Biological Factors Influencing Optimum Fractionation in Radiation Therapy

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Optimum fractionation in radiotherapy occurs when tumor control is improved without enhancement of complications. The main influence on choice of overall time, total dose and fraction size is biological: the proliferation status of tumors. For rapidly proliferating tumors, shorter schedules than 6 to 8 weeks are necessary. Optimum overall time is similar to Tk, the time after beginning cytotoxic treatment when rapid proliferation in tumors starts: 21 to 35 days in head and neck tumors. These, and non-small cell lung tumors, have a clonogenic cell doubling time during radiotherapy of about 3 days. New developments in designing optimum schedules for such tumors are presented: carefully regulated hypofractionation (CRH). For slowly proliferating tumors, especially prostate adenocarcinoma, intracellular repair is large, so larger doses per fraction will be necessary. New evidence is presented showing that their α/β ratio may indeed be lower than 3 Gy. For an entirely different reason from that above, hypofractionation should be tested.

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Optimum fractionation can be defined as a schedule providing the maximum tumor control for the minimum normal-tissue complications. It depends critically on the proliferative state of the tumor cells relative to that of the normal tissue at risk. This is where basic biology, particularly the understanding of cell proliferation—perhaps eventually the control of proliferative rate—and clinical radiation oncology join hands. Two examples that are leading-edge projects in developing new, optimum, non-standard fractionation schedules for specific tumor sites can be given. One is for tumors that proliferate so fast that shorter schedules are required, the other is for tumors in which slow proliferation allows so much repair between fractions that larger doses per fraction become necessary.

In the first example, radiation oncologists are getting close to an optimum schedule for head and neck (H&N) tumors. Tumors in this site have provided the most data on alternative fractionation schedules, because significant results of tumor control can be obtained with only two or three years of follow-up. In the 1980s it was established that prolongation of radiotherapy treatment reduced the probability of local control and survival (1–3). The rate of loss was subsequently quantified (3–5) as an average of 0.6 Gy/day in 2 Gy fractions, equivalent to 0.72 Gy_{10} in BED (Biologically Effective Dose or ERD units), or 10% loss of LC per week, or a tumor cell doubling time of about 3 days. In the mid 1980s measurements of the potential doubling time (Tpot) of cells from H&N tumors showed a median of about 5 days, with a range of 2 to 20 days (6, 7). Most other types of epithelial tumor had similarly rapid population doubling times, with the exception of the hormonally controlled tumors, prostate and breast. These had median Tpot values of 40 and 14 days, respectively (8, 9). Tpot was always measured in tumors before the start of cytoxic therapy, and it is possible that proliferation speeds up as a response to effective cell killing.

Recent clinical trials of accelerated fractionation have demonstrated that increased local control could indeed be achieved by shorter schedules, at the rate of 7 to 10% improvement in local control per week of shortening (10–12). However, there were always increased acute reactions and sometimes a serious problem of unacceptably severe late complications. One trial attempting to use 2 Gy twice a day to 66 Gy in $3\frac{1}{2}$ weeks was closed prematurely because of unacceptable reactions, both acute and late (13). Shorter schedules that do not give unacceptable complications are difficult to design.

However, the CHART trial, consisting of a very short schedule of 12 days, using 3 fractions per day without a weekend break to the relatively low total dose of 54 Gy, achieved the same tumor control as 66 Gy in $6\frac{1}{2}$ weeks in

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H&N cancer but with less severe late complications (14). In non-small cell lung carcinomas CHART also achieved an increase of 10% in local control compared with the control arm of 60 Gy in 6 weeks, also with fewer complications (15). This schedule, and the Danish trial (11) using 6 fractions instead of 5 per week, employed a reduction of total dose smaller than the time-BED trade-off of 0.72 Gy_{10}/day, together with shorter overall time. They succeeded in opening the therapeutic window to some extent. Other schedules for H&N cancer which successfully applied shorter overall times with no or slight reductions in total dose included the Concomitant Boost (16) and schedules with two doses per day of 1.6 Gy (17, 18).

