does not result in a 3-fold difference in cell survival, the survival fractions from 2 Gy being 60 and 30% for resistant and sensitive phase cells, respectively.) The curves trace the factor by which the survival of relatively radioresistant nonproliferating, nonrepopulating (Go) target cells, which remain static in the cycle, exceeds that in a fully redistributing (tumor) cell population composed of mixtures of up to 40% sensitive phase cells, after exposure to three different regimens: a single dose of 20 Gy, 35 fractions of 2 Gy, and 70 fractions of 1.175 Gy. (As discussed below, two fractions of 1.175 Gy produce late injury equivalent to that from one fraction of 2 Gy, based on an α/β ratio of 4 Gy.) The differential between survival of nonproliferative cells in normal tissues and tumor clonogens is dramatic when a single fraction is replaced by a regimen of 35 fractions. The advantage from replacing 35 fractions of 2 Gy with 70 fractions of 1.175 Gy is less but still important when considering total doses above the threshold in a threshold-sigmoid dose response for tumor control (for which small increments in dose are reflected in measurable gains in cure).

Repair Capacity, Isoeffect Curves, and α/β Ratios. When treatment is given in multiple doses, it is necessary to increase the total dose for a constant level of tissue response or tumor control. This increase in total “isoeffect” dose as a function of increasing dose fractionation was originally plotted against overall treatment time (22).

After Puck cloned mammalian cells in vitro (3), it was possible to determine X-ray dose-survival curves. They showed an initial shoulder preceding a logarithmic decline at higher doses. Elkind and Sutton

vascularization are active areas of investigation (15), they will not be considered here.

For reasons to be discussed, the two modifications of standard dose fractionation of the most current clinical interest are the use of smaller dose fractions (hyperfractionation) and the intensification (acceleration) of dose delivery.

Hyperfractionation

Cell Cycle Redistribution. Most cell death after irradiation is linked to disruption of reproductive integrity, although apoptosis also occurs. The rate of expression of injury is related to the proliferative activity of the tissue. Highly proliferative tissues, such as bone marrow, skin, hair, mucous, and seminiferous epithelium, manifest a response within days or weeks, whereas slowly proliferating or nonproliferative structures, such as fibrovasculature, kidney, central nervous system and peripheral nerves, bones, and so on, may not develop detectable changes for months or years. Likewise, regeneration after radiation injury occurs at different rates, being quicker in more proliferative tissues.

Cells vary widely in their radiosensitivity as they progress through the division cycle (16-19). As a consequence, when a population of proliferating cells distributed asynchronously throughout the division cycle is irradiated, the more radiosensitive phases are selectively sterilized, leaving a partially synchronized subpopulation of relatively radioresistant survivors. Cultured Chinese hamster V79 cells show an ~7-fold variation in the effective slope of a survival curve between 0 and 2 Gy, yielding ~80% survival of late S-phase cells and ~20% survival of G2-M cells (18). Such variation is consistent with in vivo data (20) that show as much as a 100-fold phase-related difference in jejunal crypt cell survival after a γ-ray dose of 11 Gy (Fig. 2).

Because cells surviving immediately after a dose of 2 Gy are partially synchronized in relatively resistant phases of the mitotic cycle, their subsequent progression and redistribution into other phases will result in a net average radiosensitization of the surviving cell population. Tumor cells progress through the cycle at highly variable rates and soon revert to asynchrony. Thus, multifraction irradiation of a tumor produces a net radiosensitization relative to a nonproliferative cell population that does not progress (from Go) between dose fractions.

