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Attachment (2) Factsheet Human Experimentation 143

SPLIT-COURSE RADIATION THERAPY PROJECT

VICTOR A. MARCIAL, MD

THE SPLIT-COURSE RADIATION THERAPY PROJECT is one of the prospective clinical collaborative trials presently conducted by the Radiation Therapy Oncology Group. Shortly after the methotrexate radiotherapy project was approved by the Committee for Radiation Therapy Studies, with subsequent funding by the National Cancer Institute, the CRTS gave its endorsement to the split-course project with the aim of testing the value of this technique in modern radiotherapy. For reasons beyond the wishes of the CRTS, the Project Director, and the Protocol Committee (composed of Dr. Henry Kaplan, Dr. William Powers, Dr. Mario Vuksanovic, Dr. William Caldwell, Dr. Marvin Lougheed, and Dr. Victor A. Marcial, as Chairman), the project could not be initiated until the Radiation Therapy Oncology Group began functioning early in 1971. During the year 1971, the project has been operating on a pilot basis. The project has the objectives of determining by means of a cooperative prospective clinical trial if split-course irradiation has similar or better tolerance, tumor control, and curability than standard uninterrupted radiotherapy in carcinomas of the nasopharynx, base of tongue, tonsillar fossa, uterine cervix (Stages III and IVA), and urinary bladder (Stages C and D_1). Only curative cases are included in this project. As of mid-October 1971, the following cases were included: base of tongue—9, tonsillar fossa—6, nasopharynx—11, carcinoma of the cervix—9, and bladder carcinoma—14. The project has progressed without difficulties except in some head and neck patients who have shown pronounced normal tissue reactions when large-field continuous irradiation has been given with daily fractions of 220 rads, with tumor doses of 6600 rads. It is expected that most of the institutions in the Radiation Therapy Oncology Group will begin accessing cases regularly in this study after January 1, 1972.

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RATIONALE AND HISTORICAL ASPECTS OF SPLIT-COURSE IRRADIATION

Split-course radiation therapy of cancer is based on the introduction of one or more planned rest periods of 2 or more weeks during the irradiation treatment course. This is in contradistinction from conventional radiotherapeutic techniques which usually consist of a continuous course of fractionated irradiation, 5 days per week for a total time of approximately 6 weeks and doses in the neighborhood of 6000 rads. With conventional continuous irradiation, patients frequently develop pronounced normal tissue reactions which may force temporary interruption or complete discontinuation of therapy. However, radiotherapists who have reported on split-course irradiation claim improved tolerance of this technique over conventional continuous radiotherapy.

An irradiation-free rest period during the radiation therapy course is expected to permit considerable repair of radiation-induced normal tissue damage, which may explain the better tolerance claimed. In addition, tumor regression occurs to a significant degree during the rest period. This should favor better oxygenation of the remaining tumor cells,[1] which, as a consequence, should be more radiosensitive in the second part of the treatment course. During the rest period, some tumor cell growth is expected, but its magnitude is not considered significant in view of the long doubling time displayed by most human malignant tumors.

Although split-course irradiation has been known since Coutard's[2] time (1935), it did not become generally accepted until the experiences of Sambrook[7] in England and Scanlon[8] in the U.S. were published. A survey conducted in the year 1965, revealed that 16% of American centers were utilizing split-course ir-

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radiation for some of their head and neck cancer cases.[4]

The two main theoretical advantages of split-course irradiation (improved patient tolerance and increased tumor curability) remain unproven on the basis of presently available data. The publications by Sambrook[7] and Scanlon,[8–11] and the experience accumulated at various radiotherapy departments, lend some support to the claimed merit of better tolerance in the split-course method, but these are based on clinical impressions and not on statistically documented clinical investigation. Improved survival with the split-course method vs. conventional uninterrupted therapy has also been claimed in Sambrook's and Scanlon's publications. Holsti[3] presented preliminary clinical data in September 1969, which suggested better tumor control with split-course irradiation.

