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ACCELERATED FRACTIONATION IN THE RADIATION TREATMENT OF HEAD AND NECK CANCER

A critical comparison of different strategies

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Abstract

There is strong clinical and radiobiological evidence that protraction of overall treatment time has an adverse influence on the radiocurability of certain human tumors. Overall treatment time can be reduced without recourse to large dose fractions by the use of accelerated fractionation, but in patients with head and neck cancer acute mucosal reactions limit the extent to which treatment can be accelerated. Three different prototypical schedules for accelerated fractionation have been devised to avoid exceeding acute mucosal tolerance. Type A consists of an intensive short course in which the overall duration of treatment is markedly decreased with a corresponding substantial reduction of total dose; type B achieves a modest decrease in overall time without reduction of total dose by using a split-course technique; type C also achieves a modest decrease in overall time without reduction of total dose by means of the concomitant boost technique. A hybrid schedule combining features of types B and C allows additional shortening of overall treatment time without reduction of total dose. Available radiobiological and clinical data suggest that schedules of types B or C which do not compromise total dose are generally preferable to those of type A in which there is a trade-off between total dose and overall time. For a given total dose and overall time, a continuous treatment of type C is likely to produce more cell kill than a split-course of type B, although the latter will be better tolerated. Because of the increased acute toxicity associated with all schedules of accelerated fractionation, rational selection of patients for such treatment is important. New techniques to measure the potential doubling time of human tumors *in vivo* offer this prospect.

Key words: Therapeutic radiology; accelerated fractionation, time factor, tumor cell regeneration, concomitant boost, consequential late effects.

Accelerated fractionation is defined here as a regimen of radiotherapy in which the duration of conventional treatment with daily fractions of 1.8–2 Gy, 5 days/week to total doses of ~70 Gy is reduced, without recourse to larger dose fractions, by the delivery of 2 or more treatments on some or all of the treatment days. Examples of 3 prototypical schedules of accelerated fractionation currently used in the treatment of advanced squamous cell carcinomas of the head and neck region are illustrated in Fig. 1. Schedules of type A consist of an intensive course of treatment in which the overall duration of treatment is markedly reduced with a corresponding substantial decrease in the total dose. Schedules of types B and C represent techniques where the duration of treatment is more modestly reduced, but the total dose is kept in the same range as for a conventional treatment regimen. This is achieved by using either a multiple fraction per day split-course or the concomitant boost technique, i.e. giving the boost as a second daily dose during the basic treatment course.

In this paper, we consider the relative merits of each of the above mentioned schedules and their variants both on radiobiological grounds and on the basis of available clinical data.

Rationale for accelerated fractionation

The primary rationale for all accelerated fractionation schedules is to limit the extent of tumor cell regeneration that occurs during a course of fractionated radiotherapy by reducing the overall time of treatment. Since little, if any, regeneration occurs in late reacting normal tissues over the time span of a course of radiotherapy, a reduction in overall treatment time would not be expected to

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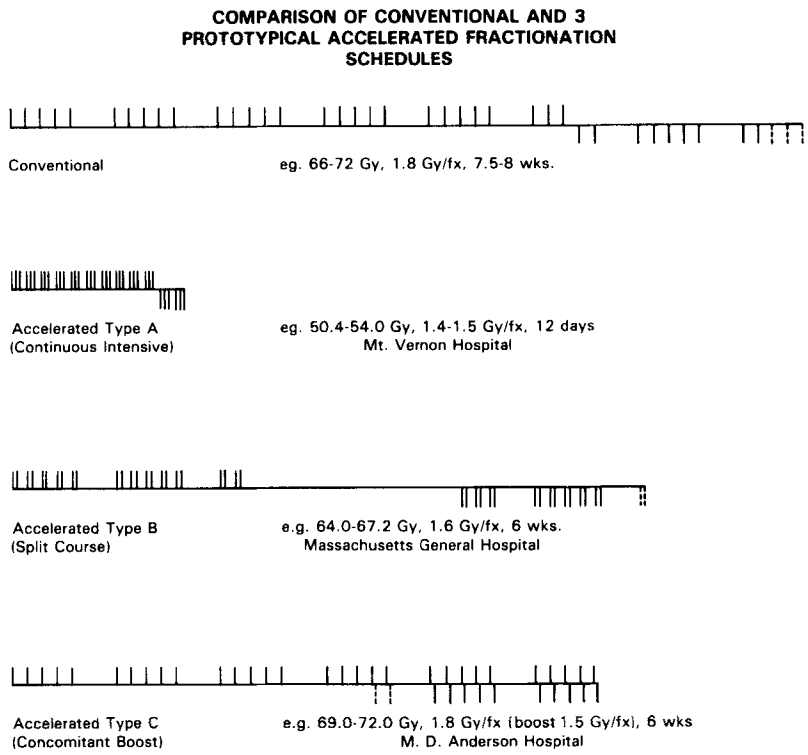


Fig. 1. Conventional and accelerated fractionation schedules. For each schedule, the large field treatment is denoted by the bars above the line, and the boost field treatment by the bars below the line. The dotted bars represent treatments omitted in the lower ranges of total dose.

affect the severity of late normal tissue injury provided the size of dose per fraction is not increased. On the other hand, the tolerance of acutely reacting normal tissue is markedly influenced by overall treatment time since these tissues do regenerate during a conventionally fractionated treatment. Thus, accelerated fractionation regimens may be considered to be dose limited by the tolerance of acutely reacting normal tissues, and consequential late damage that may occur as a result of severe and persistent acute reactions. (See below.)

The 3 types of schedules for accelerated fractionation, schematically shown in Fig. 1, may therefore be distinguished on the basis of the strategy adopted to avoid intolerable acute reactions; A) reduction in total dose, B) break in treatment, and C) reduction in volume exposed to accelerated treatment.

A secondary consideration in the rationale for accelerated fractionation is the kinetics of tumor reoxygenation which may, in different circumstances, increase or decrease the therapeutic ratio as discussed below.