The difference in net radiosensitivities between redistributing “self-sensitizing” proliferative tumor cells and static, relatively radiosensitive target cells in late-responding normal tissues favors the use of multiple small doses to achieve a therapeutic advantage in radiotherapy of cancer (21). Fig. 3 was constructed assuming only two averaged subpopulations of tumor cells: one resistant and one sensitive, varying by a factor of only 3 in the effective slopes of their survival curves between 0 and 2 Gy. (This 3-fold difference in radiosensitivity relates to the slope of the survival curves and does not result in a 3-fold difference in cell survival, the survival fractions from 2 Gy being 60 and 30% for resistant and sensitive phase cells, respectively.) The curves trace the factor by which the survival of relatively radioresistant nonproliferating, nonrepopulating (Go) target cells, which remain static in the cycle, exceeds that in a fully redistributing (tumor) cell population composed of mixtures of up to 40% sensitive phase cells, after exposure to three different regimens: a single dose of 20 Gy, 35 fractions of 2 Gy, and 70 fractions of 1.175 Gy. (As discussed below, two fractions of 1.175 Gy produce late injury equivalent to that from one fraction of 2 Gy, based on an α/β ratio of 4 Gy.) The differential between survival of nonproliferative cells in normal tissues and tumor clonogens is dramatic when a single fraction is replaced by a regimen of 35 fractions. The advantage from replacing 35 fractions of 2 Gy with 70 fractions of 1.175 Gy is less but still important when considering total doses above the threshold in a threshold-sigmoid dose response for tumor control (for which small increments in dose are reflected in measurable gains in cure).

Repair Capacity, Isoeffect Curves, and α/β Ratios. When treatment is given in multiple doses, it is necessary to increase the total dose for a constant level of tissue response or tumor control. This increase in total “isoeffect” dose as a function of increasing dose fractionation was originally plotted against overall treatment time (22).

After Puck cloned mammalian cells in vitro (3), it was possible to determine X-ray dose-survival curves. They showed an initial shoulder preceding a logarithmic decline at higher doses. Elkind and Sutton
reconstitution of the shoulder for the second and subsequent expo-
the survival curve for the second dose regained, within a few hours, a
ological observation led radiation oncologists to realize that the total
N or T, an interesting pattern emerged (Fig. 4). Acutely responding
fractions (N) into which the total dose was divided (10), rather than
isoeffect formula developed as a consequence of the quantitation of
repair of sublethal injury involved the number of fractions (N) but, for
overall time (T) taken to deliver N fractions. The most popular
normal tissues, continued with a time component (T) to account for
(4) showed that when a dose was divided into two (or more) fractions,
the survival curve for the second dose regained, within a few hours, a
shoulder similar to that characteristic of the first exposure. This
reconstitution of the shoulder for the second and subsequent exposures
resulted from repair of sublethal injury and leads to an increase in
total dose required for a constant level of cell survival. This radiobi-
ological observation led radiation oncologists to realize that the total
dose for an isoeffect should be plotted as a function of the number of
fractions (N) into which the total dose was divided (10), rather than
over time (T) taken to deliver N fractions. The most popular
isoeffect formula developed as a consequence of the quantitation of
repair of sublethal injury involved the number of fractions (N) but, for
normal tissues, continued with a time component (T) to account for
repopulation (23).

The use of N in an isoeffect formula was an improvement over just
T. However, the major factor determining the influence of repair
of sublethal damage on the response to a series of small doses is the
amount of sublethal injury accumulated during and repaired after each
dose fraction. This is determined by the size of each dose fraction, not
the number of fractions per se (24).

Once isoeffect curves for a variety of tissues in experimental
animals were replotted as a function of dose per fraction, rather than
N or T, an interesting pattern emerged (Fig. 4). Acutely responding
tissues had isoeffect curves with slopes that were consistently more
shallower than those for late-responding normal tissues; i.e., as the dose
per fraction was lowered, the total dose for a constant effect increased
less steeply for acutely responding than for slowly responding tissues
(25, 26).

This generic difference in the slopes of isoeffect curves for early-
and late-responding normal tissues can be explained in terms of
differences in the shapes of dose-survival curves for the “target” cells,
which determine tissue responses. Dose-survival curves, which plot
the logarithm of the number of cells surviving as a function of dose,
can be adequately described by two coefficients of radiosensitivity, α
and β, which relate to the dose (d) and the square of dose (d²),
respectively:

\[ \text{Surviving fraction} = e^{-(\alpha d + \beta d^2)} \]

The relative values of α and β determine the curvature of the
dose-survival relationship (Fig. 5). If the α/β value is large, as it is for
acutely responding normal tissues and many tumors, the slope and
shape of the curve are dominated by the value of α, and the survival
relationship described by αd shows little deviation from linearity over
the range of low doses used in fractionated radiation therapy. If the
α/β ratio is low, as it is for late-responding normal tissues, there is a
more pronounced downward curvature because cell killing is rela-
tively more related to the square of dose (i.e., to βd²). Therefore, the
late-responding tissues, characterized by a low α/β ratio, show a more
pronounced change in response with change in fraction size, and this is
reflected in a steep curve relating total isoeffect dose to change in
dose per fraction (Fig. 4).

