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### Fractionation in Radiation Therapy of Carcinoma of the Uterine Cervix: Results of Prospective Study of 3 VS. 5 Fractions per Week<sup>1</sup>

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Dose fractionation in radiation therapy of cancer has been a subject of frequent discussion during the last 15 years. A recent publication by the senior author reviewed various aspects of this problem [7]. We are yet far from having available scientifically sound clinical experimental data on which to base the dose-time-fractionation schemes that would result in optimal radiation therapy for our cancer patients. Optimal radiation therapy should lead to the highest curability of cancer with an acceptable level of normal tissue damage.

A survey of fractionation schemes for epidermoid carcinoma of the upper air and food passages prevalent in American radiotherapy centers, conducted in the year 1965 [7], revealed that the majority of radiotherapists prefer a 'conventional' technique which is as follows: individual fraction doses of 200 rads, 5 fractions per week, and total doses of approximately 6000 rads. The reason for the acceptance of this 'conventional' technique seems to be historical and based on COUTARD's original work [3]; its preservation with time only proves that in general it is reasonably well tolerated by human normal tissues.

Except for tumors of limited volume such as T<sub>1</sub> neoplasms of the oral and pharyngeal cavities, and early Stage I carcinoma of the cervix, we find that the 'conventional' technique as used for epidermoid carcinoma, results in very modest curability. To improve on this, we are forced to employ one or more adjuvant methods, namely, a boost of additional external irradiation, interstitial or intracavitary irradiation, or a surgical procedure.

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For the benefit of our patients we must explore the value of unconventional radiation therapy schemes through well controlled clinical trials that may lead us to optimal dose-time-fractionation combinations. Among the areas to be explored I would like to mention: reduced fractionation of total dose, shorter and longer inter-fraction time periods, variations in total dose-time combinations, 'split-course' regimes, combinations of fractionated and continuous (low dose rate) irradiations, etc. At all times we must use as controls the accepted conventional irradiation techniques.

The present report relates to the preliminary evaluation of a clinical trial in which we have used a reduced fractionation scheme of the external irradiation of carcinoma of the uterine cervix.

#### *Material and Methods*

In July 1963 we began a prospective study with the objective of comparing a new fractionation regime of three fractions per week *versus* our conventional five fractions per week practice, utilizing the same total weekly dose. Patients who came for curative radiotherapy were registered in the Department's accession book; odd numbers received their radiotherapy in three fractions per week and even numbers in five fractions per week. Private cases were not required to be registered in this study, unless the particular attending radiotherapist wished to do so.

An initial revision of cases with a minimum one year follow-up revealed an error of randomization; patients were not being accessed evenly in the two fractionation programs. From then on we began to access the cases in our bio-statistician's office by site and by stage (for carcinoma of the cervix). During the course of this study we have felt that the delivery of our weekly dose in three instead of five fractions, at no time has given undue or excessive reactions that may have motivated the interruption or alteration of the treatment plan. The reduced fractionation has given us extra machine time and has reduced some of the patient congestion in our busy department; this is so on Tuesdays and Thursdays.

For the purpose of this presentation we have analyzed 200 consecutive cases with the diagnosis of carcinoma of the cervix uteri who have a minimal follow-up period of two years. We have excluded from the study the following patients: cases treated with orthovoltage roentgentherapy and post-surgical cases.

Table I. Stage distribution: 200 cases

Stage	3/week		5/week		Total	
	No.	%	No.	%	No.	%
I	24	22	20	22	44	22
IIA	23	21	26	28	49	24
IIB	20	19	22	24	42	21
III	33	31	19	21	52	26
IV	8	7	5	5	13	6
Total	108	100	92	100	200	100

In Table I, one may observe the distribution of cases by stage and fractionation program. A total of 108 patients were treated three times per week and 92, five times per week. No difference is observed in the distribution of Stage I cases; however, a tendency to have a concentration of earlier cases (Stages IIA and IIB) is noted in the five-fractions group and, in addition, more advanced cases (Stages III and IV) seem to have accumulated in the three-fractions group.

No significant difference is observed in the histological diagnoses in the two groups; 8% of all cases were diagnosed as adenocarcinoma and 92% as epidermoid carcinoma.

There exists no significant difference in the age distribution in the two groups; the youngest in the test cases was 23 years of age, the oldest 88, and the median age for this group was 52 years. The five-fractions-per-week group had a woman 27 years of age as the youngest and one 84 as the oldest with a median age of 52 years.