Tumor cell regeneration. It was once believed that tumors were entirely autonomous tissues devoid of homeostatic control mechanisms and therefore unable to regulate their proliferation kinetics. This was the reasoning, for example, that led ELLIS (12) to omit a time factor from the tumor nominal standard dose. It is now well recognized that this concept is incorrect. There are several reasons why the overall time of treatment may influence the probability of tumor control by radiotherapy. Firstly, there is the net increase in clonogenic cell number that would occur with unperturbed growth over the duration of the course of radiotherapy. With unperturbed growth, the clonogenic cell number increases in parallel with tumor volume and thus only a modest increase of one or perhaps two cell doublings (for a rapidly growing tumor) would occur by this mechanism over a 6–8-week time period. However, the volume doubling time of a tumor does not reflect the rate of cell *production* within the clonogenic fraction. Because of a continuous loss of cells from the tumor population by exfoliation, cell death and lysis, and metastasis, the observed volume doubling time (T_D) of most tumors is much longer than would be expected from the rate at which new cells are added to the tumor volume by mitosis. This expected doubling time in the absence of all cell loss was termed by STEEL (38) the 'potential doubling time' (T_{pot}), while the 'cell loss factor' was defined as $\frac{1-T_{pot}}{T_D}$. When a tumor cell population is depleted by therapeutic interventions, the net rate of increase of clonogenic cell number is much greater than in the unperturbed state since the cell loss factor decreases and clonogenic cells that had been forced into kinetic quiescence by inadequate blood supply, nutritional deprivation, etc. are recruited back into the proliferative pool. In addition the

cells of certain tumors may retain remnants of the regulatory systems that control proliferation in their normal tissues of origin (17), in which case depletion increases the rate of clonogenic cell multiplication by removal of negative feedback influences.

Evidence for an increased proliferation rate of surviving tumour clonogens after *completion* of treatment may be gleaned from a number of sources. In classical experiments on human tumor proliferation kinetics, VAN PEPERZEEL (46) showed that the doubling times of human lung metastases soon after radiation treatment were much shorter than either the pretreatment doubling times or those after the original tumor volume at the time of irradiation was surpassed. TUBIANA & MALAISE (44) and MALAISE et al. (23) also observed a phase of rapid tumor regrowth after the treatment of cutaneous metastases from human tumors. Interestingly, these authors observed that the growth rates of tumors with a long pretreatment doubling time accelerated to a greater extent than those which grew rapidly before treatment, suggesting the possibility of a greater proportional reduction of the cell loss factor in slowly growing tumors after initiation of irradiation.

Time-to-recurrence data also suggest that tumor clonogens surviving irradiation proliferate much more rapidly than might be expected from pretreatment volume doubling times. Analysis of recurrence of squamous cell carcinomas of the various head and neck sites (14) show that the median time to recurrence is approximately 6 months. As the majority of the patients in these series were cured, one can reasonably suppose that most recurrences must have arisen from a single cell or very few surviving cells. About 30 volume doublings are required for a single cell to become a clinically manifest recurrence. Thus, one can deduce that the net volume doubling time of the preclinical recurrences must have been on the order of one week. Other human data consistent with rapid proliferation of cell surviving radiation therapy include the split-course results reported by PARSONS et al. (29) and VIKRAM et al. (48). These authors reported that when stratified by total dose, patients treated with a split-course regimen fared less well stage-for-stage than those with a continuous course of radiotherapy. A similar conclusion can be drawn from the observation of OVERGAARD et al. (28), i.e. that in patients with laryngeal cancer treated with a split-course regimen the total dose must be escalated by about 20% to compensate for a treatment interrruption of 2–3 weeks. In another series of patients with laryngeal cancer treated with a split-course regimen, BUDIHNA et al. (8) calculated that the dose recovered during the treatment break, attributable to regeneration of surviving tumor clonogens, was $0.4 \simeq$Gy/day which corresponded to a clonogen doubling time during the break of 3.5 ± 0.5 days.

The first experimental data demonstrating accelerated proliferation of clonogenic tumor cells after irradiation came from BARENDSEN & BROERSE (3) using a rat rhabdomyosarcoma. With this tumor system, after fractionated radiotherapy with 3 Gy fractions given 5 times a week, the clonogenic tumor cell doubling time dropped from a pretreatment value of 4 days to about 1.5 days. This was accompanied by an increase in the growth fraction, decrease in the cell loss factor, and decrease in the cell cycle time of the tumor cells. Using the same tumor system, MARTIN et al. (24) measured the TCD_{50} in 10 equal fractions with different overall treatment times ranging from 10 to 62 days. These experiments showed no increase in TCD_{50} between 10 and 20 days, but there was an approximate doubling of the TCD_{50} dose between 20 and 60 days. At first sight, these experiments might suggest that tumor regeneration was not a significant factor with treatment times less than 20 days. However, interpretation of the data is complicated by the fact that reoxygenation was not controlled for in these experiments. A sharp increase in TCD_{50} with prolongation of total overall time of treatment beyond 9 days has been shown by SUIT et al. (39) in a mouse mammary carcinoma.

More recently, KUMMERMEHR et al. (21) have reported the results of detailed experiments using a variety of mouse tumors in which the extent of regeneration *during* fractionated irradiation has been quantitated with all radiations being given under conditions of clamp hypoxia. These experiments have shown that significant regeneration occurs in some tumors during the first and second week of fractionated irradiation. There was accelerated regeneration in the squamous cell carcinoma AT 478 during the second and third week of treatment, and during the second week of treatment of a mammary carcinoma. On the other hand, proliferation effectively stopped in 2 adenocarcinomas after one week's treatment. KUMMERMEHR (20) also investigated which kinetic parameter best predicted for tumor regeneration during treatment. Although none was a reliable indicator for all tumor types, the best overall prediction was given by the potential doubling time of the tumor, measured pretreatment.

