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MODELING DOSE AND LOCAL CONTROL IN RADIOTHERAPY

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Abstract

We discuss models for predicting local control (prevention of tumor recurrence) after therapeutic radiation in cancer patients. The probability of control is first formulated from theoretical precepts. Biophysical principles dictate that the three factors in therapy which most universally influence outcome are total dose, number of sessions in which the dose is administered, and total time under treatment. These principles also suggest the scale, or link function, on which local control probability of a tumor of given size is a linear function of these predictors. The probabilities are given clinical relevance by assigning a mixing distribution to tumor volume - effective volume, the number of actively dividing cells in a tumor, is an unmeasurable but of course quite influential quantity. It is shown in this case that a gamma distribution of tumor volume induces linearity on a subset of the class of links first proposed by Burr (1942). Next, methods of modeling control by a finite followup time are discussed. We here give a new result, that minor assumptions on the influence of tumor volume upon recurrence allow models developed for permanent control to be applied directly recurrence by a finite time. We also describe adjustments for accommodating losses to followup before that time. Finally, inference on the mixing distribution of tumor volume is developed along with results of the effect of misspecifying the distribution. The methods are illustrated with three analyses of radiotherapy studies, all published here for the first time. Though developed for a specific type of failure data, many of the results given below also apply to any time-dependent binary outcomes.

Key words: binary regression; logistic regression; linear-quadratic equation; link tests; radiotherapy; gamma distribution; negative binomial distribution; Poisson distribution.
1. Introduction

Radiation oncologists have at their disposal a wide range of radiation doses and schedules in treating malignancies. There has naturally been a great deal of study, beginning shortly after the discovery of x-rays, on optimal radiotherapeutic regimens. Statistical models are now coming to play a increasingly important role in such studies. One major arena of modeling is the prediction of recurrence for patients who have undergone radiotherapy in the treatment of cancer. These predictions are used to find treatment schedules which minimize the chance of tumor recurrence while not subjecting the patient to an overly high risk of radiation side-effects.

The traditional radiotherapeutic regimen has three fundamental variables: total dose of radiotherapy, number of doses ("fractions") of radiation given, and the time taken for the course of treatment. Dose is an obvious factor in treatment: too low and the cancer recurs after treatment, too high and radiation side effects negate the benefit of the cure. In addition to dose, however, the manner of dividing it into fractions is important in both the treatment of tumors and calculation of damage to normal tissues. These effects are quantified through "fractionation factors", which will be rigorously defined below. Oncologists use fractionation factors to define strategies which most damage one type of tissue while least damaging the other. (see, for example, Fowler et al., 1992). Since cancers are growing tissues, time under treatment is also an consideration. Its importance has not always been recognized in the past, but is coming under increasing study: Cox, et al (1985) state that: "Differing fractionation schedules can be considered as a modality in the same sense as radiation energy or sensitizers or biological modifiers: they might increase the probability of tumor control, decrease effects on normal tissues, or combine optimally with other modalities."

The "linear-quadratic formula" (Fowler, 1989 and Thames et al., 1986) is commonly used to account for the influence of dose, fractionation and time, as well as other relevant variables, upon cancer recurrence and normal tissue damage. This equation, presented in its simplest form in Equation 4, is derived from simple probabilistic principles of cell survival under radiation. Under the assumption of constant tumor volume in humans, it is
commonly extended to clinical data.

There are two aspects of the following calculations. First, computations are made on the distribution of the number of cells surviving in a tumor after a particular treatment schedule. The probability of finishing the treatment with zero viable cells will give us the probability of local control. This calculation depends on certain parameters whose value it is desired to back-calculate from observed clinical results.

The clinical results are in the form of observed frequencies of patients remaining free of local recurrence over the period of followup, usually up to 2 - 5 years after treatment. As we might expect, clinical reality is usually less convenient than cellular-kinetic theory: we are rarely lucky enough to encounter in the former the homogeneity and certainty of outcome presumed by the latter. We describe three complications inherent in extending the linear-quadratic and related models to radiotherapeutic studies on humans:

1. The standard Poisson model derived below for probability of tumor control assumes that all tumors in the population have the same volume. This is clearly unrealistic. We must consider tumor volume to be sampled from a reasonably rich class of distributions with estimatable parameters. Since a tumor's volume (or, more strictly, the number of its actively dividing cells) is typically unmeasurable, we develop mixture models which are unconditional on volume.

2. In humans, freedom from recurrence is termed "local control". We can rarely observe local control with certainty, since at a given followup time there is usually the possibility of recurrence in the future. Therefore one must model the probability of local control by some finite time. This is always done in practice, of course, though the concession is rarely admitted. The linear-quadratic equation is adapted to finite followup times through the assumption of a Lehmann family on survival probabilities, conditional on the number of cells in the tumor. Marginal probabilities are then computed by summing over the possible tumor cell counts. Under the Lehmann assumption, however, the distribution of cell counts may be arbitrary.

3. Even if we choose to model control by some finite time $T$, say, we are also faced with the possibility of censoring before $T$. If $T$ is three years, there may be some
subjects who were lost to followup before T. This could be due simply to insufficient time on trial of these patients, who were accrued less than three years prior to the last followup. Or, patients could be lost to followup in some other manner unrelated to tumor recurrence. In the former case, we could simply exclude all subjects who don't have 3 year followup (regardless of control status). However, this would be wasteful. In the latter we must make some adjustment; we introduce a few such adjustments in this paper and investigate their consequences.

The cellular foundations of the linear-quadratic equation are given in §2. The equation's statistical evolution is then followed through the three adaptations by examining Equations 9, 18, and 21 in Sections 3, 4 and 5 respectively. Section 6 describes inference on the mixing parameter introduced in §3. Section 7 gives three examples - two derived from clinical trials conducted by the British Institute of Radiology, and the third of a small observational study.

We hope to demonstrate the usefulness of a carefully developed statistical framework in modeling the effects of radiation in cancer treatment. Also, through our examples, we try to show these models to be directly relevant to the radiation oncologist in treating his or her patients.

2. Cell dynamics

We start by modeling $E$, the proportion of cells surviving in a particular tumor after irradiation, later translating this proportion to recurrence probabilities. If a cell is hit in a strategic site (i.e., in its genetic coding) it has a positive probability of dying. Thus, a single dose of $d$ Grays radiation has an approximate surviving fraction of cells abbreviated $E$:

$$E = Pr[Pr(\text{cell survives single particle of radiation})\# \text{ of particles per cell in the dose}]$$

$$= [1 - Pr(\text{cell killed by single particle})]\# \text{ of particles per cell in the dose}$$
\[ = [1 - Pr(\text{cell hit by particle}) \times \text{lineup}] \times Pr(\text{cell\ killed|hit\ by\ particle}) \sup_{\text{roman}\{\#\ of\ particles\ per\ cell\ in\ the\ dose\}} \] 

so

\[-\log(E) = d \times (\text{conversion from Grays to particles/cell}) \tag{2}\]

\[\times \log[1 - Pr(\text{cell hit by particle}) \times Pr(\text{cell killed|hit by particle})] = d \times \alpha .\]

One Gray is a unit equivalent to one Joule per kilogram of radiation reaching a target; its correspondence to particle counts varies with the energy of the particles (here, by "particle", we use a convenient though arbitrary abbreviation for a quantum of energy, either through x-rays or neutrons).

Equation 2 is true for doses near zero. However, for higher doses the response is nonlinear because: 1), "fatally wounded" cells could be hit again, thus wasting that incident radiation; and 2), there is a synergistic effect whereupon cells hit twice have probability of survival less than the square of the single-hit probability (this effect depends upon the cellular repair rates, as described below). The synergy dominates so that the nonlinearity is positive. Additionally, there is some experience that a quadratic term usually adequately models this effect over the range of doses used to treat cancer patients (Fowler, 1989). See Figure 1.