The relationship between change in size of dose per fraction and the
total dose for a constant level of effect (an isoeffect dose) can be
quantified:

\[ D_{\text{new}}/D_{\text{ref}} = (\alpha/\beta + d_{\text{ref}})/(\alpha/\beta + d_{\text{new}}) \]

where \( D_{\text{new}}/D_{\text{ref}} \) is the ratio of the new total dose to the reference total
dose when a change is made to a new dose per fraction (\( d_{\text{new}} \)) from a
reference dose per fraction (\( d_{\text{ref}} \)) and α/β is a characteristic of the
tissue. The reference doses are usually for 2 Gy per fraction because
that is the regimen for which there are most clinical data. Some
examples of estimates of α/β ratios (27–32) are shown in Table 1.
Although absolute values for α and β have been determined for some
tissues, using clonogenic cell survival assays (33, 34), most α/β ratios
are calculated from the rate of change of isoeffect dose with change in
size of dose per fraction, without knowledge of the absolute values.

That isoeffect doses could be calculated using the ratio, α/β, of
coefficients of cellular radiosensitivity without knowledge of their
absolute values was an important conceptual advance (25) because it
recognized that dose per fraction was the primary determinant of
fractionation responses and that α/β ratios varied widely among
tissues. It also rationalized, on the basis of sound radiobiology, limited

![Fig. 5](https://example.com/fig5.png)

Fig. 5. Relative shapes of survival curves for target cells in tissues that are acutely
responding (high α/β ratio) or slowly responding (low α/β ratio), illustrating how, for
x-rays, a low α/β ratio confers a greater sensitivity to changes in size of dose per fraction.
extrapolation of isoeffect curves to the low doses (e.g., 1 Gy) relevant to hyperfractionation, a dose range not readily amenable to animal experimentation (because of the difficulties of administering 50–100 dose fractions to achieve a measurable endpoint).

### Clinical Implications of Tissue-Specific α/β Ratios

With recognition of generic differences in fractionation responses between early- and late-responding normal tissues came an understanding of some disastrous results from clinical trials of hypofractionation and neutron therapy undertaken from the late 1960s into the 1980s.

Hypofractionation decreased the inconvenience and expense of five treatments per week by giving larger doses per fraction only twice per week (e.g., 8.5 Gy in two fractions to replace 10 Gy in five fractions). The universal outcome of such studies was a large increase in the incidence of severe complications in slowly responding tissues with little or no difference in the severity of acute responses or rates of local tumor control (25, 26). The problem in the design of these trials was the assumption that the fractionation responses were the same for early- and late-responding normal tissues (23, 35). We now know that, although the isoeffective dose for acute effects was correctly reduced by 15%, corresponding to an α/β value of 10 Gy, the dose for late isoeffects should have been lowered by 25% for tissues with an α/β ratio of 4.5 Gy and even more for other slowly responding tissues with lower α/β ratios (Table 1).

Neutron therapy was also associated with an increased incidence of late sequelae. The problem was not one of increased capacity of neutrons to cause late injury but rather an equivalence of neutron fractionation responses of early- and late-responding normal tissues; the apparent increase in late sequelae with neutrons, relative to the incidence with X-ray therapy, reflected a preferentially reduced incidence of X-ray-induced late damage that had existed, unknown, in the slowly responding tissues exposed to standard fractionated X-irradiation. In other words, the α/β values are similar for early and late neutron effects, whereas with X-rays, the α/β ratio is lower for late responses (Ref. 36 and Fig. 5).

For the same reason that hypofractionation yielded a therapeutic disadvantage, hyperfractionation (a larger number of smaller dose fractions) should provide a therapeutically advantageous differential between X-ray responses of late-responding normal tissues and proliferative tumors, although with an associated increase in the incidence of acute responses in normal tissues.