Reoxygenation. The vast majority of solid tumors in experimental animals has been shown to contain hypoxic clonogenic cells which are resistant to radiation and are dose-limiting when large incremental doses of radiation are given. During fractionated irradiation, however, some radioresistant hypoxic cells reacquire the radiosensitivity associated with well oxygenated cells. This phenomenon, reoxygenation, may occur by a variety of mechanisms, only some of which are related to tumor regression (11, 16, 47). The proportion of hypoxic cells varies markedly among different experimental tumors (26) as does the rate of reoxygenation (43), and one cannot make any generalizations about the completeness of reoxygenation as a function of duration of treatment. If a tumor regresses completely before the end of treatment it is reasonable to suppose that reoxygenation has been essentially complete but if regression is incomplete, reoxygenation may or may not be complete. This difference may be one reason for

the prognostic advantage associated with complete regression at the end of a conventional course of treatment (4).

Normal tissue responses

In general, the normal tissues with the greatest ability to repopulate following injury are those that react acutely to radiation. Clinically, in treatment of cancer of the head and neck the acutely responding tissues of major concern are the mucous membranes lining the upper aerodigestive tract, and the skin. It is frequently asserted that with modern day megavoltage radiation acute reactions are no longer dose-limiting, and the limitation to total effective dose is imposed by the tolerance of late reacting normal tissues. This statement is true only insofar as treatment is protracted sufficiently to allow the acutely reacting normal tissues to repopulate sufficiently during treatment to offset some of the radiation cell killing. When one considers accelerated dose fractionation, acute reactions become dose-limiting regardless of radiation quality.

The first clinical evidence of the association between overall treatment time and the severity of acute skin reactions was published in 1918 by KRONIG & FRIEDRICH (19). There were many studies of the time factor for skin in the 1920's, notably those of SCHWARZ (36) and REGAUD (32). These principles were later extended by BACLESSE (2) to develop ultraprotracted treatment schedules for breast cancer in which very large total doses could be delivered with essentially no acute skin reaction. These schedules were discontinued in the 1950's because of severe late reactions. The present conventional norm of treating head and neck cancers with daily doses of 1.8–2 Gy was derived empirically and represents a dose accumulation rate at which the majority of patients can comfortably complete large-volume irradiation without excessive acute toxicity. At the weekly accumulation rate of 9–10 Gy, the total dose is then dictated by the tolerance of late reacting normal tissues. However, when the weekly accumulation rate is substantially greater, as in the case of accelerated fractionation, acute reactions can and do become dose limiting.

Experimental studies of repopulation during fractionated radiotherapy have been performed on skin and mucous membranes. DENEKAMP (9) demonstrated that there was no detectable regeneration in the skin for up to 15 days after 4 daily fractions of 3 Gy; after 9 fractions, however, regeneration contributed the equivalent of 0.6 Gy per day and after 14 daily fractions 1.3 Gy per day to the acute tolerance dose. Because the stimulus to regenerate is cell depletion, and because radiation-induced cell killing is mitotically linked, the onset of regeneration in normal tissues varies according to the proliferation kinetics of the tissue. Thus, in contrast to the mouse skin where there is a lag of 1–2 weeks after initiation of radiation before regeneration is triggered, in the mouse colon (52) and lip mucosa (1), regeneration is clearly evident within 3 days of beginning fractionated irradiation.

Consequential late reactions. The major reason for using multiple fractions per day as a means to shorten overall time in accelerated fractionation regimens is to avoid the risk of severe late normal tissue damage associated with large incremental dose fractions. It is well established that injury to tissues which respond late after irradiation depends more on size of dose per fraction and less on time of treatment than is the case with acutely responding tissues (42). However, in certain circumstances chronic late normal tissue injury may occur as a consequence of severe epithelial denudation. If an area is completely depopulated of epithelial stem cells, a chronic mucosal or skin ulceration results, and healing if it occurs depends on migration of epithelial cells from the periphery of the denuded area. Infection and/or trauma in a chronic epithelial ulcer can lead to secondary damage to subjacent normal tissues. We term this type of injury a consequential late effect because it is not directly attributable to radiation injury of the late responding tissue but occurs as a consequence of the severe acute reaction. By definition, the dependence on dose fractionation of consequential late effects is the same as that for acute reactions and is not characteristic of that normally associated with late radiation reactions. This fact has led to some confusion in the literature and to the assertion of some authors reporting both experimental (13) and clinical (6) studies that there is no dissociation with fractionation between the severity of acute and late effects. Examples of consequential late effects in the head and neck area include soft tissue necrosis in chronic mucosal ulcers and mandibular osteoradionecrosis following breakdown of the mucoperiosteum. Injuries of this type have been reported with accelerated fractionation schedules at total doses well below those normally associated with severe late normal tissue injury (30).

Comparison of schedules

Dose equivalent of regeneration in tumors. In order to compare the relative merits of schedules of type A versus those of types B or C (Fig. 1), it is necessary to estimate whether the dose equivalent of tumor cell regeneration that would occur during the longer treatment times associated with the latter schedules is greater or less than the dose reduction required to make type A schedules tolerable.

One approach to this question is to compare calculated doses required to produce a certain level of tumor control as a function of overall treatment time with appropriate corrections being made for the different sizes of dose per fraction in different regimens. MACIEJEWSKI et al. (22) used this technique with the endpoint of local control stages T3 and T4 squamous cell carcinoma of the larynx. Their analysis indicated an increase in the TCD_{50} dose of ap-

Table

Dose equivalent (Gy) of regeneration (12 vs. 40 days)

CLF (%)	Days								
	T_{pot}			T_{pot}			T_{pot}		
	3	5	8	3	5	8	3	5	8
90	1.4	0.9	0.5	2.6	1.5	1.0	5.9	3.5	2.3
60	5.7	3.4	2.1	10.2	6.1	3.8	24.0	14.1	8.8
30	10.0	6.1	3.8	17.8	10.7	6.6	41.1	24.8	15.3
10	12.9	7.7	4.8	30.0	13.7	8.6	53.0	31.7	19.8
	SF_2=0.4 D_0 (eff): 2.2 Gy			SF_2=0.6 D_0 (eff): 3.9 Gy			SF_2=0.8 D_0 (eff): 9.0 Gy		

CLF = cell-loss factor, T_{pot} = potential doubling time, D_0 (eff) = effective D_0 for fractionated irradiation.

proximately 8 Gy as the overall treatment time increased from 5 to 7 weeks. By assuming 2 Gy to be necessary to offset each clonogenic cell doubling (corresponding to a D_O (eff) of 2.9 Gy), the authors concluded that over this time period the clonogenic tumor cells were dividing with a potential doubling time of 4 days.

