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Time-Dose-Fractionation Relationships In Radiation Therapy [1,2]

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THE availability of supervoltage radiotherapy equipment has solved the technical problem of delivering an "adequate" dose of radiation to any tumor in the human body. However, the radiotherapist is still looking for means of increasing the radiocurability of cancer, for many neoplasms display limited radioresponsiveness or are located in or near important normal anatomical structures that do not tolerate cancericidal doses of radiations. Among current attempts to increase the radiocurability of tumors we have: irradiation under increased or decreased oxygen tension at the tumor level, and the combination of radiation therapy with chemotherapeutic agents.

Before undertaking new ventures, such as combining ionizing radiations with other agents for the treatment of cancer, we should learn more of the relative merits of different time-dose-fractionation schemes presently used in radiation therapy. We are aware of the great variations existing in the various centers regarding the dose-time-fractions combinations considered adequate in yielding significant curability with minimal damage to normal tissues. One observes that the total treatment time ranges from 1 to over 100 days and the total dose from 1500–10,000 rads. The possible variations in fractionation are shown in table 1.

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TABLE 1.—Fractionation of radiation doses

Continuous irradiation
Single teletherapy dose
Curietherapy
Fractionated irradiation
Uninterrupted course
Fractions per week
11 (twice a day for 5½ days)
6 (once a day for 6 days)
5 (once a day for 5 days)
4 (rest on Wednesday)
3 (every other day)
2 (separated by 72 or 96 hours)
1 (every 7 days)
Rest periods during treatment course ("split course")

In this paper I wish to discuss time-dose-fractionation problems an suggest possible areas for research.

PREVAILING TIME-DOSE-FRACTIONATION RELATIONSHIPS

As a member of the subcommittee on Time-Dose-Fractionation Rela tionships in Radiation Therapy, which forms part of the Committee fo Radiation Therapy Studies, I sent a questionnaire to all radiotherapist listed in the roster of the American Society of Therapeutic Radiologist and to selected Canadian, British, and French radiotherapists. The que tionnaire requested information on the prevailing techniques utilized fo the treatment of cancer of the larynx, tonsil, base of tongue, hypopharyn nasopharynx, and metastatic epidermoid carcinoma in the neck. It als asked for daily dose, total dose, total time, the number of fractions pe week, and any additional important details. Of 231 forms sent, 158 replie were obtained. Sixty-five letters with pertinent information or opinion were also received. A total of 95 forms were found adequate for analysis to avoid duplication, answers from radiotherapists in the same departmer were considered as one reply. There were so many different technique reported for the treatment of metastatic epidermoid carcinoma in the nec that we eliminated this site from the analysis.

Thirty centers expressed their units of radiation in roentgens, 26 i rads, and 39 did not specify. Consequently, the unit number quoted ca refer to roentgens or rads. Sixty-six percent of the centers expressed th daily dose in a fixed number whereas 34% offered a range of doses; th most frequently quoted daily exposure or dose was 200 (R or rads) i 39% of the centers. Field size was an important factor in guiding th daily and total doses, and the total time used; as a rule, larger fields we associated with smaller daily doses and longer total times. This point w particularly important in regard to the larynx.

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The techniques could be classified in 3 major groups: One group, 37 of 95 centers (39%), treated the patients 5 times a week, with daily fractions of 200 and total doses ranging from 5–7000 (R or rads) in 5–7 weeks. A second group, 25 of 95 centers (26%), administered daily doses of 150–200, gave 5 fractions per week, and administered total doses of 5000–7000 (R or rads) in 6–8 weeks, with small variations depending on the type of tumor. A third group, 21 of 95 centers (23%), gave larger doses per fraction (200–300 R or rads), but for a shorter total time. The British radiotherapists, as a rule, treated for 3 or 4 weeks whereas most American and Canadian radiotherapists treated for a longer time, ranging from 5–7 weeks. Only one radiotherapist continued to use orthovoltage roentgentherapy for all the patients, but 5% of the centers used it for larynx only, treating other lesions with supervoltage irradiation.