If generic α/β values for late effects were 4 Gy and, for squamous carcinoma of head and neck, 20 Gy, the linear-quadratic isoeffect formula (above) indicates that, to achieve a constant level of late effect, the total dose in a regimen of 115 cGy fractions must be 16.5% higher than for a regimen of 200 cGy fractions, whereas for a constant "biological" dose to the tumor, the total dose would need to be increased by only 4%. Therefore, from simply reducing the dose per fraction from 200 to 115 cGy and raising the total dose by 16.5%, the therapeutic gain factor would be 1.165/1.04 = 1.12, or 12%.

In summary, the two major rationales for anticipating a benefit from hyperfractionation are self-sensitization of the tumor by division cycle redistribution of surviving cells between dose fractions and a curvature in the dose-response relationship for target cells, which is greater for late-responding tissues than for tumors. These are not necessarily completely unrelated phenomena; e.g., progression through the cycle may truncate the process of repair of sublethal injury. Both involve increased acute toxicity. Their relative importance in the fractionation response is difficult to evaluate. Redistribution has a subtle effect on isoeffect doses which is quickly obscured by subsequent repopulation. However, when an effect of regeneration can be excluded, as in the radiation response of the seminiferous epithelium, its importance is readily apparent (37, 38). In contrast, differences in α/β ratios among tissues are substantial (Table 1) and are now generally considered to be the more important biological rationale for changing to smaller doses per fraction, i.e., hyperfractionation. (A third possible but minor factor favoring hyperfractionation, which will not be discussed here, is a decreasing influence of hypoxia on tumor cell radioreistance at low doses per fraction (39).

### Clinical Trials of Hyperfractionation

Several pilot studies suggested that hyperfractionation yielded a therapeutic advantage (40). One large multi-institutional randomized European Organization for Research and Treatment of Cancer study has been analyzed, and the results have been published (41). The regimens compared were 7000 cGy in 35 fractions of 200 cGy over 7 weeks and 8050 cGy in 70 fractions of 1.15 Gy given twice per day over 7 weeks. The local recurrence rate of T2-T4 squamous cell carcinomas of the oropharynx was reduced from 60 to 40%, a significant 33% reduction that has subsequently been found to be associated with a significant improvement in overall survival rate. A Radiation Therapy Oncology Group trial has closed after accruing ~1100 patients, but the results have yet to be uncoded. It was a four-arm study comparing a predominantly hyperfractionated (although slightly accelerated) arm giving 67 fractions of 120 cGy twice per day for slightly less than 7 weeks with a conventional 7000 cGy in 200 cGy fractions in 7 weeks regimen and with two schedules of predominantly accelerated, although slightly hyperfractionated, treatment.

### Small Dose per Fraction in Standard Practice

The concept of preferentially reducing toxicity in slowly responding tissues by reducing dose per fraction has widespread applications in everyday radiation oncology, not just in developing new fractionation strategies for head and neck cancer, e.g., where special care is required to avoid late sequelae in such tissues as spinal cord, which is characterized by a very low α/β ratio (Table 1) or when “tolerance” has been reduced by prior irradiation. The isoeffect doses can be calculated with reasonable confidence.

### Clinical Contraindications to Hyperfractionation

Not all treatment situations resemble that in head and neck cancers, in which dose-limiting tissues have low α/β ratios and squamous carcinomas have high values (32, 42). For example, hyperfractionation for prostate cancer may be disadvantageous if the α/β value for the cancer is low (28) but is high for acute rectal mucosal injury, which predisposes to the later complication of chronic proctitis. There are also data suggesting relatively low α/β values for melanomas and liposarcomas (30, 43). It would not be surprising to also find low values for some other slowly growing tumors, e.g., meningiomas. In such situations, it is inadvisable to use hyperfractionated schedules; rather, it may prove useful to reevaluate the use of larger doses per fraction (hypofractionation), especially if doses can be largely restricted to the tumor through conformal or stereotactic techniques.
Slowness of tumor growth does not, by itself, indicate a low $\alpha/\beta$ ratio, and a consequent contraindication to hyperfractionation. Slow growth of many tumors results from a high cell loss factor coincident with a high cell production rate (i.e., a high level of mitotic activity among the malignant clonogens). A prime example is basal cell carcinoma of skin, the indolent growth of which belies a high rate of mitotic turnover (and a high cell loss factor). In general, a high cell loss factor and a high $\alpha/\beta$ ratio should be suspected in slowly growing tumors that regress quickly after irradiation.