Split-course irradiation has been of particular value in the treatment of carcinoma of the upper air and food passages, where mucosal reactions to irradiation are a frequent problem. Scanlon[8] published a retrospective study of the treatment results of carcinoma of the nasopharynx in which he said that split-course irradiation gives better treatment tolerance and curability than continuous irradiation. Marcial and Frias[5] reported the results of a prospective pilot project in a group of patients with advanced base of tongue carcinoma (the main tumor or metastatic node measured 5 cm or more in diameter), in which two split-course irradiation techniques were compared with two uninterrupted techniques. The split-course technique with two portions, each consisting of doses of 3000 R in 2 weeks delivered in 300 R fractions five times a week, separated by a 3-week rest period, resulted in the best 2-year tumor-free survival. At the Radiotherapy Division of the Puerto Rico Nuclear Center and the I. González Martínez Hospital, where split-course therapy has been used since 1963, with accumulated experience in close to 1,000 cases, this technique has become the preferred therapy for advanced carcinomas of the head and neck. Regardless of volume, 300 rad fractions are administered five times a week for doses of 3000 rads in a 2-week rest period, and a repetition of the 3000 rads in 2 weeks.

Irradiation of the pelvis, which frequently elicits intestinal and urinary bladder reactions, may be done with the split-course technique. Scanlon[9] advocates split-course irradiation for carcinoma of the urinary bladder. I claims that the tolerance to this technique better and that the curability is as good with continuous irradiation. He has favored dose of 5000 to 5500 rads in two divided do courses, each half administered in 12 to days and separated by a 3- to 4-week rest p riod. Miller[6] has found that split-course ir diation of carcinoma of the urinary bladd with fractions of 300 rads, five times per we up to 3000 rads, followed by a rest period of to 3 weeks and a repetition of the first pa (3000 rads in 2 weeks), gave a higher complic tion rate but resulted in better tumor curab ity than conventional continuous irradiatio At the Puerto Rico Nuclear Center, the a cepted split-course regimen for bladder canc is 275 rads, five times per week, up to 27 rads, followed by a rest period of 3 weeks an then a repetition of the first part (2750 rads i 2 weeks). The utilization of split-course radi tion therapy for carcinoma of the uterine ce vix has not been highlighted so far in th medical literature. At the Puerto Rico N clear Center, a small number (12) of wome with advanced (unfavorable Stage IV) lesio of carcinoma of the uterine cervix have bee treated with split-course irradiation to dete mine their tolerance to this technique. It w found that a fraction dose of 250 rads, fi times a week, up to 2500 rads in 2 weeks, fo lowed by a rest period of 2 to 3 weeks and repetition of the irradiation, is well tolerat by these patients.

Split-course irradiation has the followi apparent or potential advantages over uni terrupted therapy: better patient tolerance large volume therapy; permits larger fractio doses; tumor regression which usually occu during the rest period offers psychologic ben fits to the patient and frequently permits duction of field size for the second part treatment, and better oxygenation of t tumor in the second part of therapy may i prove curability. In addition, increased util zation of split-course therapy should result a shorter hospital stay for the hospitalized p tient, a smaller number of treatment visits fo the ambulatory patient, and less loading the department treatment facilities.

OBJECTIVES AND END POINTS OF THE SPLIT-COURSE RADIATION THERAPY PROJECT

The objectives of this study are: to det mine by means of a cooperative clinical trial

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split-course irradiation offers better treatment tolerance, tumor control, and curability than standard uninterrupted radiotherapy for carcinoma of the base of the tongue, tonsillar fossa, nasopharynx, urinary bladder Stages C and D, and uterine cervix Stages IIIA, IIIB, and IVA.

The end points of this study will be to make an accurate determination of the following parameters:

- Patient's tolerance to treatment as shown by completeness of therapy with both techniques.
- Reduction of necessary irradiation volume from first to second half of therapy.
- Immediate normal tissue reactions.
- Time from beginning of therapy to complete clinical disppearance of tumor from the irradiated volume.
- Change in patient's weight midway and at the end of therapy.
- Control of primary tumor and its direct extensions.
- Control of metastatic tumor in the irradiated volume.
- Time from the end of therapy to appearance of recurrences.
- Late tissue reactions such as fibrosis and necrosis in the irradiated volume.
- Need of additional therapy (irradiation or surgery).
- Time from beginning of therapy to death by tumor.
- Frequency of distant metastases.
- Survival at 1, 2, 3, 4, and 5 years.
- Normal tissue tolerance of surgery for persistent or recurrent tumor in the irradiated volume.
- Curability achieved with surgery for persistent or recurrent tumor in the irradiated volume.
- Frequency of regional metastases in patients who at the beginning of therapy had clinically negative nodes in both techniques.