Radiotherapy patients nearly always get more than one dose (to enable delivery of an exposure which, if instantaneous, would be dangerous to normal tissues). These doses are distributed among \( n \) sessions, also called fractions. We thus have

\[-\log(E) = n \times (\alpha d + \beta d^2) \tag{3}\]

\[= \alpha \times (nd) + \beta \times d \times (nd),\]

where \( d \) is dose in Grays per fraction and \( nd \) is total dose in Grays. This parametrization is relevant because \( \alpha \) shows the effect of a very small dose fraction. It also constitutes
the effect of many fractions of doses: increasing the number of doses \( n \) while holding the total dose \( nd \) constant diminishes the second term above and renders \( E \) nearly log-linear in \( nd \) - see Figure 2. Doses given in different sessions do not show synergy because hits which are nonfatal to the cells are repaired in an hour or two, while the minimum time between sessions is several hours. The ratio \( \alpha/\beta \), called the fractionation factor, is important: it defines the repair characteristics of a given type of tissue. A tissue having a large fractionation factor would exhibit instantaneous repair and a linear response to dose (\( \beta \) small). Late-reacting (usually noncancerous) tissues ought to have a value of about three - which reflects large amounts of repair at small doses per fraction (\( \beta \) large) - while early-reacting (typically cancerous) tissue values are nearer ten - meaning less repair in tumor tissues and smaller change of effect with fraction size. For fractionation factors of these relative magnitudes, a highly fractionated treatment is indicated.

Multi-fraction treatments usually take place over a few weeks; during this time, the tumor's cells have an opportunity to multiply. Assuming a constant growth rate, we must adjust \( E \) by a factor of

\[
2^{t/t_{\text{eff}}},
\]

where \( t \) is the number of days over which proliferation occurs while the radiation is administered and \( t_{\text{eff}} \) is the effective doubling time in days of the tumorigenic cells. This is only approximate, as surviving cells might change their proliferation rate during the course of treatment, although detailed evidence is lacking, and small tumors in general have discrete growth. We abbreviate

\[
\gamma = -\frac{\log(2)}{t_{\text{eff}}}
\]

and can now further model \( E \) as

\[
-\log(E) = \alpha \times (nd) + \beta \times d \times (nd) + \gamma \times t.
\]

We expect \( \alpha \) and \( \beta \) to be positive and \( \gamma \) negative; the reason for modeling the negative of \( \log(E) \) will be apparent in the next section.
3. Patient dynamics

We still must convert cell survival proportion $E$ into the probability of a patient's tumor being under local control, that is that it does not recur. This is done by presuming that control depends on no tumor cells surviving and that each tumor initially has $N$ cells. Since for most treatment regimens $E$ is quite small and for most tumors $N$ is large, the number of surviving cells in tumors conditional on their volume and treatment approximately follows a Poisson distribution with mean $N \times E$ (Thames et al., 1986). We can now compute the probability of local control, $P_c$, from the Poisson mass function:

$$P_c = Pr(\text{zero cells surviving}) = e^{-N \times E}$$  \hspace{1cm} (5)

and

$$-\log[-\log(P_c)] = -\log(N) + \alpha \times (nd) + \beta \times d(nd) + \gamma \times t.$$  \hspace{1cm} (6)

Of course, tumors in patients have a variety of volumes so that $N$ is not constant. The gamma distribution is convenient (for mathematical reasons, though in practice choice of mixing distribution doesn't seem to be important) for modeling such mixtures. Assume that

$$N \sim \text{Gamma}(\lambda, 1/r)$$

where $r$ is a mixing parameter with $r = 0$ representing no mixing - constant tumor volume - and large $r$ indicating high tumor volume variability; $\lambda$ is a scale parameter; and mean tumor volume equals $1/(\lambda r)$. Then, it can be shown that the number of surviving cells in tumors conditional on treatment (with tumor volume assigned a gamma mixing distribution) is a negative binomial with parameters $1/r$ and $\lambda/(E + \lambda)$ (for example, see Johnson and Kotz, 1969). The negative binomial mass function is

$$Pr(x \text{ cells surviving}) =$$  \hspace{1cm} (7)

$$\left[\frac{1/r + x - 1}{x}\right] \times \left(\frac{\lambda}{E + \lambda}\right)^{1/r} \times \left(\frac{E}{E + \lambda}\right)^x,$$

$$x = 0, 1, 2, \ldots.$$
The probability of local control is now

\[ P_c = Pr(\text{zero cells surviving}) \]

\[ = \left( \frac{\lambda}{E + \lambda} \right)^{1/r} \]

and

\[ \log \left( \frac{rP_c^r}{1 - P_c^r} \right) = \log(r\lambda) + \alpha \times (nd) + \beta \times d(nd) + \gamma \times t \]

\[ = -\log[\text{mean}(N)] + \alpha \times (nd) + \beta \times d(nd) + \gamma \times t. \]

As in the constant tumor volume case, the intercept term still represents volume, now through its mean. The function which linearizes \( P_c \), called the \textit{link function}, is here the scaled logit of a power transform of \( P_c \). This link is proposed for other purposes by Burr (1942) and Prentice (1975). See Czado and Santner (1992) for a method to improve numerical stability of estimation. The link family in Equation 9 encompasses a rich class of functions of \( P_c \) and is suitable for application here by encompassing both the common symmetric and asymmetric links: it becomes the log-log transformation used above as \( r \) approaches zero and is the logit transformation when \( r=1 \). Since the gamma distribution with \( r=1 \) is also known as the exponential distribution, logistic regression is associated with the assumption of an exponential distribution of tumor volume.

Although based on physical principles for modeling radioactive decay, the exponential distribution has no theoretical justification for describing tumor volume distributions. For all other values of \( r \) the link function of \( P_c \) is asymmetric and may be markedly so. There thus exists no mathematical or logical argument in this case for enforcing a symmetric link such as the logit.
4. Modeling recurrence fraction at finite times

The above calculations assume that we know the true state of each patient's recurrence. Since many tumors are slow growing with a recurrence detectable only after five or more years of followup, they may be mistakenly classified as a nonrecurrence when a followup is made at, say, three years after treatment. Thus, if recurrence times of those tumors which aren't successfully treated have the conditional survival function

\[ Pr(\text{recurrence after time } T \mid \text{ patient will recur}) \equiv F(T), \]  

(10)

the unconditional probability of local control up to a given time \( T = T_0 \) is

\[ Pr(\text{control up to time } T_0) = P_c + (1 - P_c) \times F(T_0). \]  

(11)

Note that \( F(\infty) = 0 \) and we have \( Pr(\text{permanent local control}) = P_c \) as above.

There are two approaches to adjusting for the possibility of recurrences after the last followup. The first approach, cure-rate modeling at \( T_0 = \infty \) (described by Gordon, 1990 and Bentzen et al., 1989) formally models the survival probability \( F(T_0) \) and the ultimate local control rate \( P_c \). Since the latter is the fraction locally controlled at \( T = \infty \), this type of model incurs an extreme and unsupportable extrapolation in this case. If a broad range of choices is allowed for \( F(T_0) \), there will be an irreducible confounding between \( F(T_0) \) and \( P_c \).

A second approach is to simply pronounce the models of Equations 6 and 9 as holding for local recurrence probabilities after a finite time and to apply them to \( Pr(\text{local control up to time } T_0) \), at a single predetermined \( T_0 \) such as three or five years, instead of to \( P_c \). The logit model has traditionally been invoked in this manner - see Lindstrom and Fowler (1991) and the analyses summarized therein, for example. All such models make the leap from permanent local control to control as of some finite \( T_0 \) without explanation. The consequences of this logical jump, and certain circumstances in which it can be justified, are elicited below.