Recent data, one set from an RTOG trial of four H&N schedules (19), another involving unplanned prolongation of treatments in non-small cell lung carcinoma (20, 21), have shown significantly inferior survival in the longer schedules. The estimated doubling time of their clonogenic cells was as short as 2 or 3 days (21, 22). Given these very short doubling times, it seemed worth while to explore the consequences of shortening overall time, with modest reductions of total dose calculated to keep late reactions constant (23).

MATERIAL AND METHODS

The standard linear quadratic formula enables this modeling to be done simply. For constant late complications, the $BED = nd(1 + d/(\alpha/\beta))$ is held constant, assuming that $\alpha/\beta = 3$ Gy. No time factor is applied for late complications or for prostate tumors, which will be our second example. Dose per fraction d for a given number of fractions n is extracted by the solution of the quadratic equation, taking the positive root:

$$nd^2/(\alpha/\beta) + nd - BED = 0 \quad [1]$$

$$So\ d = \{-n + [n^2 + 4n.BED/(\alpha/\beta)]^{1/2}\}/2n/\alpha/\beta) \quad [2]$$

For the tumor BED where proliferation is significant however, the LQ formula including a linear term for proliferation rate is used:

$$BED = E/\alpha = nd(1 + d/(\alpha/\beta)) - (\ln 2)(T - Tk)/\alpha Tp \quad [3]$$

Here E is the final log cell kill, T is overall time of treatment, and Tk is the assumed 'kick-off' time of the fast proliferation, which does not begin in tumors until Tk days after the beginning of cytotoxic therapy. Tp is the average doubling time of clonogenic cells in the tumors. For this calculation, it was assumed that α/β was 10 Gy (with a range of other values assumed in sensitivity tests) (24). Tk was assumed here to be 28 days, as discussed later. Values of α and Tp that we have found not to contradict any published results of H&N radiotherapy published to date are 0.35 ln/Gy and 3 days, respectively. These values correspond to a time-dose trade-off of 0.72 Gy_{10} per day in BED units, or 0.6 Gy/day for 2 Gy fractions. The corresponding loss of local control is 1.6% per day or 11% per week. This loss of BED per day of prolongation was applied at all overall times beyond Tk. The resulting BED was converted to tumor control probability (TCP) using the dose-response parameters published by Martel et al. (25) for non-small cell lung carcinoma (NSCLC).

RESULTS FOR FAST-PROLIFERATING TUMORS

Computer modeling for tumors that proliferate rapidly shows that an optimum overall time exists because of two opposing trends, when treatment schedules are shortened to less than the common 7 weeks' overall time. These trends are illustrated in Fig. 1, where TCP is shown plotted against number of dose fractions, or weeks since 5 fractions per week are assumed to be standard. As overall time is lengthened, more fractions (at 5 per week) can be given, so fraction sizes become smaller, in the well-known hyperfractionation mode. In order to keep late complications constant (these are sensitive to fraction size), total dose can be increased, which would increase TCP if overall time were constant. This is represented by the full curve, which *rises from left to right*. However, the longer overall times allow more proliferation in tumors, so TCP falls, shown by the curve (dashed line) *falling from left to right*. The combined result of multiplying these probabilities together has an optimum value of TCP, which occurs where the slopes of the two curves are equal and opposite. This is a few days later than the assumed value of Tk. The optimum level TCP is specific to the incidence of late complications that are acceptable, because the complications are held constant by an appropriate selection of dose per fraction Equations [1] and [2] above).