A more generic approach yielding perhaps the best estimates of the dose equivalent of regeneration for comparative purposes is based on measured values of kinetic parameters and intrinsic cellular radiosensitivity of human squamous cell carcinomas of the head and neck. In their review of the published data, SASAKI et al. (34) reported on 198 squamous cell carcinomas with a median potential doubling time of 4.1 days. The range of labeling index in 160 of the tumors was 6 to 30% corresponding to a range of potential doubling times of approximately 2–10 days. Cell loss factors were in the range of 90%. Estimates of the cellular radiosensitivity of a variety of human tumor cells obtained from primary biopsies have been reported from our laboratory by BROCK et al. (7). More recent results show that for squamous cell carcinomas of the head and neck, the mean surviving fraction at 2 Gy (SF2) was ~0.36 with a range of ~0.18 to ~0.64 in a total of ~40 measurements. These values measured *in vitro* may well be lower than those *in vivo* because of the lack of the 'contact effect' (27), and the possibility of incomplete reoxygenation. Thus, for these calculations, values of SF2 of 0.4, 0.6, and 0.8 which include any plausible estimate of *in vivo* cell survival have been used.

Under the simplest assumption (exponential growth kinetics and cell kill) the dose equivalent of regeneration, D, that would occur in the relatively more protracted schedules of types B and C is given by:

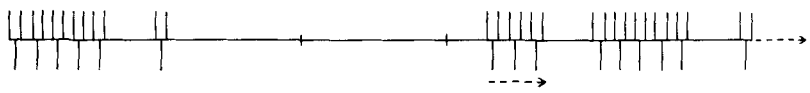
D = [exponential rate constant for accelerated clonogen multiplication after initiation of therapy, λ] × [difference in overall treatment time, T] × [effective D_0 for fractionated irradiation with the fraction size of the more protracted regimens D_O (eff)]

where $\lambda = (1-\text{CLF})\frac{\ln 2}{T_{pot}}$ day^{-1}; T is measured in days;

and $D_O(\text{eff}) \doteq \frac{2}{\ln SF_2}$ Gy for fraction sizes of 1.5–2.0 Gy

Using these equations with the values of potential doubling times (T_{pot}) and cell loss factor (CLF) cited by SASAKI et al. (34) and the range of adjusted SF2 values derived from the data of BROCK et al. (7) we have calculated the dose equivalent of regeneration between the 12 day schedule of type A (35) and the 40 day schedule of type C (18). Only when this value exceeds the actual difference (18–22 Gy) is type A preferable. As shown in the Table if SF2 =0.6 a therapeutic advantage accrues to schedule A only under the most extreme assumptions for the CLF and T_{pot}, i.e., that the CLF would have to decrease from the 90% range typical of the unperturbed tumor to 10–20%, and that the T_{pot} would be 3 days or less, i.e., among the shortest known for human tumors. If the SF2 is as high as 0.8 the dose equivalent of regeneration increases, but the same general conclusion emerges: Schedule A is superior only when a substantial reduction in the CLF occurs and/or T_{pot} is very short. Finally, if the lower range of SF 2 of 0.4 is used, schedule C is always superior regardless of CLF and T_{pot}.

Two additional points should be made. First, the comparisons in the Table are relative. Although it is true that with higher values of SF2, schedule A becomes relatively more effective vis-à-vis schedule C, the absolute probability of cure decreases commensurately. For example, if SF2 =0.8 a dose of 54 Gy in 1.5 Gy fractions would achieve only about 2.6 logs of cell kill, and the chance of tumor control would be remote. By the same token, if SF2 =0.4 most tumors would be cured regardless of fractionation schedule. Second, it has been assumed that tumor regeneration proceeds at its maximum rate throughout the 28 day time difference between the two schedules. If in fact, accelerated regeneration during a continuous course becomes significant only after ~4 weeks of treatment as



Split Course, Concomitant Boost: 72 Gy, 1.6 Gy/fx, 5-5½ wks

Fig. 2. EORTC accelerated fractionation schedule. Resumption of treatment after the break depends on the mucosal reaction, and may be delayed for a few days. Thus, the overall duration of treatment varies from 5 to $5^1/_2$ weeks.

proposed by WITHERS et al. (53), the dose equivalent of regeneration between 12 and 40 days would be much lower for all values of SF2, further favoring schedules of type B or C.

Split course vs. continuous accelerated fractionation (B vs. C). As noted above, under any reasonable assumptions of proliferation kinetics and cellular radiosensitivity, both schedule B and C are more effective than schedule A. Schedule B and C deliver approximately the same total doses in the same overall time, and differ significantly only in that schedule B is split whereas schedule C is continuous.

To compare the absolute efficacy of these 2 schedules in terms of the probability of tumor sterilization, the primary consideration is the rate of proliferation of tumor clonogens during a break in treatment relative to that during the same time segment of a continuous treatment. Although no experimental data directly address this question, the fact that division delay is induced by radiation, and the observation *in vitro* that continuous irradiation can completely suppress cell division (25) would suggest that any difference must favor schedule C. In terms of acute mucosal tolerance, schedule B is preferable and the therapeutic ratio in a given course depends on the relative proliferation kinetics of the tumor clonogens vis-à-vis the stem cells of the mucous membranes.