In §4.1, we consider the case in which \( F(T_0) \) does not depend on the number of surviving cells in a tumor, given that at least one cell survives. In this situation, a rigid functional form is induced for \( F(T_0) \). We then allow, in §4.2, \( F(T_0) \) to vary with the number
of cells surviving treatment. This relaxation results in a form for $F(T_0)$ which, though still seemingly arbitrary, can be quite reasonable and robust. We give a surprisingly simple result, presented here for the first time to our knowledge, in which conditioning $F(T_0)$ on the number of tumor cells after treatment and then modeling the mixture of the conditional probabilities $\{F(T_0 \mid \# \text{ of tumor cells})\}$ using Equation 9 induces only a minimal assumption on the conditional functional form. This result gives a reasonable justification, previously lacking, for applying the linear-quadratic model at convenient finite instead of longer followup times.

4.1. Modeling at finite $T_0 - F(T_0)$ independent of the number of surviving cells in a tumor

The most primitive assumption on tumor recurrence, as also used in cure-rate modeling, is to consider all tumors with at least one surviving cell to have the same recurrence probability $F(T_0)$. Unlike the mixture model in the next section, this leads to stringent restrictions on $F(T_0)$. For example, setting $r = 1$ in Equation 9 and applying it to $Pr(\text{local control up to time } T_0)$, denoting the linear terms as

$$L \equiv -\log[\text{mean}(N)] + \alpha \times (nd) + \beta \times d(nd) + \gamma \times t,$$

yields

$$\logit[Pr(\text{local control up to time } T_0)] = L + \log \left[ \frac{1 + F(T_0) \times L}{1 - F(T_0)} \right]. \quad (12)$$

This does not correspond to a linear model unless

$$F(T_0) = \frac{f(T_0) - 1}{f(T_0) + e^L}, \quad (13)$$

where $f(.)$ is an decreasing function such that $f(0) = \infty$ and $f(\infty) = 1$. The inverse exponential $f(T_0) = e^{1/T}$ is a convenient function which qualifies. If we use it with $r$ still equal to 1, then

$$\logit[Pr(\text{local control up to time } T_0)] = L + 1/T_0 \quad \text{(14)}$$
\[ = 1/T_0 + \log[\text{mean}(N)] + \alpha \times (nd) + \beta \times d(nd) + \gamma \times t \]

(here, $1/T_0$ is a known constant referred to as an offset in nonlinear modeling references).

4.2. Modeling at finite $T_0$ - $F(T_0)$ a simple function of the number of surviving cells in a tumor

$F(T_0)$ naturally depends on the number of tumor cells surviving the initial radiotherapy; if zero cells survive, for example, $F(T_0; 0) = 1$ [abbreviating $F(T_0; x$ tumor cells surviving) as $F(T_0; x)$]. The case where $F(T_0; x)$ is constant for positive $x$ was treated in §4.1. Consider here the family on $F(T_0; x)$

\[ F(T_0; x) = \left[ F(T_0; 1) \right]^x. \]  

This is known as the Lehmann family (Lehmann, 1953) at the e point $T = T_0$ with baseline recurrence probability $F(T_0; 1)$; it has been used in other circumstances to produce the proportional hazards model. Note that this formulation allows the baseline probability to be completely arbitrary: it merely requires probability of local control at the single time point $T_0$ to decrease with the number of cells in the tumor at the end of treatment, and to do so as a exponential function of the number of cells. The advantage of assigning the Lehmann family to probabilities of recurrence at $T_0$ given the number of tumor cells is that the unconditional probability will be shown to retain the linearity of Equation 9.

To compute the unconditional probability of local control at $T_0$ (recurrence after time $T_0$ or never), we must sum over conditional probabilities. Here however, there will be an infinite sum with each term corresponding to the number of cells surviving treatment:

\[ Pr(\text{local control up to time } T_0) \]

\[ = Pr(0 \text{ surviving cells}) \]

\[ + Pr(1 \text{ surviving cell}) \times F(T_0; 1) \]

\[ + Pr(2 \text{ surviving cells}) \times \left[ F(T_0; 1) \right]^2 \]
\[ + \cdots + Pr(i \text{ surviving cells}) \times \left[ F(T_0; 1) \right]^i + \cdots \]

and under the assumptions of negative binomial distribution for number of tumor cells and Lehmann family for recurrence probabilities at \( T_0 \) conditional on the number of tumor cells (Equations 7 and 15, respectively),

\[
Pr(\text{local control up to time } T_0) = \left[ \frac{\lambda}{E + \lambda} \right]^{1/r} \\
+ \left[ \frac{1/r}{1} \right] \times \left[ \frac{\lambda}{E + \lambda} \right]^{1/r} \times \frac{E}{E + \lambda} \times F(T_0; 1) \\
+ \left[ \frac{1/r + 1}{2} \right] \times \left[ \frac{\lambda}{E + \lambda} \right]^{1/r} \times \left[ \frac{E}{E + \lambda} \right]^2 \times \left[ F(T_0; 1) \right]^2 \\
+ \cdots + \left[ \frac{1/r + i - 1}{i} \right] \times \left[ \frac{\lambda}{E + \lambda} \right]^{1/r} \times \left[ \frac{E}{E + \lambda} \right] \times \left[ F(T_0; 1) \right]^i + \cdots \\
= \sum_{i=1}^{\infty} \left[ \frac{1/r + i - 1}{i} \right] \times \left[ \frac{\lambda}{E + \lambda} \right]^{1/r} \times \left[ \frac{E}{E + \lambda} \right] \times \left[ F(T_0; 1) \right]^i \\
= \left[ \frac{\lambda}{E + \lambda} \right]^{1/r} \times \left[ 1 - F(T_0; 1) \times E/(E + \lambda) \right]^{-1/r} \times \\
\sum_{i=0}^{\infty} \left[ \frac{1/r + i - 1}{i} \right] \times \left[ 1 - F(T_0; 1) \times E/(E + \lambda) \right]^{1/r} \times \left[ F(T_0; 1) \times E/(E + \lambda) \right]^i \\
= \left[ \frac{\lambda}{E + \lambda} \right]^{1/r} \times \left[ 1 - F(T_0; 1) \times E/(E + \lambda) \right]^{-1/r}.
\]

The summation in the penultimate line is unity because its terms correspond to a negative binomial mass function. Canceling out terms, we find

\[
Pr(\text{local control up to time } T_0) = \left[ \frac{\lambda}{E + \lambda - E \times F(T_0; 1)} \right]^{1/r}.
\]  \hspace{1cm} (17)

We can thus model local control up to time \( T_0 \) exactly as we did permanent local control in Equation 9:

\[
\log \left[ \frac{r \times Pr(\text{control up to time } T_0)^r}{1 - Pr(\text{control up to time } T_0)^r} \right] 
\]  \hspace{1cm} (18)
\[ = -\log[\text{mean}(N)] - \log[1 - F(T; 1)] + \alpha \times (nd) + \beta \times d(nd) + \gamma \times t. \]

With a minimum of assumptions, we again have a model which is linear in \( nd \), \( d(nd) \), and \( t \). Note that no assumptions are made on the form of \( F(T; i) \) for general \( T \); only on \( F(T_0; i) \) for a single fixed \( T_0 \) (typically 3, 5 or 10 years). Also, only the Lehmann restriction at \( T_0 \) is used - \( F(T_0; 1) \) may be arbitrary. The only alteration to Equation 9 is that the constant coefficient now has two parts: the first corresponding to minus log mean tumor volume and the second adjusting for incomplete observation of recurrences by time \( T_0 \). The linear-quadratic model for finite times has been shown to have a theoretical basis.