The most frequently reported fractionation was 5 fractions per week (85% of centers). Ten centers (10%) used 3 fractions per week, 2 of them for all patients, 7 for some of the patients, and in 1 a controlled study of 3 versus 5 fractions per week was under way. Nine centers (9%) treated with 6 fractions per week; in 5 of them, some of the patients were so treated, but in 4 centers all patients received 6 fractions per week. The deliberate interruption of the treatment course by rest periods ("split-course technique") was reported by 15 centers (16%); 12 did it on some patients, 1 in all patients, and 2 were conducting controlled studies to test the value of this method. The prevailing daily doses for those centers treating their patients with 5 fractions per week in 4 or more weeks varied from 100–275 (R or rads); the most frequently employed dose for all stated tumor locations was 200 (R or rads) (table 2).

TABLE 2.—Prevailing daily doses*

Site	Range of dose†	Most frequent dose†
Larynx	100–275	200
Tonsil	150–275	200
Hypopharynx	100–275	200
Base of tongue	100–275	200
Nasopharynx	100–275	200

*Centers treating 5 times/week in 4 or more weeks.
†Roentgens or rads.

The prevailing techniques for the treatment of carcinoma of the larynx are shown in table 3. In general, the treatment techniques used for larnyx were observed in other locations, but as a rule, the other sites required larger fields. Curietherapy was used as part of the main treatment in 15 institutions, whereas three centers used it for residual disease at the end of external irradiation. Some centers reduced the size of the field near the end of external irradiation to limit the high dose irradiated volume.

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Dr. J. K. Fowler, Secretary to the British Institute of Radiology Fractionation Working Party, has provided data on the prevailing techniques at 11 radiotherapy centers that will participate in a proposed fractionation clinical trial. This is shown in table 3a.

TABLE 3.—Prevailing radiotherapy techniques used for treatment of larynx

	Range	Most frequent
Dose per fraction*	100 to 300	200.
Total dose range*	3200 to 6500	6000.
Total time range	2½ to 8 weeks	6 week.
Field size	4 × 4 to 8 × 10	5 × 5.
Fractions per week	3/week to 6/week	5/week.
Radiation energy	Orthovoltage and supervoltage.	Supervoltage.

*Roentgens or rads.

TABLE 3a.—British centers: Prevailing techniques

Radiotherapy center	Fractions	Time (days)	Total dose (R)
A	16	21	5500
B	15	18	5500
C	13	28	5000
D	15	18	5250
E	15	18	5100
	12	25	5100
F	12	25	5500
G	25	32	6000
	30	39	6000
H	30	39	6000
I	30	39	6300
J	30	39	6000
K	30	39	6300

RADIOBIOLOGICAL CONSIDERATIONS

In the last few years various authors (*1–10*) have discussed the possible application of available radiobiological data to the solution of time-dose-fractionation problems in radiation therapy. The results of their experimental findings indicate that the greatest cellulicidal effect is obtained by single dose irradiation; however, as a rule, the concomitant damage to normal tissues necessarily included in the irradiated volume is not well tolerated by man in the usual clinical situations of cancer radiotherapy and we are forced to fractionate. Fractionation results in less efficient irradiation; the loss of effectiveness is related to the size and number of fractions, and to the time interval between them. This loss of cellulicidal effect has been demonstrated in animal and tissue culture systems (*11–13*). Published data indicate that the maximum effi-

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ciency in fractionated treatments is achieved with the least number of fractions.

Several workers have attempted to explain the loss of efficiency in fractionation (*2, 3, 6–10*). It appears that an exponential type of dose response curve with an extrapolation number of 1 would permit fractionation without loss of efficiency; yet in most instances the dose response curve using low-LET radiation has an extrapolation number of about 2. Consequently, any fractionation is less efficient than the single dose.

It has been found that normal and tumor tissues growing *in vitro* in cell cultures do not vary greatly in radiosensitivity. After a given dose of radiations (or between 2 fractions in a fractionated treatment) some repair of the cell damage takes place. Elkind (*11*) has shown that mammalian cells surviving an acute exposure to radiations rapidly repair the sublethal damage sustained (before the first postirradiation division). The Elkind type of recovery should be distinguished from repopulation of cell compartments which depends on cell division postirradiation, and its speed is related to cell cycle time and how irradiation has affected it.