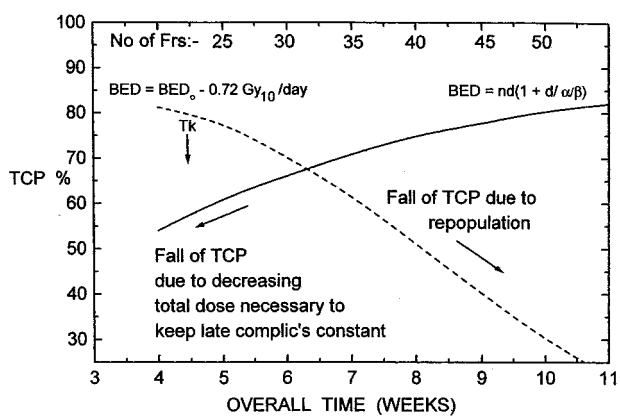

Fig. 1. The opposing trends when overall time is lengthened in radiotherapy using 5 fractions per week, maintaining constant late complications. TCP is the estimated tumor control probability. Full line: As more fractions are used, dose per fraction can be smaller, so total dose can be increased without increasing the late BED (biologically effective dose), as in standard hyperfractionation. Dashed line: As overall time is increased, repopulation of tumor cells (starting at Tk = 28 days) causes a reduction in TCP. An optimum TCP occurs near Tk.

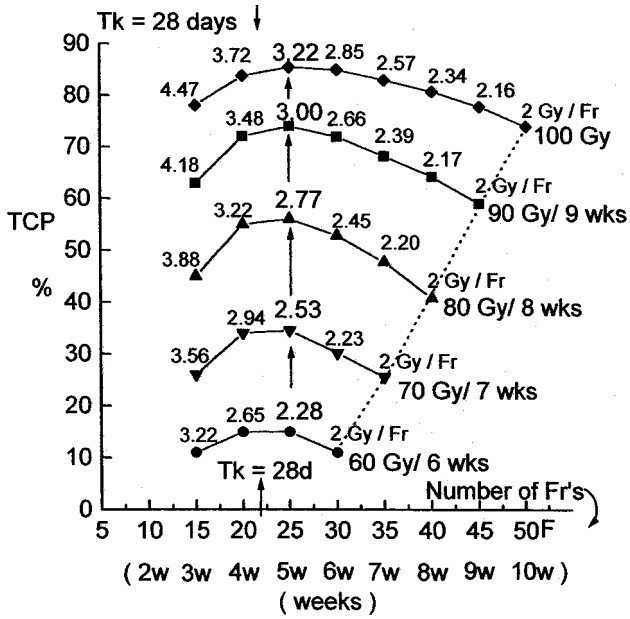

Fig. 2. A series of modeled curves, each for a constant level of late complications, showing the dose per fraction calculated for equal late BED (biologically effective dose) as overall time is shortened, assuming a clonogenic cell doubling time of 3 days. The TCP (tumor control probability) values were taken from the 30-month survival data of Martel et al. (25) for non-small cell carcinoma patients (dotted curve). Successive curves start at a higher level of complications as if another 5 fractions of 2 Gy and a week were added.

Fig. 2 represents a set of such optimum curves, with doses per fraction designed for a clinical trial of escalated total dose using a constant 25 fractions in 5 weeks (26). This set of calculations was designed for lung cancer, where tumor doses escalated in the standard way approached 100 Gy in 10 weeks, an obviously too long overall time. This approach can be called 'carefully regulated hypofractionation' (CRH). The schedules are equally applicable to H&N tumors, which proliferate equally fast. Sensitivity to the value of Tk is illustrated in Fig. 3. The absolute increase from a given longer overall schedule, say 70 Gy in 35 fractions, is the same for all values of Tk, but the shortness of schedule to aim at depends on Tk. Unfortunately we do not know Tk well enough.

DISCUSSION FOR FAST-PROLIFERATING TUMORS

Although there are many biological indicators which are upregulated within hours or minutes of irradiation by a radiotherapy-fraction sized dose of irradiation, the gross clinical information, extracted by careful analysis of H&N tumor results, is that Tk is as long as 21 to 35 days (27, 28). We are unlikely to have any better information until a series of clinical results are available with overall times spanning from 2 to 5 weeks. Such data might become available in the next few years. (For example, CHART at 2 weeks (14, 15), Bourhis et al. at 3 weeks (29), TROG at 4 weeks (30), etc.) Meanwhile, the currently suggested good practice for H&N cancer appears to be 6 fractions of 2 Gy per week to a total dose of 66–68 Gy in an overall time of just under 6 weeks. The 6th fraction can be given either on a Saturday or as a second dose at least 6 h after the first dose, on one of the days of the week.