4.3. Justification for assumptions in §4.2

The Lehmann family is quite a broad one, permitting arbitrary baseline recurrence probability \( F(T_0; 0) \), and so allows linear-quadratic modeling at finite times as derived in §4.2 to be a fairly robust procedure. In addition, note that even if Equation 9 does not hold, Equation 12 shows that the linear relation is approximately preserved for \( T_0 \) such that \( F(T_0) \) is small (i.e., \( T_0 \) large enough that a recurrence after \( T_0 \) is unlikely).

Later "recurrences" in many tumors, of the oropharynx for instance, may not be true recurrences but reseedings from nearby lymph nodes to which the cancer had metastasized. Such cases should not be considered events for the purposes of fitting the linear-quadratic equation, but they are very difficult to identify and exclude.

These considerations apparently lead Thames et al. (1986) and many others to use logistic regression for local control at some constant \( T_0 \), the time of last followup. Section 4 has provided an \textit{ex post facto} justification.
5. Censored Observations - the linear-quadratic formula at multiple times

We have assumed so far that local control status is known for all subjects, at least up to a fixed followup time $T = T_0$. In clinical studies, however, this is usually not the case - some patients may be lost to followup before $T_0$. Furthermore, in both clinical and laboratory settings subjects may die without disease before $T_0$. These occurrences are said to censor the event of interest, local control at $T_0$. However, the studies may be salvaged via one of two approaches:

1. Showing that the effect of losses to followup upon parameter estimates is trivial. This typically involves imputing all the censored observations "both ways" - that is, as under local control and otherwise - and comparing the resultant estimates. If the estimates achieved under the two extremes are similar, we can presume that the bias due to censoring will be small. The strategy involves no extra assumptions and is quite general, though strictly applicable only to studies with very small censoring proportions.

2. Parametrically modeling the behavior of recurrence times for $T \leq T_0$. Suppose that the $i$th observation is censored at time $T_i < T_0$ in a condition of apparent local control. One cannot assume control would still hold at $T_0$; however observation $i$ contributes some time at risk from $T = 0$ to $T = T_i$, so neither can one ignore observation $i$ entirely. By modeling the behavior of recurrence times we assign a weight to the time at risk $T_i$. For example, under exponentially distributed recurrence times a patient censored at $T_i$ would contribute $T_i/T_0$ the time at risk as one under local control at $T_0$. Other distributions assign more complicated (though often more appropriate) weights.

Besides the assumption of a distribution, recurrence time modeling usually assumes noninformative censoring (see Kalbfleisch and Prentice, 1980). That is, the distribution of censoring times is independent of that for recurrence. This would be violated, for example, if patients become weak and more subject to other ailments just before a recurrence were detectable. There are ways in which this assumption can be examined using outside information - see the BIR local control example, in which the number of
losses to followup due to deaths unrelated to cancer is compared to the expected number computed from national vital statistics tables.

The first approach is convenient if possible, such as in BIR local control at three years. However, it has the following disadvantages:

A. It provides information only on \( P_c(T_0) \); we may be interested in \( P_c(T) \) for another time point(s). Parametric modeling can fit the entire recurrence curve - this property, of course, may be desirable even in the absence of censoring.

B. The first approach does not accommodate large-scale censoring.

C. It ignores information on the timing of recurrence events, except for whether or not they occur before \( T_0 \). It therefore requires larger data sets than does the second approach to achieve the same precision (under the admitted benefit of fewer assumptions).

Point A. is of apparent clinical importance as illustrated by the number of reports which give rates at, e.g., three five and ten years. Point B. is crucial for analyzing long-term events such as normal tissue damage, for which most of the subjects may be censored merely due to insufficient time on study. Finally, even local control trials may require recurrence time modeling when, as noted in C., they are in their initial stages and have low enrollment and short followup times on their more recent recruits; this will be illustrated using the data of Ozyar.

We now develop a parametric approach tailored to the requirements of modeling local control. Certainly Equation 18 should still apply; in addition we require a model, consistent with it, for times \( T \leq T_0 \). The easiest modification - and, as we shall see, a practical one - is to add another linear term representing the decreasing probability of local control over this time range. Call this term \( g(T) \). Then \( g(T_0) = 0 \) for consistency with Equation 18, \( \lim_{{T \to 0^+}} g(T) = \infty \) reflecting a large probability of early control, and since probability of local control decreases with time \( g(\cdot) \) should be monotonic. It would also be convenient to incorporate an estimatable parameter, say \( \kappa \), to model the rate of decrease of local control probability with time. In agreement with these requirements, we can choose
\[ g(T) = -\kappa \times \log(T/T_0). \]  

(19)

With this \( g(T) \) added to the linear terms, the probability in Equation 8 is modified to be a function of time (a survival function):

\[
Pr(\text{local control up to time } T) = \left[ \frac{\lambda}{\lambda + (T/T_0)^{\kappa} \times E \times [1 - F(T_0; 1)]} \right]^{1/r},
\]

(20)

\[ T \leq T_0, \]

and monotonic non-increasing but otherwise arbitrary for \( T > T_0 \). Equation 20 is the survival function for the family of distributions called compound Weibull by Dubey (1973) and is a special case of Prentice’s log-F model (1975). The compound Weibull incorporates several commonly used survival distributions: when \( r = 1 \) it is the log-logistic distribution with index \( \kappa \); as \( r \rightarrow 0 \) it becomes Weibull with index \( \kappa \); if \( r \rightarrow 0 \) and \( \kappa = 1 \) is approaches the exponential distribution. Finally, since \( E \) is log-linear in dose per fraction, total dose and time on treatment, these covariates have multiplicative effects on recurrence time. This implies that the standard accelerated life parametrization holds. See Chappell (1991) for another application of the compound Weibull distribution.

Note that all the considerations for modeling at finite times in §4.2 still apply here. We only need the Lehmann family assumption to apply for all \( T \leq T_0 \). This requirement is still quite general, also allows the baseline survival function \( F(T; 1) \) to be arbitrary, and makes no stipulations at all for \( T > T_0 \).

A pleasant consequence of this adjustment for censoring is that, because it is linear on the link scale, any software that estimates coefficients for the uncensored binary model of control at \( T_0 \) can also be used to compute the adjusted estimates.

In sum, we have created a model which allows recurrence times censored before \( T_0 \) by extending the applicability of Equation 18 to times less than \( T_0 \). The linear-quadratic model is now expressed in its utmost generality - after accommodating variability in the tumor volume distribution, measuring control at a finite time, and the possibility of loss to followup before that time - as
\[
\log \left[ \frac{r \times Pr(\text{control up to time } T_0)^r}{1 - Pr(\text{control up to time } T_0)^r} \right] \\
= -\log[\text{mean}(N)] - \log[1 - F(T; 1)] - \kappa \log(T/T_0) \\
+ \alpha \times (nd) + \beta \times d(nd) + \gamma \times t .
\]