We conclude, therefore, that while a split-course may under certain circumstances offer a better therapeutic ratio, a continuous course is more likely, in absolute terms, to sterilize the tumor. Thus, provided a continuous course is tolerated by the patient population, it is safer than a split course of the same total dose and duration. Because of improved mucosal tolerance, however, a split-course approach offers the possibility of a further reduction in overall time without dropping the total dose below that achievable with a continuous course. The new EORTC protocol 22851 incorporates the rationales of both a treatment break, and a concomitant boost to deliver a total dose of around 72 Gy in 5–5.5 weeks (Fig. 2). The relative merit of this schedule in relation to schedule C (Fig. 1) depends on whether the extra 0.5–1 week of reduction in overall time will more than offset the inherent disadvantage of the split in terms of tumor cell regeneration. This is too close to predict on the basis of available data; we await results of the clinical studies outlined below with interest.

Clinical results and current trials

Continuous short intensive schedules (type A). The first published report on the results of an intensive multiple fraction per day short course regimen was that of SVOBODA (40). These results were updated by RESOULY & SVOBODA (33) and SVOBODA (41) with data on 59 head and neck cancer cases. The initial treatment regimen used consisted of 50–55 Gy in 24–34 fractions (1.75–2.3 Gy per fraction) over 10–16 days. Initially, very limited treatment volumes were used and acute tolerance was satisfactory. However, when larger volumes including elective nodal irradiation was attempted, it became necessary to limit the size of dose per fraction to 1.75 Gy, and from 1979 on all patients in this series were treated by a technique similar to the EORTC schedule of 48 Gy in 30 fractions over 12 days to the large volume followed after 3–4-week rest by a 12–20 Gy boost. In their total series of 59 patients the complete response rate was 86% and the 3-year survival 44%. Five severe and 4 moderate late complications were reported. This experience is generally confirmed in a small series of 9 patients reported by GONZALEZ-GONZALEZ et al. (15). Their patients received 48.6–54 Gy in 11–12 days using thrice daily fractions of 1.8 Gy. Six of this group remained disease-free for 6 months or more, and only 1 severe complication was recorded. By contrast, PERACCHIA & SALTI (30) reported very severe acute and consequential late reactions in 12 of 22 patients receiving 2 Gy 3 times a day to total doses of around 51 Gy in 10 days.

In 1985 a prospective nonrandomized study was initiated by SAUNDERS & DISCHE at the Mount Vernon Hospital (Northwood, Middlesex, UK) to evaluate an accelerated fractionation schedule consisting of 1.4 Gy 3 times daily for 12 consecutive days to a total dose of 50.4 Gy in the treatment of patients with head and neck, bronchial, and esophageal carcinomas. Preliminary data from this trial (35) showed complete clinical regressions for the first 4 head and neck patients treated. After initial experience with 38 patients the dose was increased to 1.5 Gy per fraction to give a total of 54 Gy in 36 fractions over 12 days. Updated results appear elsewhere in this issue.

Several observations can be made concerning these published data. 1) Fractional doses of 2 Gy or more given 3 times a day cannot be tolerated unless very small treatment volumes are used. 2) The total dose from which

acute reactions will heal is limited to no more than 55 Gy in 2 weeks depending on the size of dose per fraction; hence, the dose equivalent of regeneration must be high for a therapeutic gain to be realized. 3) Perhaps most significantly, accelerated schedules of type A are very similar to the first phase of the treatment regimen tested in the EORTC protocol No. 22811. This randomized study compared a standard continuous course of 70 Gy in 35 fractions over 7 weeks with an accelerated split course consisting of 1.6 Gy 3 times a day to a dose of 48 Gy in 2 weeks. The accelerated split-course was followed by a variable rest period (usually 3–4 weeks) and a subsequent boost (again with 1.6 Gy 3 times a day) to yield a total dose of 67.2–72 Gy in 6–7 weeks or longer, depending on the duration of the rest period. Interim results of this trial reported by VAN DEN BOGAERT & VAN DER SCHUEREN (45; personal communication) show no difference in 2-year actuarial local control rate or survival between the 2 treatment arms. Given the result of this randomized study, none of the type A accelerated fractionation schedules so far proposed or piloted seem likely to yield better results than conventional therapy and further trials would seem unwarranted unless they are done in conjunction with kinetic measurements to select only the most rapidly regenerating tumors for entry.

Accelerated split course schedules (type B). Evolution of the fractionation schedule designated type B is found in the work of WANG et al. (50) and WANG (49). In 1979 these investigators substituted conventional once daily fractionation to total doses of ~65 Gy in 7.5 weeks for head and neck cancer patients with a program designated 'b.i.d/q.d'. This program consisted of 2 fractions of 1.6 Gy, with a minimum of 4 h between fractions, 5 days a week for 2.5 weeks (12 treatment days), a 2-week rest, and then once daily treatment with 1.8 Gy to reduced fields to a total dose of ~65 Gy in a total of 7 weeks elapsed time. In August 1982, the b.i.d/q.d. schedule was changed into one designated 'b.i.d./b.i.d.' in which, after the rest period, patients resumed treatment with 1.6 Gy fractions given twice daily for 8–9 additional treatment days, resulting in a total dose of 64–67.2 Gy in 6 weeks elapsed time (1–1.5 weeks less than with standard once daily treatment). Comparison of the overall results of patients treated by either b.i.d. schedule with the historic controls treated prior to 1979 show a highly significant improvement in 3-year actuarial local control rates (68 vs. 46%). Further analysis shows that the b.i.d./b.i.d. protocol achieved superior results to the b.i.d./q.d. protocol. The authors attribute this to the reduced overall duration of the latter schedule. A note of caution must be expressed in accepting this interpretation since the b.i.d./b.i.d. patients were treated more recently and have, therefore, been followed for a shorter average time than the patients on the b.i.d./q.d. protocol. Furthermore, it must be pointed out that the overall duration of the b.i.d./q.d. protocol is hardly less than that of conventional q.d. fractionation, and it is difficult to ascribe the improved results obtained in the first 3 years of the b.i.d. program to treatment acceleration. By the same token, one might explain the lack of benefit in the EORTC randomized study No. 22811 mentioned above to the fact that the average overall duration of treatment was identical in both the multiple-fraction-per-day and conventional treatment arms.