For lung cancer it will obviously be necessary to give higher doses to reach survival rates beyond about 20% at 3 years (20, 25, 26). One way to do this is to move upwards from curve to curve in Fig. 2, by carefully regulated hypofractionation. It is hoped that this can be done using IMRT (intensity-modulated radiation therapy) to deliver highly conformal dose distributions with on-line verification and adaptive capabilities (31). An alternative fractionation approach would be to use two well-spaced fractions per day of 2 Gy on some of the days in order to restrict maximum overall time to say 6 weeks. Assuming five treatment days per week, 100 Gy would be delivered in 2 Gy fractions once 'daily' for 2 weeks followed by 4 weeks of twice-a-day (b.i.d.) doses of 2 Gy. This approach would be closer to standard radiobiological teaching, which favors hyperfractionation over hypofractionation. And hyperfractionation is successful, at least up to 7 weeks and just over 80 Gy in H&N radiotherapy (19, 32, 33). The modeled comparison is shown in Fig. 4. There is a slightly higher therapeutic gain predicted by the 'standard' radiobiological approach using 2 Gy fractions given b.i.d where necessary to limit overall time to 6 weeks. This shows a gain of about 22% in TCP compared with 17% by the carefully regulated hypofractionation method, for equal late effects. It would require a two-arm clinical trial with a

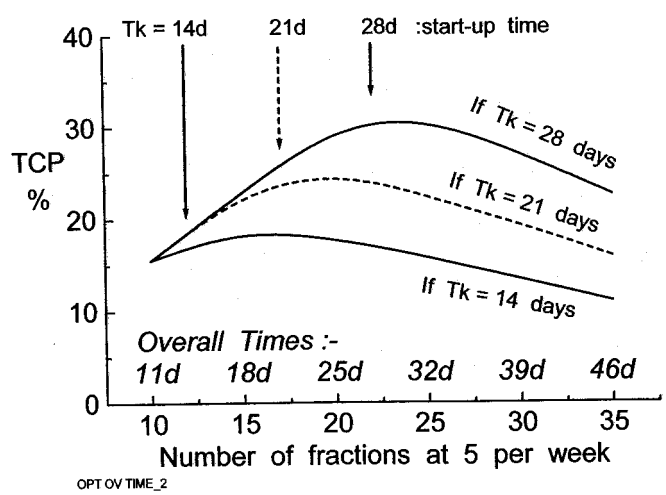

Fig. 3. Modeled curves showing that the optimum overall times are slightly longer than each of the assumed values of Tk (the time when rapid repopulation of tumor cells begins). The absolute increase of TCP (tumor control probability) above the level of 70 Gy in 7 weeks is 17% for all values of Tk.

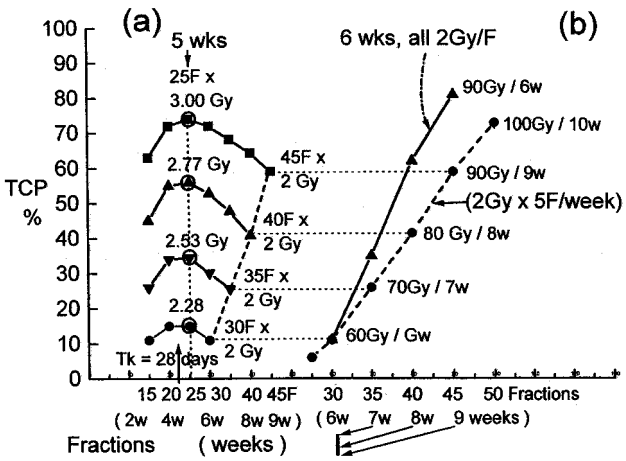

Fig. 4. Modeled comparison of two methods of dose escalation for tumors repopulating as rapidly as Tp = 3 days after Tk = 28 days. (a) full curves: carefully regulated hypofractionation; (b) full curve: b.i.d. on some of the days, as necessary to limit overall time to 6 weeks. The dashed curves in both (a) and (b) are the same escalation protocol of 2 Gy five times a week.