#### *Treatment Technique*

Our accepted technique for the treatment of carcinoma of the cervix consists of external cobalt teletherapy followed by intracavitary curietherapy; this technique has given satisfactory five-year survival in our department (Table II) with a complication rate of less than 3%. In the initial period of this study our practice was to administer cobalt teletherapy to patients with AP pelvic diameters of 18 cm or over; patients with smaller pelvic diameters were treated with orthovoltage roentgen-therapy. Three years ago we stopped using orthovoltage roentgen-therapy for carcinoma of the uterine cervix.

The external irradiation for the patients included in this analysis was delivered by an El Dorado Co<sub>60</sub> unit, 8000 Ci, source-skin distance of 80 to 100 cm, anterior and posterior pelvic fields of 16 × 12 cm, and calculated exposures at the mid pelvic plane of 4500 R in approximately 42 days. Individual fractions were 150 R for the conventional five-fractions per-week group and 250 R three times per week for the study cases. Total exposures of 750 R per week were given to both groups.

The intracavitary curietherapy was administered with an intrauterine tandem containing three sources of 10 mg of radium (or equivalent Co<sub>60</sub>) each and a vaginal colpostat with two sources of 10 mg each. The most frequently used colpostats were the Ter-Pogossian and the Fordyce types. Narrow vaginas were treated with a long tandem containing four or five sources of 10 mg each, to cover the uterine cavity and part of the vaginal canal. Intracavitary therapy exposures have been approximately 4000 R calculated at point A.

Table II. Carcinoma of the cervix uteri cobalt teletherapy and curietherapy, 1958-1961. Percent survival<sup>1</sup>

Stage	No. cases	Years				
		1	2	3	4	5
I	13	100	100	92	92	92
II	40	98	93	92	80	75
III	38	85	59	56	53	50
IV	16	88	56	38	31	19
Total	107	92	76	72	64	60

<sup>1</sup> 2 lost cases excluded.

*End Points*

The following end points have been evaluated in both groups: treatment-induced symptoms during external irradiation, post-curietherapy early treatment reactions, completeness of planned treatment, long-term treatment complications, and two-year survival.

*Results of the Study*

Follow-up information at two years post-radiotherapy was obtained in all but 7 cases.

### A. External Irradiation-Induced Symptoms

The most frequently encountered external irradiation-induced symptoms were diarrhea and soreness on urination; these were found in 14% of the five-fractions-per-week group and in 16% of the three-fractions-per-week group. In no case was the external irradiation interrupted because of reactions to treatment (Table III).

Table III. Treatment related symptoms. Percent frequency

	3/week	5/week
End of external irradiation	14%	16%
Post curietherapy	54%	56%

### B. Post-Curietherapy Symptoms

The most common post-curietherapy reactions were rectal tenesmus with or without diarrhea and/or bladder symptoms such as frequency and burning on urination. These symptoms usually appeared by the end of the first week post-curietherapy and, in the majority of cases, had subsided by one month post-curietherapy. The symptoms were present in 54% of cases in the study group and in 56% of cases in the five-fractions-per-week group (Table III).

### C. Frequency of Intracavitary Curietherapy

Table IV shows the distribution of cases who could not have curietherapy, classified by stage and by fractionation regime. All patients with Stage I and II A lesions completed their treatment with intracavitary curietherapy. One can observe the tendency to have less number of patients with curietherapy in the five-per-week fractionation; 18% of the Stage III, and 50% of the Stage IV in the test cases did not have curietherapy, *versus* 32% for Stage III and 80% in the Stage IV in the five-per-week fractionation.

### D. Long Term Severe Bladder and/or Rectal Complications

Table V shows the distribution of long term severe rectal and/or bladder complications; 10% of the test cases and 11% of the five-fractions-per-

week cases showed this complication. Colostomies were required in two test cases and in three of the patients in the five-fractions-per-week group.

Table IV. Patients without curietherapy

Stage	3/week No.	%	5/week No.	%
I	0/24	0	0/20	0
IIA	0/23	0	0/26	0
IIB	0/20	0	1/22	4
III	6/33	18	6/19	32
IV	4/8	50	4/5	80
Total	10/108	9	11/92	12