6. Inference concerning the mixing parameter \( r \)

6.1. Link tests for \( r \)

As noted above, there is no \textit{a priori} justification for assuming exponential tumor volume inducing the logit link, \( r = 1 \), or indeed any other value of \( r \). One method of inference on \( r \) is through the use of link tests (introduced by Pregibon, 1980 and extensively described by Atkinson, 1985), which can be easily applied here. A link test in this case is performed by creating, for some hypothesized value of the mixing parameter \( r_0 > 0 \), the following constructed variable:

\[
w(r_0) = -\frac{\partial}{\partial r} \log \left[ \frac{r \hat{P}_c^r}{1 - \hat{P}_c^r} \right]_{r=r_0}
\]

\[
= -\frac{\log(\hat{P}_c)}{1 - \hat{P}_c^{r_0}} ,
\]

dropping a constant, where \( \hat{P}_c \) is estimated from the model of Equation 18. The constructed variable is then included in the linear model

\[
\log \left[ \frac{1 - P_c^{r_0}}{r_0 P_c^{r_0}} \right] = -\log[\text{mean}(N)] + \alpha \times (nd) + \beta \times d(nd)
\]

\[
+ \gamma \times t + \delta \times w(r_0)
\]
and \( \hat{\delta} \) is obtained. The crux of the link test lies in the fact that a score test of the hypothesis

\[
H_0 : \quad \delta = 0
\]

is equivalent to a score test of the hypothesis

\[
H_0 : \quad r = r_0
\]

and that \( \hat{\delta} \) provides a rough estimate of \( r - r_0 \) so that, approximately,

\[
\hat{r} = \hat{\delta} + r_0 .
\] (24)

Of course a more precise (and much more computationally laborious) estimate of \( r \) can be obtained by maximizing the likelihood. In addition, the link function may be generalized by considering it a function of two or more parameters. For more results on these cases, see Czado and Chappell (1992). Newton, Czado and Chappell (1992) examine nonparametric link function estimation with an example using the linear-quadratic function.

6.2. Effect of \( r \) misspecification on parameter estimates

A model using a link with, say, \( r = .7 \) is inconvenient both to fit and to interpret. The preference may be for one of the more traditional links using \( r = 0 \) (log-log) or 1 (logit). How can we determine the effect of this type of simplification on our parameter estimates without taking the trouble to jointly estimate \( r \) (requiring us to abandon standard software)? One approximate method is now demonstrated for when we use the logit link, \( r = 1 \). Similar computations are possible for the \(-\log\log\) link, \( r = 0 \).

Suppose the true value of \( r \) is \( r_0 \). Suppose also that the linear terms in the true model are denoted \( L(r_0) \). However, we choose to use the logit link for simplicity. Then, by inverting the true link and substituting into the logit function we have

\[
\log \left[ \frac{P_c}{1 - P_c} \right] = -\log \left[ (r_0 \times e^{-L(r_0)} + 1)^{1/r_0} - 1 \right] .
\] (25)

This expression is linear in \( L(r_0) \) when \( r_0 = 1 \), of course, but not otherwise. For
moderate $L(r_0)$ and $r_0$ near one, we may use the bivariate Taylor expansion to give an approximate linearization:

$$\log \left[ \frac{P_c}{1 - P_c} \right] \sim L(r_0) + (r_0 - 1) \times [1 - 2\log(2)].$$

This shows that assuming $r$ unity is not too great a misspecification, our estimates of $\alpha$, $\beta$ and $\gamma$ are about right; only the constant is biased by $(r - 1) \times [1 - 2\log(2)]$. For another perspective on the effects of incorrectly specified link functions upon estimates of event probabilities and model coefficients see Czado (1989).

There are other reasons why the constant term should not be taken seriously as an estimate of $-\log[\text{mean}(N)]$. Besides that induced by misspecifying $r$, there is a bias due to applying the model at finite times, discussed in the last section. In addition, there is evidence of a lag in regrowth in both normal (Thames, 1992) and cancerous (Kummermehr, 1992) tissues. If, for some baseline $t_0$, we should be using $t - t_0$ in Equations 18 or 21 then our estimate of $\log[\text{mean}(N)]$ will be biased by $\gamma \times t_0$ but the estimated $\gamma$ will be unbiased. Joiner et al. (1992) also give evidence of a lag in dose effect. In summary, the constant is not a reasonable estimate of mean tumor volume but the other coefficients in the linear-quadratic model may have valid estimates from clinical data.

7. Examples

7.1. The BIR fractionation studies - local control of laryngeal carcinoma

7.1.1. Description

The British Institute of Radiology (BIR) conducted two large-scale randomized clinical trials to assess the effectiveness of different treatment schedules in radiotherapy of the larynx and pharynx. The first trial (Rezvani et al., 1989 and 1990), begun in 1966, compared treatment frequencies of three fractions per week vs. five fractions per week. The former group had an average dose 12% lower than the latter's (this difference was
intentional because of the known greater biological effectiveness with fewer - and thus larger - doses per session). The second trial (BIR Working Party, 1989 and Wiernik et al., 1991) began accrual in 1986 and randomized patients into short (at most 4 weeks) vs. long (over 4 weeks) overall treatment times. Here also the shorter radiation regimens had a reduction in average dose, in this case about 20%. Neither study showed any statistically significant difference in local control between the two arms, but the second trial showed significantly fewer complications in normal tissue.

Each BIR study in effect addressed the reasonableness of a tradeoff between the factors in the linear-quadratic formula: in one case, total dose \( nd \) vs. dose per fraction \( d \); in the other, \( nd \) vs. treatment time \( t \). As an alternative to examining the tradeoff by utilizing the randomization in treatment regimen, we may consider the BIR trials to be observational studies providing information on dose, fractionation and time factors. This especially holds because there was, within each regimen, large variability in scheduling and dosing between clinical centers. For example, the second BIR study had subjects with 3 and others with 5 fractions per week in both the short and long groups. We can make use of this variability to perform inference about the coefficients in the linear-quadratic formula. Followup was attempted for at least three years on all participants, with 124 either lost to followup or dead of other causes before that time. Chappell, Nondahl and Fowler (1992) give a more complete analysis of these data.

In the results given below, we use the combined data from 858 subjects with laryngeal squamous cell carcinomas and no nodal involvement in both BIR trials. A logit model is fitted and some interpretations are given. Then the mixing parameter \( r \) is examined, giving evidence about the adequacy of the logit link.

### 7.1.2. The logit model

We first fit a logistic regression for three year local control of laryngeal carcinoma on the combined data. There was control in 590 out of 858 cases. Table 1 shows the coefficients for the logit model, estimated by the method of maximum likelihood. In addition to \( \alpha \), \( \beta \) and \( \gamma \), linear terms were estimated for the effects of status in the TNM
staging system, reflecting extent of the tumor’s invasion. Below, estimates are given for the decreased chance of local control in stage II and III tumors with respect to stage I tumors. The model is now

\[
\log \left( \frac{1 - P^c_c}{rP^r_c} \right) = \log[\text{mean}(N)] + \alpha \times (nd) + \beta \times d(nd) + \gamma \times t + \text{stage effect} \tag{27}
\]

The "percentage scale" column shows the approximate effects on the $\%100 \times$ probability scale of each covariate (see Chappell, 1992). These are obtained by linearizing the logistic equation, and are presented for their ease in interpretation. For example, increasing total dose by one Gray increases the estimated logit local control probability by .0591 and hence increases the raw control percentage by approximately 1.3%.

**Table 1: the estimated logistic linear-quadratic equation for BIR data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated Coefficient</th>
<th>Standard Error</th>
<th>p-Value</th>
<th>Percentage Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-.937</td>
<td>.979</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$nd$</td>
<td>$\alpha = .0591/Gy$</td>
<td>.0186</td>
<td>.002</td>
<td>1.3%/Gy</td>
</tr>
<tr>
<td>$d(nd)$</td>
<td>$\beta = .00221/Gy^2$</td>
<td>.00285</td>
<td>.4</td>
<td>.049%/Gy$^2$</td>
</tr>
<tr>
<td>$T$</td>
<td>$\gamma = -.0419/day$</td>
<td>.0124</td>
<td>.0007</td>
<td>-.92%/day</td>
</tr>
<tr>
<td>Stage</td>
<td>$I_{\text{level } 1} = 0$</td>
<td>.188</td>
<td>.0001</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>$I_{\text{level } 2} = -.711$</td>
<td>.187</td>
<td>.0001</td>
<td>-15.6%</td>
</tr>
<tr>
<td></td>
<td>$I_{\text{level } 3} = -1.044$</td>
<td>.187</td>
<td>.0001</td>
<td>-23.0%</td>
</tr>
</tbody>
</table>

We see from Table 1 that, of course, higher doses decrease recurrence rates. Also expectedly, but more controversially, longer treatment times increase recurrence: one extra day of treatment subtracts nearly 1% from the estimated control rate. The $\beta$
We also give the estimated covariances in Table 2 in order to allow inference on predicted values for arbitrary combinations of covariates.