total of 4000 patients to detect a 5% difference in TCP. There are two disadvantages of the b.i.d. method. One is the obvious one of utilization of resources in planning 50 fractions in 6 weeks instead of 25 fractions in 5 weeks. The other, which is less clear, is the question of possibly incomplete repair between two fractions of 2 Gy each day, even if spaced by 6–8 h. There is only slight evidence that this might be a real problem for tissues other than spinal cord or brain (34–36).

A further point is the lack of a good measure of rapid proliferation in individual tumors that correlates with clinical outcome (37). Whilst the prospect of therapeutic gain from shorter schedules is good for patients in whom tumor cells proliferate rapidly during radiotherapy, it would be an advantage to select for these demanding schedules only those patients who are likely to benefit from them.

In summary, for fast-proliferating tumors in which the α/β ratio is definitely larger in tumors than in the critical normal tissues, a good case can be made for optimum fractionation schedules whose overall time is close to Tk, achieved by carefully regulated hypofractionation with larger doses per fraction. Alternatively, treatments using two fractions per day of somewhat less than conventional size, such as 1.6–1.8 Gy, are also a possibility. These are expected to mean overall times of 3 to 5 weeks, but further estimates of the value of Tk are required. It remains very important to find reliable measures of proliferation rate in tumors so that only those patients most likely to benefit from the more intense accelerated treatments need be subjected to them. For example, poorly differentiated tumors and secondary nodes have been reported not to give as much gain with accelerated fractionation as well-differentiated tumors (38).

RESULTS FOR SLOWLY PROLIFERATING TUMORS

The most slowly proliferating tumors known are prostate adenocarcinomas, median Tpot 40 days and range 15–170 days (9). Even the fastest-proliferating prostate tumor recorded has a longer Tpot than the median of the next slowest type of tumor, which is breast cancer, with a median of 14 days. A reasonable biological expectation would then be that there is more time available for repair, including misrepair, in cells of prostate tumors than in those of faster proliferating tissues and tumors. The α/β ratio—intrinsic radiosensitivity divided by repair capability—would be expected to be low. Brenner & Hall (39) studied this question by comparing the external beam doses of about 70 Gy with isoeffective doses from permanent I-125 implants of 145 Gy in an LQ model. They concluded that the α/β ratio was 1.5 Gy (95% CI 0.8–2.2 Gy).

This is indeed much lower than the $\alpha/\beta = 10$ Gy or above found for other types of carcinoma, which mostly proliferate very rapidly. The consequences are twofold, based on the LQ equations in Materials and Methods. First, substituting 40 days in Equation [3] shows that there is a very small loss of local control with prolongation, even if alpha is found to have a somewhat lower value. Secondly and more importantly, the sensitivity to fraction size of prostate tumors would be at least as great as that for the late complications in rectum and bladder that limit total dose in radiotherapy. If α/β were the same in prostate tumors and in rectum, any fractionation schedule would give the same therapeutic ratio and there would be no need to go to as many small fractions as we conventionally do. Furthermore, if it is confirmed that prostate tumors do have a smaller α/β ratio than the late-responding normal tissues at risk, then the therapeutic ratio would theoretically be improved by using much larger doses per fraction than previously. At the same time, logistic economy would be achieved. This point is very important in practice.