**Fractionation Intervals and Completeness of Repair of Sublethal Injury.** Repair of sublethal injury continues for longer in some tissues than in others (27), being slow in some critical late-responding tissues, notably, the spinal cord. This is a major concern if the cord is treated more than twice per day (44) because there is then no 16-18-h overnight interfraction interval characteristic of twice per day regimens. To obtain the maximum benefit from hyperfractionation, it is necessary to use fractionation intervals as long as possible, preferably 8 h or more.

**Accelerated (Intensified) Fractionated Treatment**

**Growth Rate of Tumors before Treatment.** It has been conventionally taught that tumors grow autonomously and are not subject to homeostatic feedback mechanisms. When they are large enough to be clinically detectable, they grow with a median volume doubling time of ~2 months (45). Therefore, growth during a course of radiation therapy was considered to be essentially irrelevant to ultimate tumor response, and the influence of overall treatment time on tumor control rate was largely ignored. It was excluded as a factor in Nominal Standard Dose calculations of isoeffective tumor doses (23), and even in the recent past, it was common to introduce ad hoc or planned breaks in standard therapy for social or logistic reasons or to reduce the severity of acute normal tissue responses.

Some tumors (e.g., Burkitt’s lymphoma) characteristically grow rapidly, and within all histologies, there is a wide spread of growth rates, a small proportion showing clinically apparent rapid growth (46). Rapidly growing tumors should be treated with an intensive regimen, even at the expense of reducing total dose, as was done, for example, in the CHART4 regimen (44, 47). However, of more general concern, rapid growth of surviving tumor clonogens has been shown to develop during treatment and threaten cure, even in tumors that are growing slowly at the time of diagnosis (27, 48-54).

**Accelerated Growth during Treatment.** Regression of a tumor mass during radiation therapy or chemotherapy has deceived oncologists by masking very rapid regrowth occurring within the small subpopulation of clonogens that are still not sterilized late in treatment. After 4-week exposure to five fractions of 200 cGy per week, the proportion of the original tumor clonogens still surviving approaches 1 in 1 million. Their rapid regrowth within a regressing mass of mainly sterilized cells is invisible.

Detection and measurement of the rate of accelerated tumor clonogen repopulation in a regressing tumor during a course of radiation therapy requires analysis of the effect on tumor control rates of changing the overall duration of a course of therapy. It is evidenced by an increase in the total dose necessary for a constant rate of tumor control as treatment is prolonged (Fig. 6) or as a decrease in the rate of tumor control if there is not a concomitant increase in the total dose (Fig. 7). An increase in the total dose needed for a constant (e.g., 50%) probability of local tumor control ($TCD_{50}$) has been estimated to average about 60 cGy/day for cancers of head and neck (Fig. 6 and Refs. (32) and (48-57). Decreases in local control rate have been estimated to range between 0.5 and 3% for each day’s extension of treatment for tumors of the head and neck (Fig. 7 and Refs. 32, 48, and 56-61), cervix (56, 62), bladder 63, and lung (64). Whether a similar phenomenon applies to prostate cancer has not been established (65, 66).

Scattergram analysis of data from only a single center (Fig. 6A) can be criticized because of the possible bias resulting from the experienced radiation oncologist’s selecting high doses in protracted regimens to treat patients with tumors predicted to have the highest probability of failure. A second limitation is that the range of overall

---

4 The abbreviation used is: CHART, continuous hyperfractionated accelerated radiotherapy.
treatment duration is usually not very wide, diminishing the ability to resolve its effect. Third, it is unusual for most centers to use overall times shorter than 30 days, and therefore, although the effect of accelerated tumor growth after 30 days can be measured, its time of onset can not be established. These limitations were addressed by further studies in cancer of the head and neck.