**Table 2: covariances of estimated coefficients in Table 1, × 100**

<table>
<thead>
<tr>
<th></th>
<th>$-\log[\text{mean}(N)]$</th>
<th>$\hat{\alpha}$</th>
<th>$\hat{\beta}$</th>
<th>$\hat{\gamma}$</th>
<th>$\hat{I}_{\text{level 2}}$</th>
<th>$\hat{I}_{\text{level 3}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-\log[\text{mean}(N)]$</td>
<td>95.793</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\hat{\alpha}$</td>
<td>-1.74</td>
<td>3.5220</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\hat{\beta}$</td>
<td>0.6075</td>
<td>1.2618</td>
<td>3.4867</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\hat{\gamma}$</td>
<td>-1.436</td>
<td>-0.01305</td>
<td>-0.06823</td>
<td>0.034722</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\hat{I}_{\text{level 2}}$</td>
<td>-0.1795</td>
<td>0.0056674</td>
<td>0.0032197</td>
<td>0.0008056</td>
<td>0.0008130</td>
<td></td>
</tr>
<tr>
<td>$\hat{I}_{\text{level 3}}$</td>
<td>0.34347</td>
<td>0.010177</td>
<td>0.039962</td>
<td>-0.01663</td>
<td>0.0001891</td>
<td>0.015306</td>
</tr>
</tbody>
</table>

estimate of fractionation is expected to be positive (conditional on nd and T, cumulative effects predict higher control for larger fraction sizes) and it is, but there is no evidence for $\hat{\beta}$ differing from zero. Higher stage subjects, as usual, are at considerably higher risk in the BIR studies as shown by the last two rows of Table 1.

In addition to contributing to scientific theory, the model of Equation 18 addresses direct and interesting clinical questions. For example, some patients in the second BIR study got 50 Gy in 16 fractions over 3 weeks and others 63 Gy in 31 fractions over 6 weeks. If both such patients had stage I tumors, we can substitute ($nd = 50 \text{ Gy}$, $d(nd) = 156.3 \text{ Gy}^2$, $T = 21 \text{ days}$) and ($nd = 63 \text{ Gy}$, $d(nd) = 128.0 \text{ Gy}^2$, $T = 42 \text{ days}$), to yield the estimated local control percentages 82% and 79% respectively with an odds ratio of 1.19. However, the 95% confidence interval for the odds ratio is (0.83, 1.71), so that the evidence cannot discriminate between the two regimens.

As these calculations show, radiation oncologists traditionally trade off dose and treatment time in order to get a therapy with maximum tumor effect without excessive harm to other tissues. This tradeoff can be made explicit: in the absence of synergistic effects (such as a highly fractionated study in which $d(nd)$ is small) we may equate

$$\hat{\gamma} + \hat{\alpha} = 0.$$
Here,

\[-0.0419 \text{ days} + 0.0591 \text{ Gy} = 0\, ,\]

and we get the conversion factor

\[1.41 \text{ Gy/day} \, .\]

Thus increasing treatment time by 1 day and dose by 1.41 Gy is predicted to be a therapeutically neutral strategy, with respect to local control. More practically, we can perhaps shorten overall times by subtracting 1.41 Gy/day and obtain briefer, and so more economonical, treatments - provided that no disadvantages arise. This factor has a 95% confidence region of (.78 \text{ Gy/day}, 2.38 \text{ Gy/day}) by Fieller's method (1954). For regimens and tissues for which the repair factor \( \beta \) effect is large, we must calculate the ratio conditionally on the fractionation covariate \( d(nd) \). The tradeoff between dose and treatment time is illustrated in Figure 3, which shows local control probabilities for a range of these characteristics' values. The probabilities are conditional on the disease being stage I and number of fractions equal to 19, the median for this variable in the BIR studies.

Lastly, we can examine the fractionation factor \( \alpha/\beta \). Its estimate here is \( 0.0591 \text{ Gy}/0.0022 = 26.7 \text{ Gy}^{-1} \). This is large, consistent with tissues such as tumors with a low simultaneous repair capability. However, this estimate is extremely uncertain due to the proximity of its denominator to zero: the 95% confidence region is the union of the two intervals \((-\infty, -13.6) \) and \((6.0, \infty) \). The major evidence here is that the fractionation factor is not small. There has been radiobiological debate about whether the ratio \( \alpha/\beta \) for tumors is about 10 Gy or much higher, such as 20-30 Gy or above. These results are consistent with both opinions.

### 7.1.3. Diagnostics for the logit link

Section 4 shows how we can use a score test to diagnose the adequacy of our mixing distribution and thus link function. In this analysis we used the logit link, \( r=1 \), so the constructed variable \( w(1) \) of Equation 22 was calculated. We then fit the model of Equation 23 and performed a score test on \( w(1) \). The test indicated the logit link may be unsatisfactory, with a two-sided p-value of .044. Furthermore, the estimate \( \hat{\delta} = -9.7 \) suggests
that, from Equation 24, \( r \) should be smaller than 1 and illustrates the need of an asymmetric link in our model. The induced estimate \( \hat{r} = r_0 + \hat{\delta} = -8.7 \) is clearly impossible; the approximation incurred in using the score statistic in here inadequate due to the asymmetry of the log-likelihood for small \( r \). Czado and Chappell (1992) more fully investigate estimating the link for these data.

### 7.1.4. Analysis issues

There are several analysis issues, involving missing values and other concerns, which were addressed but are not explained here. These include the following.

#### 7.1.4.1. Censoring due to loss to followup

Twenty-eight out 858 subjects were lost to followup prior to 3 years. There was no evidence available as to the reason for loss, only that they were alive and without disease at the last visit. The safest course in this case was taken by considering both extremes, that all recurred and that none recurred. This was done, without a qualitative change in the coefficient estimates. As a result, these subjects were dropped from analysis, a middle strategy (details appear in Chappell, Nondahl and Fowler, 1992).

#### 7.1.4.2. Censoring due to early death

Ninety-six patients were also "censored" before three years by dying without disease. There are various explanations, such as death due to undetected head and neck cancer or death from unrelated causes. The first cause was examined and rejected for the majority of decedents by computing the expected number of deaths, standardized by age and sex, in the English and Welsh population from which the BIR study group was drawn (Great Britain Office of Population Censuses and Surveys, 1982). The standardized number of deaths is 82 as compared to 97 observed. This is only marginally less than the observed early mortality among BIR subjects - especially considering their higher rate of tobacco and alcohol use, a strong correlate of laryngeal cancer for which the English
population figures are unadjusted. Our conclusion is that the majority of the early deaths were not due specifically to cancer and to treat them as nonrecurrences. This of course is an approximation, because we are not accounting for the time at risk lost between death and 3 years. Therefore, early deaths were treated both ways, as above, and again there were no major differences in the estimates.