Concomitant boost schedules (type C). The concomitant boost technique was pioneered at U.T. M.D. Anderson Hospital and the results obtained in a series of 53 patients with advanced squamous cell carcinoma of various head and neck sites treated between 1972 and 1983 were reported by KNEE et al. (18). The concomitant boost technique is a variant of accelerated fractionation in which the boost is delivered as a second daily fraction during the basic treatment course. By this means, the duration of treatment can be reduced by the time usually taken for the boost (1.5–2 weeks). In the series reported by KNEE et al., the patients were selected on the basis of documented rapid growth of either untreated or recurrent tumors including, in 12 patients, the appearance of gross recurrence before initiation of planned postoperative radiotherapy. In most cases, the concomitant boost was delivered in fractions of 1.2–1.5 Gy separated by 3–6 h from the basic daily treatment of 1.8–2 Gy. The boost treatments were given 2–3 times a week for 3–5 weeks to final total doses of 70–74 Gy in 6 weeks. In this unfavorable treatment group, a 2-year local regional control rate of 65% prompted initiation of a randomized phase II study in 1984 to evaluate 3 different schedules using the concomitant boost technique in patients with T2 or T3 carcinomas of the oropharynx or nasopharynx. All 3 arms called for the delivery of a basic treatment dose of 54 Gy in 30 fractions of 1.8 Gy over 6 weeks. A concomitant boost was given either during the first two weeks of treatment, the last two weeks of treatment or evenly throughout the entire basic treatment to bring the total dose to 69–72 Gy, depending on tumor size. Different rationales can be advanced for delivery of the boost early or late in the basic treatment course. Delivery of the boost during the first two weeks of treatment results in a more rapid rate of tumor regression, and as demonstrated in the pilot study of KNEE et al. (18) will in nearly all cases arrest the growth of tumors that grow under therapy at 9–10 Gy per week. The probability of complete tumor regression by the end of treatment is enhanced, and this has been associated with improved ultimate tumor control (4). The major disadvantage of this schedule is that the risk of treatment interruption is greatest since the enhanced cell depletion of the mucous membranes attributable to the boost occurs *during* treatment. Another theoretical disadvantage is that the boost is delivered, at least in part, before reoxygenation by volume regression has had a chance to take place. However, this is not a major concern since functional reoxygenation has been demonstrat-

ed experimentally within hours of radiation exposure without any volume changes (16, 43, 47).

Delivering the boost during the last part of the basic treatment course has the greatest probability of insuring that the full dose will be given without treatment interruption, even though an exacerbation of the acute reaction may be predicted following completion of therapy. Moreover, since the regenerative response of the mucous membranes is already in full swing at the time of the boost, tolerance should be improved. For tumors that show regression during the basic course, a somewhat smaller boost volume may be possible. On the other hand, in tumors that regenerate rapidly a boost early in the course of treatment would be preferred.

As of October 1986, 52 patients had been entered into this study. All patients completed the treatment without interruption, even though acute reactions have been, as expected, more severe than with conventional therapy. The feasibility of shortening the overall duration of treatment routinely by 1.5–2 weeks without reducing the total radiation dose has been confirmed and when the best of the schedules has been identified, a randomized study against conventional once-daily treatment will be undertaken.

Hybrid split course-concomitant boost (Fig. 2). A new EORTC study has recently been activated by which a total tumor dose of around 72 Gy is delivered in 5–5.5 weeks total time. According to this protocol, thrice daily fractions of 1.6 Gy are delivered over 6 treatment days followed by a 2–2.5 week split and a further 9 days of treatment with 1.6 Gy t.i.d. Radiation dose fractions are separated by a minimum of 4 h and the second treatment on each day is to the reduced volume boost field. The underlying rationale of this schedule is that the first course should stop just as the regenerative spurt in the mucous membranes is triggered into full swing to assure that the maximum amount of regeneration occurs during the split. The second part of the treatment is slightly larger than the first part since one can accept a rather more severe acute reaction after all the treatment has been delivered than during the split when a delay in healing will compromise the resumption of therapy. This protocol design offers a full 2-week reduction in overall treatment time without any reduction in total dose compared with a standard treatment regimen. It will, therefore, provide a rigorous test of the importance of overall treatment time and the results of this trial are awaited with interest. To date a total of ~100 patients have been accrued (Horiot J-C, personal communication, 1987).

Conclusions

There is strong clinical and radiobiological evidence that overall treatment time is an important determinant of the curability of certain human tumors. For patients with tumors having significant regenerative potential, protraction of treatment to minimize acute radiation reactions is counterproductive and likely to contribute to treatment failure. Reducing overall treatment time by increasing the size of dose per fraction is also counterproductive in that the probability of severe late normal tissue injury is increased. Thus, there is a clear rationale for the use of accelerated fractionation regimens when one suspects or has evidence for high tumor regenerative potential. If accelerated fractionation is to be used, then the weight of clinical and radiobiological data would support schedules of the types B or C which do not compromise total dose rather than type A in which there is a tradeoff between total dose and overall time. Randomized studies to evaluate these strategies rigorously are to be encouraged.