The Patterns of Fractionation Study involved nine separate institutions in England, Canada, and the United States, which used widely divergent dose-time fractionation prescriptions adopted as institutional policy, not based on patient prognostic factors (32, 42). The study was confined to squamous carcinomas of the tonsil in 676 patients treated over a decade (1976–1985) in which there was limited staging by CT scans, and few patients would be excluded because they received adjuvant chemotherapy. Ninety % of the treatments were given within a range of 20–56 days. All data were peer reviewed by a radiation oncologist, physicist, and data manager from another of the participating institutions.

This large survey confirmed the results of earlier retrospective studies of regrowth. Over the clinically relevant range of doses per fraction, the α/β ratio for tumor was high enough to be of negligible influence on fractionation responses. The best estimate of the increment in TCD50, resulting from each day's extension of treatment was ~70 cGy (Fig. 6). The reduction in local control rate for a constant dose was ~1% per day (Fig. 7). The data were better fitted (but not significantly so) by nonlinear regression analysis when a lag period of 30 days was introduced before the onset of accelerated regrowth.

Another approach to quantifying tumor regrowth is to calculate values for TCD50 (or other levels of TCD) as a function of overall treatment duration using reported results in groups of patients in a large number of publications. The estimates of TCD50 are presented as symbols in Fig. 8, together with regression lines for TCD50 values from scattergrams from the relatively small number of publications that presented data for individual patients. The estimates plotted in Fig. 8 suggest that there is no measurable change in TCD50 values between 12 and ~28 days, followed by a rapid increase with time thereafter, consistent with a lag time of ~4 weeks before the average tumor of head and neck initiates a rapid repopulation response. Other statistical analyses of this type of data led to the same conclusions (67). Additional support for such a lag period is that the isoeffect regression lines for scattergrams (drawn in Fig. 8), or a line fitted through the TCD50 plots (not drawn in Fig. 8), would extrapolate to doses on the ordinate (i.e., to TCD50 values in the absence of repopulation), which, from clinical experience and from radiobiological knowledge are unrealistically low (e.g., 36 Gy in 2-Gy fractions). Also, new data from a large prospective randomized clinical trial of hyperfractionated accelerated treatment (CHART; Ref. (47), shown in Fig. 8 (squares), support the concept of a lag period followed by accelerated repopulation in squamous cell carcinomas of the head and

---

**Fig. 7.** Effect of overall treatment duration on the tumor control rate after a constant total dose of irradiation. A, decrease in local (pelvic) control rate in 621 cases of Stage III carcinoma of the cervix as a function of overall duration of therapy at a single institution (Ref. 56; reprinted with permission of W. B. Saunders Company). B, a nine-center study of squamous carcinoma of tonsil. Actuarial curves calculated using a mixture model for a total dose of 64 Gy in 2 Gy fractions to T2N+ tumors in four different overall times are shown (Ref. 32; reprinted with permission of Elsevier Science Inc.).
neck. When the duration of treatment for head and neck tumors was shortened from 47 to 12 days, a constant, ~50% tumor control rate was obtained with a dose decreased by ~12 Gy. Such a decrease is equivalent to only 34 cGy/day assuming a lag time of 12 days or less, but it would be equivalent to 80 cGy/day if the lag time were 30 days, a value more consistent with scattergram analyses (32, 48, 49, 54).

In summary, there is strong evidence for a lag time before the onset of accelerated repopulation by surviving tumor clonogens. On the basis of the diverse growth kinetics among tumors, the lag time in individuals is likely to vary, but the best current estimate of the average lag time in head and neck cancer is ~28 days (58, 67, 68).

The clonogen doubling rate after about 30 days of treatment can be estimated from the 60–70 cGy per day increment in isocontrol doses. Because ~200 cGy is required to reduce tumor cell survival by a factor of 2 and, in a standard radiation therapy regimen, the daily dose is 200 cGy, the daily increase of ~60 cGy in isoclinic doses can be interpreted as reflecting a doubling time of ~3 days (200/60) for tumor clonogens. When compared with pretreatment tumor volume doubling times, which average 45–60 days, the data indicate that surviving tumor clonogens in head and neck cancer accelerate their growth rate 15–20-fold from their pretreatment values.