7.1.4.3. Potential selection bias in assigning treatment

Selection effects are always a potential source of bias in observational studies. Although regimens are often assigned according to the oncologist’s opinions and training there is a possibility of treatment varying with a patient’s condition (though this was discouraged in the BIR studies and analyses were performed using planned rather than actual values of dose, dose per fraction, and treatment time) thereby non-causally affecting outcome.

We can make partial use of the randomization to address this issue. The second trial was randomized with respect to total treatment time, so that we would expect $\hat{\gamma}$ to be less subject to selection bias (it could not completely avoid potential bias because treatment time was randomized only with respect to exceeding 4 weeks). Likewise, number of fractions was randomized in the first trial so that, if dose were also assigned without much selection according to patient, $\hat{\beta}$ would also be nearly unbiased. These speculations were examined by stratifying the analysis presented in Table 1 by trial. The two sets of estimated coefficients and fractionation factors showed no systematic variation; and a likelihood ratio test of homogeneity between the two trials gave a p-value of .86 computed from the asymptotic $X^2$ distribution with 6 degrees of freedom.

7.1.4.4. Interactions with tumor stage

We examined various interactions, notably those involving tumor stage. It is reasonable to consider different stages of laryngeal cancer to be different diseases for the purposes of our model. For the BIR data, there was a small increasing trend observed in $\hat{\alpha}$ with stage. The interaction effects as a whole were not significant (p = .25), and so
weren't included in the model.

7.1.4.5. Lower order term as model diagnostics

The simultaneous repair rate variable $d(nd)$ is a product, and its coefficient $\beta$ can be considered an interaction term. One lower term, of $nd$, is part of the linear-quadratic equation but the other, for dose per fraction $d$, is not. As derived in §2 the latter term is unnecessary, though it should be included as a convenient model diagnostic. This was done for the BIR data, for which the estimate was very near zero.

7.1.4.6. Outlier treatment centers

The BIR studies were multicenter trials; each center had its own method of computing and recording dosage. The center coded "19" (clinic identities are confidential) had a different dosing standard, rendering it a possible outlier. However, its deletion fortunately had no influence on the estimates.

7.2. The second BIR fractionation study - normal tissue damage among laryngeal carcinoma patients

We return to the second BIR study to illustrate an instance in which Equation 21 is used. Here, the need is not due to small sample size, as in the next example, but to large scale censoring. An additional analysis is done to examine side effects of the radiotherapy upon healthy tissues of 479 node-negative patients treated for laryngeal carcinoma in the second BIR study (side effects were not recorded in the first BIR study). Evidence of normal tissue damage may not appear until five years after treatment. Symptoms include telangiectasia of skin or mucus membranes, dyspigmentation of skin, edema, and severe pain. Since similar processes underlie normal tissue damage and tumoricidal effects of radiotherapy, and the effects of radiotherapeutic factors upon both tissue types are considered before administration, the linear-quadratic model is often applied to each.
Because of their delay in appearance, a considerable number of potential side effects were unobserved in patients who died or were lost to followup - almost one fourth were censored before five years. Note that any analysis which adjusts for censoring must presume that it is noninformative - this assumption could be reasonable, in that cancer recurrence and mortality is a separate disease process from normal tissue morbidity, but it is an unverifiable assumption nonetheless. The censoring is of course worse after 5 years, which is why \( T_0 \) was set at that value. Kaplan-Meier estimates of the probability of freedom from normal tissue damage is given in Figure 4 a).

We use the logit link \( (r = 1) \) as above and consider \( T_0 = 5 \) years. This link, implying the assumption of the log-logistic distribution, is examined in Figure 4 b) in which the logits of the estimated effect-free probabilities are plotted against time. As noted by Nelson (1982), this plot should be approximately linear for data which are generated from the log-logistic distribution. Figure 4 b) shows that the distributional assumption is not violated seriously before 5 years. The linear-quadratic estimates are given in Table 3, with covariances in Table 4.

Like the tumors in the first example, normal cells also appear to show more damage with higher dose shorter treatment times. In contrast to the first example, \( \hat{\beta} \) is negative. A \( p \)-value of .03 gives only moderate evidence to the hypothesis that \( \beta \) is negative here; we can only conclude that comparing \( \hat{\beta} \) for the normal tissues against \( \hat{\beta} \) of tumors in the BIR studies indicates that higher fractionation favors the latter. Also as opposed to cancerous cells, stage apparently exhibits little influence on normal tissue*p propensity to damage. This is logical because characteristics of normal tissue are independent of and predate tumor stage.

We compute the "time-dose tradeoff" here as \( .0954/.116 = .82 \text{ Gy/day} \), with a confidence region \((.32, 2.25)\). When compared with the 1.41 Gy/day figure for local control, the point estimate indicates that a short treatment-time / high dose regimen maximizes damage to tumors with respect to normal tissues. However, The confidence intervals in the two tissue types almost completely overlap.
Table 3: the estimated linear-quadratic equation for probability of normal-tissue effect by 5 years in the second BIR study assuming log-logistic recurrence times \( (r = 1) \).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated Coefficient</th>
<th>Standard Error</th>
<th>p-Value</th>
<th>Percentage Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>3.690</td>
<td>1.250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-\log(T/S))</td>
<td>(\kappa = 1.045)</td>
<td>.057</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(nd)</td>
<td>(\alpha = .116/Gy)</td>
<td>.029</td>
<td>&lt; .0001</td>
<td>3%/Gy</td>
</tr>
<tr>
<td>(d(nd))</td>
<td>(\beta = -.00808/Gy^2)</td>
<td>.00375</td>
<td>.03</td>
<td>-.2%/Gy^2</td>
</tr>
<tr>
<td>(T)</td>
<td>(\gamma = -.0954/day)</td>
<td>.0212</td>
<td>&lt; .0001</td>
<td>-2%/day</td>
</tr>
<tr>
<td>Stage</td>
<td>(\hat{I}_{level_1} \equiv 0)</td>
<td>.234</td>
<td>.25</td>
<td>-7%</td>
</tr>
<tr>
<td></td>
<td>(\hat{I}_{level_2} = -.269)</td>
<td>.261</td>
<td>.63</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>(\hat{I}_{level_3} = .125)</td>
<td>.261</td>
<td>.63</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: covariances of estimated coefficients in Table 4, \( \times 100 \)

<table>
<thead>
<tr>
<th></th>
<th>constant</th>
<th>(\hat{\kappa})</th>
<th>(\hat{\alpha})</th>
<th>(\hat{\beta})</th>
<th>(\hat{\gamma})</th>
<th>(\hat{I}_{level_2})</th>
<th>(\hat{I}_{level_3})</th>
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<tr>
<td>constant</td>
<td>156.266</td>
<td>1.1933003</td>
<td>0.322204</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>(\hat{\kappa})</td>
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<tr>
<td>(\hat{\alpha})</td>
<td>-2.62069</td>
<td>-0.0029564</td>
<td>0.0008671</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\hat{\beta})</td>
<td>-0.287127</td>
<td>-0.0356548</td>
<td>-0.0537438</td>
<td>-0.0000106</td>
<td>0.0450749</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\hat{\gamma})</td>
<td></td>
<td>-0.0982967</td>
<td>-0.0122706</td>
<td>0.0058036</td>
<td>0.0206028</td>
<td>5.49443</td>
<td></td>
</tr>
<tr>
<td>(\hat{I}_{level_2})</td>
<td>-3.29299</td>
<td>-0.123983</td>
<td>-0.167757</td>
<td>0.0029528</td>
<td>0.116583</td>
<td>1.76399</td>
<td>6.78778</td>
</tr>
<tr>
<td>(\hat{I}_{level_3})</td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

Most of the analysis issues in the previous example also apply here, and were similarly resolved.
7.3. Craniopharyngioma data of E. Ozyar

Dr. E. Ozyar of the Hacettepe University Hospital Dept. of Radiation Oncology in Ankara, Turkey, kindly supplied us with the histories of twenty-three patients treated with radiation for craniopharyngioma. Although the number is small, the series allows us to demonstrate some important points of analysis. The data are listed in Table 5. Dose level, number of fractions and time of treatment are given as well as time to last followup or first detection of recurrence. The clinical interest lies in estimating the coefficients of the linear quadratic model. A Kaplan-Meier curve of the estimated probability of local control is given in Figure 5 a).