As a contribution to this question, we recently reviewed 17 clinical trials published since 1994, concentrating on Intermediate Risk prostate patients treated solely with external beam or with permanent implants of I-125 or Pd-103. In Fig. 5 the BED values are shown for the external beam dose (dashed curves) which is isoeffective for 5-year biochemical control with permanent I-125 implants prescribed to 145 Gy (full curves for three different values of T $\frac{1}{2}$ of sublethal damage repair in the tumors). Using a slightly different LQ analysis from that of Brenner & Hall (39), we calculated (40) a best estimate of $\alpha/\beta =$ 1.49 Gy (95% CI 1.35–1.63 Gy). Also by direct analysis, the T $\frac{1}{2}$ of sublethal damage repair of prostate tumor cells was estimated to be 1.90 h (95% CI = 1.42–2.86 h), so the upper full curve in Fig. 5 is the relevant one. These results add to the evidence that the α/β value for prostate tumors

might really be lower than that of the relevant late complications. The case for increasing therapeutic ratio by hypofractionation is thereby building up for this slowly proliferating tumor too, for a totally different reason.

DISCUSSION FOR SLOWLY PROLIFERATING TUMORS

The practical clinical importance of the suggestion that α/β might be very low in prostate tumors is obvious. Even the possible use of a large single dose, as in stereotaxic radiotherapy, has been mooted. In this author's opinion that would be a mistake, because there is then no chance of improving cell kill for any tumor cells that are temporarily in a resistant phase or state. A second reason is that acute reactions could then become dose limiting, possibly more severely than in tumors; and if so no therapeutic advantage would accrue in practice. However, if α/β is really less than 3 Gy in prostate tumors, the use of 5 or 6 large fractions would be reasonable, (as now used, with much less biological justification, in treatments of carcinoma of the uterine cervix).

It has been argued that these low values of α/β are artefactually low because heterogeneity of radiosensitivities (α) should have been considered (41). We considered, however, that our use of clinical data to determine the isoeffect doses used in the analysis had already taken into account heterogeneity within and between tumors, and also heterogeneity of dose within the tumors, so it should be unnecessary to assume further inhomogeneity (40).

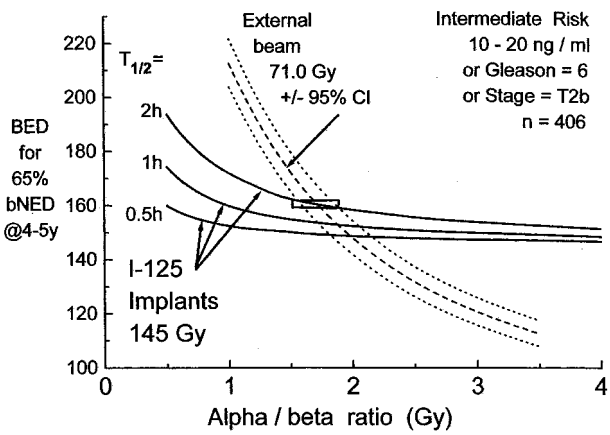

Fig. 5. Modeled comparison of BED (biologically effective dose) as a function of α/β for treatments of prostate carcinoma. Full lines: BED for permanent implants of I-125, prescribed to 145 Gy. Dotted lines: BED for external beam dose of 71 Gy, isoeffective for biochemical tumor control at 5 years of intermediate risk patients, from a recent review of 17 published clinical results (40). Where the curves cross indicates the estimated α/β ratio for prostate tumors, likely to be less than 2 Gy. A half time of 1.9 h was calculated by direct analysis, so we match to the 2 h curve here.

CONCLUSIONS

Hypofractionated schedules, using fewer and larger fractions, seem to be justified in future clinical trials for both rapidly and very slowly proliferating tumors, although for totally different reasons. For rapidly proliferating tumors we need to obtain better values for the onset time of rapid proliferation, in order to know whether optimum overall times should be nearer 3 weeks than 5 weeks. We also need good predictive tests to indicate rapid proliferation in individual tumors. For the slowly proliferating prostate tumors, we need further confirmation that the α/β value is indeed as low as, or lower than, the value of 3 Gy associated with rectal complications.

It should be noted that these considerations of optimum schedules are purely radiobiological and are not influenced by economic or resource-utilization considerations, except that people might now listen. However, doses larger than 2 Gy are contrary to the previous radiobiological preference for hyperfractionation. It is therefore appropriate and safe to embark on such non-standard clinical trials with the best conformal dose delivery, verification and adaptive capabilities that modern IMRT can provide.

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