Due to increased acute toxicity with accelerated fractionation it would obviously be desirable to separate patients whose tumors need to be treated rapidly from those in whom the time factor is less important. As indicated previously, the single best kinetic parameter on which to make this judgement is probably the potential doubling time of the untreated tumor. Until recently, the only method available to measure kinetic parameters was the use of radioactive precursors of DNA such as tritiated thymidine and autoradiography. This technique suffers several drawbacks in human tumor research. Firstly, its use is limited *in vivo* by ethical considerations associated with administering a radioactive DNA precursor, and secondly weeks must elapse before autoradiographs can be processed. Thus, studies using this technique have been restricted mainly to *in vitro* estimations of labeling index relating proliferative status to histopathology and clinical outcome (37). The development of monoclonal antibodies recognizing BrdU incorporated into DNA, and of flow cytometric techniques to measure simultaneously total DNA content and BrdU uptake (10) has created new possibilities for measuring human tumor cell kinetics *in vivo*. It has recently been demonstrated by WILSON et al. (51) that sufficient labeling for flow cytometric analysis can be achieved by the intravenous injection of 500 mg of BrdU. Tumors are biopsied several hours after BrdU injection and estimates of potential doubling time can be obtained from analysis at a single time point (5). By performing studies of this type in conjunction with the randomized clinical studies needed to assess the merits of different accelerated fractionation schedules, it should ultimately be possible to integrate kinetic data with other parameters needed to recommend the best treatment approach for individual patients (31).

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REFERENCES

1. Ang K. K., Xu F. X., Vanuytsel L. and van der Schueren E.: Repopulation kinetics in irradiated mouse lip mucosa. The relative importance of treatment protraction and time distribution of irradiation. Radiat. Res. 101 (1985), 162–169.
2. Baclesse F.: Carcinoma of the larynx. Br. J. Radiol. 3 (Suppl) (1949), 1.
3. Barendsen G. W. and Broerse J. J.: Experimental radiotherapy of a rat rhabdomyosarcoma with 15 MeV neutrons and 300 Kv x-rays. II. Effects of fractionated treatments applied five times a week for several weeks. Eur. J. Cancer 6 (1970), 89.
4. Barkley Jr H. T. and Fletcher G. H.: The significance of residual disease after external irradiation of squamous cell carcinomas of the oropharynx. Radiology 124 (1977), 493.
5. Begg A. C., McNally N. J., Shrieve D. C. and Karcher H.: A method to measure duration of DNA synthesis and the potential doubling time from a single sample. Cytometry 6 (1985), 620–626.
6. Bourne R. G., Kearsley J. H., Grove W. D. and Roberts S. J.: The relationship between early and late gastrointestinal complications of radiation therapy for carcinoma of the cervix. Int. J. Radiat. Oncol. Biol. Phys. 9 (1983), 1445–1450.
7. Brock W. A., Baker F., Spitzer G., Peters L. J., Bock S. and Williams M.: Radiosensitivity testing of human tumor cells in primary culture. Proc. Natl. Acad. Sci. (1987). (In press.)
8. Budihna M., Skrk J., Smid L. and Furlan L.: Tumor cell repopulation in the rest interval of split-course radiation treatment. Strahlentherapie 156 (1980), 402–408.
9. Denekamp J.: Changes in the rate of repopulation during multifractionation irradiation of mouse skin. Br. J. Radiol. 46 (1973), 381–387.
10. Dolbeare F. A., Gratzner H. G., Pallavicini M. G. and Gray J. W.: Flow cytometric measurement of total DNA content and incorporated bromodeoxyuridine. Proc. Natl. Acad. Sci. USA 80 (1983), 5573–5577.
11. Dorie M. J. and Kallman R. F.: Reoxygenation in the RIF-1 tumor. Int. J. Radiat. Oncol. Biol. Phys. 10 (1984), 687–693.
12. Ellis F.: Fractionation in radiotherapy. *In*: Modern trends in radiotherapy, pp. 34–51. Edited by T. J. Deeley and J. Wood, Butterworths, London 1967.
13. Field S. B., Morris C., Denekamp J. and Fowler J. F.: The response of mouse skin to fractionated x-rays. Eur. J. Cancer 11 (1975), 291–299.
14. Fletcher G. H.: Textbook of Radiotherapy, third edition, pp. 330–363, Lea & Febiger, Philadelphia 1980.
15. Gonzalez-Gonzalez D., Breur K. and van der Schueren E.: Preliminary results in advanced head and neck cancer with radiotherapy by multiple fractions a day. Clin. Radiol 31 (1980), 417–421.
16. Howes A. E.: An estimation of changes in the proportions and absolute numbers of hypoxic cells after irradiation of transplanted C3H mouse mammary tumors. Br. J. Radiol. 42 (1969), 441–447.
17. Karp J. E., Burke P. J. and Humphrey R. L.: Induction of serum stimulation and plasma cell proliferation during chemotherapy of multiple myeloma. Blood 49 (1977), 925–934.
18. Knee R., Fields R. S. and Peters L. J.: Concomitant boost radiotherapy for advanced squamous cell carcinoma of the head and neck. Radiother. Oncol. 4 (1985), 1–7.
19. Kronig S. and Friedrich W.: Physikalische und biologische Grundlagen der Strahlentherapie. Strahlentherapie 20 (Suppl) (1918).
20. Kummermehr J.: Regeneration in tumors. *In*: Abstracts of papers for the thirty-third annual meeting of the radiation research society, Abstract No Fd-4, May 5–9 Los Angeles 1985.
21. — Schropp K. and Neuner M.: Repopulation in squamous carcinoma AT 478 during daily irradiation. (Annual Report 1985.) Experimentelle Tumortherapie, Munich, GSF-Bericht 3/85, (1986), 31–39. Reviewed by Thames H. D. and Hendry J. H., Fractionation in Radiotherapy, Taylor and Francis, London 1987.
22. Maciejewski B., Gunhild P. B. and Trott K. R.: The influence of the number of fractions and of overall treatment time on local control and late complication rate in squamous cell carcinomas of the larynx. Int. J. Radiat. Oncol. Biol. Phys. 9 (1983), 321–328.
23. Malaise E. P., Charbit A., Chavaudra N., Combes P. F., Douchez J. and Tubiana M.: Change in volume of irradiated human metastases. Investigation of repair of sublethal damage and tumour repopulation. Br. J. Cancer 26 (1972), 43.
24. Martin D. F., Moulder J. E. and Fischer J. J.: Tumour response endpoints in the BA1112 rat sarcoma. Br. J. Cancer 41 (Suppl IV) (1980), 271–274.
25. Mitchell J. B., Bedford J. S. and Bailey F. M.: Dose rate effects in mammalian cells in culture. III. Comparison of cell killing and cell proliferation during continuous irradiation for six different cell lines. Radiat. Res. 79 (1979), 537–551.
26. Moulder J. E. and Rockwell S.: Hypoxic fractions of solid tumors. Experimental techniques, methods of analysis, and a survey of existing data. Int. J. Radiat. Oncol. Biol. Phys. 10 (1984), 695–712.
27. Olive P. L. and Durand R. E.: Effect of intercellular contact on DNA conformation, radiation-induced DNA damage, and mutation in Chinese hamster V79 cells. Radiat. Res. 101 (1985), 94–101.
28. Overgaard J., Hjelm-Hansen M., Vendelbo Johansen L. and Andersen A. P.: Comparison of conventional and split-course radiotherapy as primary treatment in carcinoma of the larynx. Acta Oncologica 27 (1988), 147–152.
29. Parsons J. T., Bova F. J. and Million R. R.: An evaluation of split-course technique for squamous cell carcinoma of the head and neck. Int. J. Radiat. Oncol. Biol. Phys. 6 (1980), 1645–1652.
30. Peracchia G. and Salti C.: Radiotherapy with thrice-a-day fractionation in a short overall time. Clinical experience. Int. J. Radiat. Oncol. Biol. Phys. 7 (1981), 99–104.
31. Peters L. J., Brock W. A. and Chapman J. D.: Predictive assays of tumor radiocurability. *In*: NCI Monograph (1987). (In press.)
32. Regaud C.: Principes du traitement des epitheliomas epidermoides par les radiations. Applicatin aux epidermoides de la peau et de la bouche. J. de Radiologie et de l'Electrologie 7 (1927), 297.
33. Resouly A. and Svoboda V. H. J.: Management of advanced head and neck squamous carcinoma by multiple daily sessions of radiotherapy and surgery. *In*: Progress in Radio-Oncology, pp. 339–347. Edited by K. H. Karcher, H. D. Kogelnik and G. Reinartz, Raven Press. New York 1982.
34. Sasaki T., Sato Y. and Sakka M.: Cell population kinetics of human solid tumors. A statistical analysis in various histological types. Gann 71 (1980), 520–529.
35. Saunders M. I. and Dische S.: Radiotherapy employing three fractions in each day over a continuous period of 12 days. Br. J. Radiol. 59 (1986), 523–525.
36. Schwarz G.: Zur Kenntnis der Roentgenreaktion der Haut. Der Begriff der Schadigungsquotienten. Strahlentherapie 18 (1924), 845–848.
37. Silvestrini R., Daidone M. G. and Gasparini G.: Cell kinetics as a prognostic marker in node-negative breast cancer. Cancer 56 (1985), 1982–1987.
38. Steel G.: Cell loss from experimental tumours. Cell Tissue Kinet. 1 (1968) 193–207.
39. Suit H. D., Howes A. E. and Hunter N.: Dependence of