**Clinical Implications of Accelerated Tumor Growth during Treatment.** The phenomenon of rapid (but invisible) clonogen regrowth is presumably a response to the microenvironment of the surviving cells [e.g., abundant cytokines, decreased ratio of tumor cell numbers to vascular endothelial surface area, decreased interstitial pressure (69), and an improved blood flow yielding better oxygenation and nutrition]. It is unlikely to be a specific response to irradiation. That it occurs after effective chemotherapy is suggested by the overall lack of improvement in local control rates from adding two or three cycles of pretreatment chemotherapy to radiation therapy for head and neck cancers (70), even though some degree of regression was commonly achieved before irradiation began. This is consistent with the cytotoxicity of the drugs being counterbalanced, on average, by accelerated regrowth of surviving cells occurring during the extended overall duration of the two therapies (drugs and radiation: Ref. 68).

The most important immediate clinical consequence from understanding that rapid tumor clonogen repopulation can develop during radiation or chemotherapy is the avoidance of unnecessary protraction of standard therapy. This may involve “catching up” after missed treatments, the use of techniques to circumvent breaks in treatment (e.g., medications, tube feeding, rescheduling boost doses, and so on), and minimizing the duration of the total treatment package (surgery, radiation, and chemotherapy; Ref. 68). For perspective, it can be calculated that three doublings of clonogen number, which is equivalent to a 9–12-day extension of radiation therapy in the case of head and neck cancer, is roughly equivalent to an average 1-unit increase in T stage.

Tumor control rates may be improved by intensifying treatment. There are numerous ways to intensify dose delivery, all of them characterized by increased acute toxicity.

Obviously, shortening the overall time taken to complete a standard treatment represents intensification. However, intensification can also be achieved by adding concomitant chemotherapy without shortening overall treatment duration (68). Also, hyperfractionation delivered in a standard overall time selectively intensifies treatment because the higher physical doses (given in smaller fractions) and intensified rate of dose accumulation translate into higher biological doses to the tumor, although not to the late-responding normal tissues. For example, in the European Organization for Research and Treatment of Cancer and Radiation Therapy Oncology Group trials the total physical dose was increased by 15%. After adjustment for the reduced dose per fraction, using an \( a_b \) ratio of 20 Gy for the tumor, this represents a 10.6% increase in the “biological” tumor dose. Because the overall treatment duration was essentially the same as in the standard arm, dose intensity was similarly increased by 10.6%. A 10.6% increase in biological dose over that given in 2-Gy fractions represents an increment of 740 cGy in total dose in a standard regimen (or 770 cGy if hyperfractionated). On the basis of an average of 60 cGy/day required to counterbalance 1 day’s tumor clonogen regrowth, an increment of 740 cGy in the biologically effective tumor dose translates to the equivalent of a 12-day (740/60) shortening of treatment.

**Conclusion**

Understanding the biology of dose fractionation increases flexibility in treatment prescriptions. Reducing dose per fraction and minimizing the overall duration of therapy can yield therapeutic gains in head and neck cancer and also, predictably, in other tumor sites. Current standard dose-time patterns may represent an excellent average, but a variety of better schemes are emerging for specific tumor types and, ultimately, for different individuals, based on well-quantified biology.

**Acknowledgments**

I thank my many mentors and colleagues, especially Mort Elkind, Jacek Maciejewski, Kathy Mason, Bill McBride, Lester Peters, Oliver Scott, Herman Suit, Jeremy Taylor, and Howard Thames. Jan Haas helped prepare the manuscript.

**References**

20. Withers, H. R., Mason, K., Reid, B. O., Dubravsky, N., Barkley, H. T., Jr., Brown, B. W., and Smathers, J. B. Response of mouse intestine to neutrons and gamma rays. 11.0 Gy.

Downloaded from cancerres.aacrjournals.org on August 15, 2017. © 1999 American Association for Cancer Research.
Radiation Biology and Treatment Options in Radiation Oncology

H. Rodney Withers


Updated version  Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/59/7_Supplement/1676s.2.citation

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.