The usual procedure would entail applying Equation 18 to the probability of local control at one or two years. This raises several difficulties. How do we treat the subject who was lost to followup at twelve months? What if we are interested in the probabilities of local control at both one and two years? With traditional binary regression, information is wasted and we have no information to spare here - there are only two events prior to two years.

Admittedly, patient accrual is small and some followup times are short. However, some initial results can be obtained by using the method of §5 and modeling recurrence times within the context of the linear-quadratic equation. We set \( r = 1 \), implying the log-logistic distribution. This assumption is examined with a plot of the estimated logit probability of local control vs. log time. Although the sample size is small and no definite conclusions can be reached, Figure 5 b) shows no gross deviations from the log-logistic distribution.

Table 6 gives maximum likelihood estimates of the linear-quadratic coefficients for Ozyar's data assuming log-logistic recurrence times. They correspond to the model of Equation 21. In order to utilize the maximum amount of information possible, \( T_0 \) was chosen to exceed the largest failure time (\( T_0 = 10 \) years, for definitiveness). Due to the small number of observations the estimates are quite subjective; for this reason the standard errors and p-values are not given.
Table 5: Craniopharyngioma data of E. Ozyar

<table>
<thead>
<tr>
<th>Total dose (Gray)</th>
<th>Number of fractions</th>
<th>Time of treatment (days)</th>
<th>Time to last followup (months)</th>
<th>Status at last followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.5</td>
<td>34</td>
<td>175</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>59.5</td>
<td>34</td>
<td>175</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>55.8</td>
<td>31</td>
<td>180</td>
<td>44</td>
<td>31</td>
</tr>
<tr>
<td>51.2</td>
<td>32</td>
<td>160</td>
<td>51</td>
<td>46</td>
</tr>
<tr>
<td>60</td>
<td>40</td>
<td>150</td>
<td>57</td>
<td>44</td>
</tr>
<tr>
<td>40.6</td>
<td>29</td>
<td>140</td>
<td>52</td>
<td>72</td>
</tr>
<tr>
<td>51.5</td>
<td>34</td>
<td>151.5</td>
<td>52</td>
<td>105</td>
</tr>
<tr>
<td>55.6</td>
<td>36</td>
<td>154.4</td>
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<td>24</td>
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<td>34</td>
<td>175</td>
<td>51</td>
<td>12</td>
</tr>
<tr>
<td>54</td>
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<td>147</td>
</tr>
<tr>
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<td>32</td>
<td>175</td>
<td>51</td>
<td>49</td>
</tr>
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<td>40</td>
<td>150</td>
<td>58</td>
<td>13</td>
</tr>
<tr>
<td>55</td>
<td>37</td>
<td>148.6</td>
<td>59</td>
<td>12</td>
</tr>
<tr>
<td>51.5</td>
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<td>151.5</td>
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<td>24</td>
</tr>
<tr>
<td>54.25</td>
<td>31</td>
<td>175</td>
<td>42</td>
<td>119</td>
</tr>
<tr>
<td>60</td>
<td>40</td>
<td>150</td>
<td>86</td>
<td>51</td>
</tr>
<tr>
<td>51.5</td>
<td>34</td>
<td>151.5</td>
<td>56</td>
<td>109</td>
</tr>
<tr>
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<td>151.5</td>
<td>47</td>
<td>72</td>
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<td>59.5</td>
<td>34</td>
<td>175</td>
<td>65</td>
<td>125</td>
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<td>30</td>
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<td>150</td>
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<td>52</td>
</tr>
<tr>
<td>56</td>
<td>32</td>
<td>175</td>
<td>45</td>
<td>44</td>
</tr>
</tbody>
</table>

These results seem at first to be nonsensical - $\hat{\alpha}$ is negative, when it is clear that dose should increase local control rates ($\hat{\beta}$ and $\hat{\gamma}$ have the expected signs). This apparent paradox is explainable by the high correlation between $\hat{\alpha}$ and $\hat{\beta}$ - their respective terms, $nd$ and $d(nd)$, each depend quite strongly upon dose (in these data, their correlation is 87%). This fact in combination with the small sample size implies that the data are not useful for estimating $\alpha$ and $\beta$ separately. However, the linear-quadratic equation can still be used to give estimates of local control probabilities at, say, three years. Using Equation
Table 6: the estimated linear-quadratic equation for Ozyar’s data assuming log-logistic recurrence times ($r = 1$).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated Coefficient</th>
<th>Percentage Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>6.63</td>
<td></td>
</tr>
<tr>
<td>$-\log(T/10)$</td>
<td>$\kappa = .702$</td>
<td></td>
</tr>
<tr>
<td>$nd$</td>
<td>$\alpha = -.294/Gy$</td>
<td>$-7.4%/Gy$</td>
</tr>
<tr>
<td>$d(nd)$</td>
<td>$\beta = .185/Gy^2$</td>
<td>4.6%/Gy$^2$</td>
</tr>
<tr>
<td>$T$</td>
<td>$\gamma = -.0161/day$</td>
<td>-.40%/day</td>
</tr>
</tbody>
</table>

21, we generate Figure 6 which relates local control to dose and number of fractions conditioning on treatment time at the median of 51 days. This plot makes sense: within the range of the data, dose increases control and fractionation decreases it, as we expect.

8. Conclusion

We have seen that the conditions for cellular kinetic models such as the linear-quadratic equation undergo consider stress in the transition from theory to in vitro and (especially) to clinical application. We cannot assume constant tumor volume in a population of human subjects (and in animal subjects as well, unless very stringent staging is undertaken). In addition, except in the case of very fast-growing malignancies, we often cannot be sure about the eventual status of local control in every patient. Lastly, subjects may be lost to followup for various reasons.

Despite these hurdles, binary regression methods such as logistic regression have been applied to fit the linear-quadratic equation to clinical data. This is not necessarily unjustified; nevertheless it involves implicit assumptions, as shown above, some of which may be checked with the data and all of which should be recognized and considered. In
the case of heavy censoring, the logistic and other binary models can be generalized to adjust for losses to followup. These methods have been illustrated with three real examples.
References


Figure 1: Effect of single fraction on proportion of cell kill
Figure 2: Effect of multiple fractions (sessions) on proportion of cell kill

Surviving Proportion of Cells E

Dose after 1st session

Dose after 2nd session

Dose after 3rd session

Initial slope \( \alpha \)

Net slope nearly \( \alpha \)

\( (n = 3) \)

0 Gray

Total Dose \( nd \)
Figure 3: Probability of Local Control at 3 Years vs. Dose & Treatment Time; 19 Fractions, Stage I (BIR)
Figure 4 a): Estimated Probability of No Normal Tissue Effect for BIR
Figure 4 b): Diagnostic plot of the Log-Logistic Distribution for BIR Normal Tissue Effect
Figure 5 a): Estimated Probability of Local Control for Ozyar's Craniopharyngioma Patients
Figure 5 b): Diagnostic plot of the Log-Logistic Distribution for Ozyar's Craniopharyngioma Patients
Figure 6: Probability of Local Control at 3 Years vs. Dose & # of Fractions; Treatment Time = 51 Days (Ozyar)