response of a C3H mammary carcinoma to fractionated irradiation on fractionation number and intertreatment interval. Radiat. Res. 72 (1977), 440–454.
40. Svoboda V. H. J.: Radiotherapy by several sessions a day. Br. J. Radiol. 48 (1975), 131–133.
41. — Accelerated fractionation. The Portsmouth experience 1972–1984. *In*: Proceedings of Varian's fourth European clinac users meeting, Malta, May 25–26, 1984, pp. 70–75, Varian, Zug, Switzerland 1984.
42. Thames Jr H. D., Withers H. R., Peters L. J. and Fletcher G. H.: Changes in early and late radiation responses with altered dose fractionation. Implications for dose-survival relationships. Int. J. Radiat. Oncol. Biol. Phys. 8 (1982), 219–226.
43. Thomlinson R. H.: Reoxygenation as a function of tumor size and histopathological type. *In*: Conference on time and dose relationships in radiation biology as applied to radiotherapy, pp. 242–247. Edited by V. P. Bond, H. D. Suit and V. Marcial, Clearinghouse Federal Scientific Technical Information, Brookhaven National Laboratory Report BNL 50203 (C-57), Springfield, Virginia 1970.
44. Tubiana M. and Malaise E. P.: Cell kinetics of tumour growth and cancer treatment. Pathol. Biol. 21 (1973), 647.
45. Van den Bogaert W. and van der Schueren E.: Interim report of the EORTC Radiotherapy Cooperative Group, 1985.
46. Van Peperzeel H. A.: Effects of single doses of radiation on lung metastases in man and experimental animals. Eur. J. Cancer 8 (1972), 665.
47. Van Putten L. M. and Kallman R. F.: Oxygenation status of a transplantable tumor during fractionated radiotherapy. J. Natl. Cancer Institute 40 (1968), 41–45.
48. Vikram B., Mishra U. B., Strong E. W. and Manolatos S.: Patterns of failure in carcinoma of the nasopharynx. I. Failure at the primary site. Int. J. Radiat. Oncol. Biol. Phys. 11 (1985), 1455–1459.
49. Wang C. C.: Accelerated fractionation. *In*: Innovation in radiation oncology research, p. 239. Edited by H. R. Withers and L. J. Peters. Springer-Verlag, Heidelberg 1987. (In press.)
50. — Blitzer P. H. and Suit H.: Twice-a-day radiation therapy for cancer of the head and neck. Cancer 55 (1985), 2100–2104.
51. Wilson G. D., McNally N. J., Dunphy E., Karcher H. and Pfragner R.: The labelling index of human and mouse tumors assessed by bromodeoxyuridine staining in vitro and in vivo and flow cytometry. Cytometry 6 (1985), 641–647.
52. Withers H. R. and Mason K. A.: The kinetics of recovery in irradiated colonic mucosa of the mouse. Cancer 34 (1974), 896–903.
53. — Taylor J. M. G. and Maciejewski B.: The hazard of acceleraled tumor clonogen repopulation during radiotherapy. Acta Oncologica 27 (1988), 131–146.