STUDY PATIENT POPULATION

All patients who are registered in the collaborating radiotherapy departments with untreated carcinoma of nasopharynx, tonsillar fossa, base of tongue, uterine cervix Stages IIIA, IIIB, and IVA, and urinary bladder Stages C and D_1 will be included in this study. Excluded are patients over 80 years of age, patients with adenocarcinoma or other cancer (previous or present) except skin carcinoma, distant metastases, when the medical condition of the patient makes treatment completion unlikely, and when the prospects for follow-up appear to be unpromising.

PROCEDURE

Patients who are registered in the collaborating centers with the stated diagnoses and who meet the criteria of the study will be submitted to the pretreatment studies stated in the project protocol and the tumor will be staged according to a system proposed by the Committee for Radiation Therapy Studies for head and neck cancer, the International Classification for uterine cervix cancer, and the American Joint Committee for Cancer Staging for urinary bladder cancer.

When the eligible patient has been clinically evaluated and staged and the pretreatment studies have been performed, the collaborating center will telephone the Radiation Therapy Oncology Group Center for the random allocation of the case to one of the two treatment categories. Randomization will be made by site, stage, socioeconomic level, sex for carcinomas of the head and neck, and treatment category (continuous vs. split-course irradiation).

The protocol calls for special pretreatment management of the teeth, correction of urinary or rectal obstruction, and raising hemoglobin levels to at least 10 g.

Treatment will be given with teletherapy energy of 1 mev or higher with a minimal source skin distance of 75 cm. The various irradiation techniques to be utilized for each site and the choice and size of treatment fields are described in the protocol. Verification films will be taken of all the main fields of treatment. Reduction of the size of treatment field will be permitted during therapy according to the instructions included in the protocol.

Patients who are randomly allocated to *split-course irradiation* will be treated as follows:

Head and neck cases will receive 10 fractions of 300 rads each, 5 times per week, up to a dose of 3000 rads in 2 weeks, followed by a 3-week rest period and a repetition of the irradiation identical to the first part: 10 daily fractions of 300 rads each up to a dose of 3000 rads. Table 1 shows that the Nominal Standard Dose for this irradiation plan is 1908 rets when the total time is 49 days. The NSD is

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TABLE 1. Split-course Project, Nasopharynx, Base of Tongue, Tonsillar Fossa

	Irradiation plan	NSD*
Split	300 rads × 10 3 wks. rest 300 rads × 10	1908
Continuous	220 rads × 30	1934

* Based on Kroening, P. M., and Deiterman, L. H.: A table for the normalization of time-dose relationships. *Am. J. Roentgen.* 112: 803–805, 1971.

1914 rets when the total time is 47 days and 1902 rets when the time is 50 days.

Uterine cervix cases will be treated with 10 fractions of 250 rads each, five times a week, up to a dose of 2500 rads in 2 weeks. This will be followed by a rest period of 2 weeks and a repetition of the irradiation identical to the first part: 10 fractions of 250 rads, five times per week, up to a dose of 2500 rads in 2 weeks. Table 2 shows that the NSD for this regime is 1615 rets when the total time is 42 days, 1625 rets when the time is 40 days, and 1610 when the time is 43 days.

Urinary bladder cases will be treated with 10 fractions of 275 rads each, five times per week, up to a dose of 2750 rads in 2 weeks followed by a rest period of approximately 3 weeks and a repetition of the irradiation identical to the first part: 10 fractions of 275 rads, five times per week, up to a dose of 2750 rads in 2 weeks. Table 3 shows that the NSD for this treatment plan is 1749 rets when the total time is 49 days. For the total times of 47 and 50 days, the NSD is 1754 rets and 1743 rets, respectively.