Besides immediate and late cellulicidal effects, irradiation causes temporary arrest of mitosis. This subject has been reviewed by Scanlon (*14*), and Sambrook (*5*). The postirradiation cell division delay is dose dependent and varies in different tissues. The exact quantitative relationship between dose and duration of suppression of mitosis for different normal tissue and tumor cells is not known. Sambrook cites data from Koller and states: "a dose of 500 R can cause mitotic arrest for from 24 hours in jejunum epithelium in rats—to several days—in basal cell and squamous cell carcinoma in man." "After doses of the order of 2000–2500 R, mitosis appeared to be suppressed for several weeks."

It has been demonstrated experimentally that cells are more radiosensitive at the beginning of the S phase and again during the M phase of the generation cycle (*15, 16*). Tudway (*17*) has reported that cyclic variations in P^{32} uptake occur in tumor tissue under irradiation. He relates these to phases of the generation time of the tumor when it is most sensitive to irradiation and proposes that this be used as a guide to fractionation. The mechanism involved in this phenomenon is unknown, and the work must be confirmed by other workers before we can reach any conclusions.

Our success with fractionated irradiation of cancer in humans has been attributed to different cell repopulation kinetics in the normal versus the neoplastic irradiated tissues (*5, 8, 9*). There is little precise knowledge available regarding the generation time of the various normal and neoplastic tissues and how they are affected by irradiation. Some normal tissues are expected to show cell cycle times of around 24 hours, whereas malignant tumors show longer times; the majority show doubling times longer than 7 days and some as long as several months (*8, 9*). Consequently, fractionated irradiation permits greater relative damage to the tumor tissue, while normal tissues may repair loss of cells by repopula-

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tion mechanisms during the course of treatment. Rest periods during the treatment course (split-course technique) are utilized to enhance the repair process of normal tissues.

L. G. Lajtha, in a personal communication in 1962, stated that to overcome cell anoxia in human tumors, individual fractions of irradiation, as used clinically, should have a magnitude of 500 rads or more. Andrews (*10*) theorizes that small fractions are superior to large ones in respect to the oxygen effect in cancer radiotherapy, as they lie within the shoulder of the survival curve where the oxygenated and anoxic curves approach each other. A theoretical improvement of oxygenation of tumor tissue may be expected with fractionation. Irradiation-induced tumor regression in the first part of a treatment course may permit a closer proximity to the source of oxygen for the remaining cells during the last part of therapy.

Fowler (*6*, *13*) reported interesting experimental data on fractionated irradiation of the pig skin. He found that, for the type of effect he was seeking, a single dose of 1900 rads is equivalent to 5000 rads in 29 days given in 5 fractions per week or 3500 rads in 29 days in 5 total fractions. He concluded that the over-all time is relatively unimportant, at least between the 5th and 28th days and that the size and number of the individual fractions are more important in fractionation than the total time. With conventional fractionation when the over-all time is lengthened, an increase in the total dose is required; Fowler attributes this to decreased effectiveness of the small individual fractions and/or to slow tissue repair.

Various authors (*5*, *9*, *18*) have published estimates of the total doses and dose per fraction needed in various fractionation regimes. These are based on theoretical cell survival curve models, and on published radiotherapy results and animal experimental data. Table 4 shows Fowler's (*18*) estimate of total dose related to number of fractions; in column A the estimate is based on published clinical data and animal experiments, and the corresponding values in column B are based on a theoretical survival curve with $n = 2.8$ and $D_0 = 140$ rads. Dutreix (*19*) has published

TABLE 4.—Number of fractions-total dose relationships* (assuming 6000 rads in 30 fractions in 6 weeks as a basis)

Number of fractions	(A) Animal experiments and modal clinical data	(B) Survival curve $n = 2.8$, $D_0 = 140$ rads	Difference between estimates A and B (as % of A)
30	6,000	6,000	0
20	5,460 ± 50	5,040	−8
15	5,070 ± 70	4,380	−13
12	4,810 ± 70	4,020	−17
10	4,560 ± 70	3,790	−17
8	4,300 ± 80	3,540	−18
6	4,010 ± 80	3,260	−18
4	3,490 ± 120	2,980	−15
2	2,730 ± 160	2,700	−1
1	2,000 ± 250	2,560	+28

*From Fowler (*18*).

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