Patients whose random allocation is for *continuous irradiation* will be treated as follows:

Head and neck cases will receive continuous irradiation of 30 daily fractions of 200 to 220 rads each, five times per week, for a total of 6600 rads in 6 to 6½ weeks. Rest periods during weekends, etc., should not exceed 3 days each. When given with fractions of 220 rads and total time of 42 days, this irradiation plan will have an NSD value of 1934 rets. For to times of 40 and 43 days, the NSD is 1947 a 1927 rets, respectively. When the patient ceives a tumor dose of 6600 rads with 200 r fractions in 45 days, the NSD is 1874 rets.

Uterine cervix cases will receive 30 fractio of 170 rads each, five times per week, for a t tal of 5040 rads in approximately 6 weeks. Re periods during weekends should not exceed days. Table 2 shows that this plan of tre ment has an NSD value of 1477 rets when t total time is 42 days. The NSD is 1487 rets f 40 days and 1472 rets for 43 days. These v ues are lower than when the patient receiv 5000 rads with fractions of 200 rads in 35 da when the NSD is 1560 rets.

Urinary bladder cases will receive 30 fra tions of 200 rads each, five times per week, f a total dose of 6000 rads in 6 weeks. Rest pe ods during weekends should not exceed 3 da each. The NSD value for this continuous the apy when administered in 42 days is 1758 re With total times of 40 and 43 days, the NS will be 1770 and 1752 rets, respectively.

Uterine cervix cases will have a standard i tracavitary application of radioactive materi in the vagina and the uterus 2 weeks follo ing external irradiation. The dose from th intracavitary irradiation will be 4000 rads i approximately 4 days, calculated at point when a standard colpostat-tandem arrang ment is used or at 2 cm from the center of th linear source, when a long tandem is em ployed. No additional radiotherapy or surger is permissible besides the stated treatment pr gram mentioned in the protocol unless th case is considered a treatment failure. Whe additional therapy needs to be given it shoul not be administered earlier than 2 months fo lowing protocol irradiation.

Clinical evaluations of the patient with em phasis on the status of the tumor and norma tissues will be performed prior to therap during therapy, and at regular intervals there after. Special forms are provided for reportin pretreatment evaluation, treatment data, fo

TABLE 2. Split-course Project, Cervix

	Irradiation plan	NSD*
Split	250 rads × 10 2 wks. rest 250 rads × 10	1615
Continuous	170 × 30	1477

* Based on Kroening, P. M., and Deiterman, L. H.: A table for the normalization of time-dose relationships. *Am. J. Roentgen.* 112: 803–805, 1971.

TABLE 3. Split-course Project, Urinary Bladder

	Irradiation plan	NSD*
Split	275 rads × 10 3 wks. rest 275 rads × 10	1749
Continuous	200 rads × 30	1758

* Based on. Kroening, P. M., and Deiterman, L. H. A table for the normalization of time-dose relationship *Am. J. Roentgen.* 112: 803–805, 1971.

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in- and end-of-treatment normal tissue reactions and tumor response, post-irradiation evaluations, and death information.

SAMPLE SIZE CALCULATIONS

The Statistical Center for this study, directed by Dr. Marvin Zelen, is of the opinion that the information necessary to reach an inference for comparing the survival associated with two different therapies depends on the number of patients entered, and the years of follow-up after patient accession ceases. The Statistical Center has prepared tables which state the probability of detecting differences between a control and treated group as a function of average patient entry per year and years of additional follow-up. The comparison is made on the difference between the median survivals. The median survival can be converted into a 5-year survival figure using a conversion table prepared by Dr. Zelen's group. This group has concluded that the sample sizes necessary for this protocol cannot be realistically calculated at this time, since the accession rates are unknown. Once the trial starts, they will be in a better position to estimate required sample size.

DISCUSSION

If the result of this study justify wider applicability of split-course radiotherapy, there are a series of questions that future studies should attempt to answer. Those related to the rest period are: When should it start, what is the optimal duration, and what are the merits of more than one rest period? The questions which relate to fractionation in split-course therapy are: Should the fraction dose be the same as in comparable uninterrupted therapy, what are the clinical limits of reduced fractionation in split-course therapy, and should one vary the number and size of the fractions in the second part of therapy? We also need to determine if split-course therapy should have a higher total dose level than continuous irradiation to compensate for the rest period, when the size of the fractions are the same with both techniques.

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