#### E. Two-Year Survival

The two-year survival achieved in the test cases in this study is shown in Table VI. The last column on the right shows the percent of two years overall survival and next to it is the percent of cases with no evidence of disease. After excluding five cases that could not be traced at the end of two years, we are left with 103 test cases of which 72% lived two years and 65% had no evidence of disease. The two years survival by stage of the disease for the 'conventional' five-per-week fractionation is shown in Table VII. In this group, 2 cases could not be traced at the end of two years and have been excluded for the calculation of survival; out of 90 patients eligible, 66% survived two years and 59% had no evidence of disease. In Table VIII we show a comparison of the two-year survival in both groups. No significant difference in the two-year survival is noted in the Stage I cases. A tendency towards a better survival in the test cases is noted in the Stages II A, II B, III and IV; this difference appears more notable in the Stage III group. Table IX shows a comparison of two-year survival in the test cases, the controls ('conventional fractionation'), and the previously treated group of cases seen during the years 1958-61. This latter group was treated with a technique similar to the controls. There appears to be a tendency to better survival in the 1958-61 group, particularly in the Stage II cases. Noteworthy is the fact that there was a concentration of Stage IV cases in the 1958-61 group of cases, inasmuch as at that period we were treating most of our carcinoma of the cervix

cases with orthovoltage roentgentherapy and telecobalt was restricted to Stage IV cases and to patients with antero-posterior pelvic diameters of 18 cm or more. Consequently, the two-year survival achieved for all Stages in the 1958-61 group of 76% represents a more meaningful sur-

Table V. Severe rectal and/or bladder complications. 179 cases with complete treatment

Cases with severe rectal or bladder complications	3/week 10/98 (10%)	5/week 9/81 (11%)
Hemorrhagic cystitis	2 (2%)	3 (4%)
Bladder and rectal fistulae	-	1 (1%)
Rectal fistula	1 (1%)	-
Rectal stenosis	2 (2%)	-
Hemorrhagic proctitis	6 (6%)	5 (6%)

Table VI. Two year survival: 3/week. All cases<sup>1</sup>

Stage	Number followed	2-year survival		% 2-year survival	
		NED	AWD	NED	Overall
I	23	20	1	87	91
IIA	21	18	1	86	90
IIB	20	13	1	65	70
III	31	13	4	42	55
IV	8	3	-	38	38
Total	103	67	7	65	72

<sup>1</sup> Lost cases excluded: 1 Stage I; 2 Stage IIA; 2 Stage III.

Table VII. Two-year survival: 5/week. All cases<sup>1</sup>

Stage	Number followed	2-year survival		% 2-year survival	
		NED	AWD	NED	Overall
I	20	19	-	95	95
IIA	24	16	3	67	79
IIB	22	13	2	59	68
III	19	4	1	21	26
IV	5	1	-	20	20
Total	90	53	6	59	66

<sup>1</sup> Lost cases excluded: 2 Stages IIA.

vival than what was achieved in the test cases and the controls in this study.

Table VIII. Two-year survival: All cases<sup>1</sup>

Stage	Percent two-year survival		Overall	
	NED 3/week	5/week	3/week	5/week
I	87	95	91	95
IIA	86	67	90	79
IIB	65	59	70	68
III	42	21	55	26
IV	38	20	38	20
Total	65	59	72	66

<sup>1</sup> Lost cases excluded.

Table IX. Carcinoma of the cervix uteri. Cobalt teletherapy and curietherapy. Two-year survival

Stage	3/week		5/week		1958-1961	
	No.	%	No.	%	No.	%
I	23	91	20	95	13	100
II	41	80	45	76	40	93
III	25	64	13	38	38	59
IV	4	75	1	—	16	56
Total	93	78	79	75	107	76

*Discussion*

The results of this study are preliminary in view of the fact that we do not have yet three or five year survival figures; needless to say, these would be more reliable for the evaluation of the absolute effectiveness of these two techniques. In addition, by October 1, 1967, we have registered an additional group of 355 patients in this study, which makes a total of 555 cases for future analysis. This more recent group of cases will permit us to achieve better statistically valid data.

In comparing these two groups of cases we must remember the fact that the test cases had a larger concentration of advanced patients. An

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additional adverse factor is constituted by the fact that in the test group there was a larger percent of cases, with intervals between external and internal irradiation of 3 weeks or longer. (Table X). A previous publication of ours points out the fact that when this interval is prolonged, it may be detrimental to the patient [1]. Another dissimilarity in the two groups is constituted by the fact that there was a larger accumulation of private cases in the controls than in the test group (11 *versus* 4). Table XI shows the difference in survival during the study period between indigent and non-indigent patients; private cases have a better survival.

We were able to apply curietherapy more frequently in the test cases than in the conventional group although the difference between 91% and 82% respectively, is not statistically significant. The incidence of normal tissue reactions at the end of external irradiation and in the immediate post-curietherapy period, and the long-term severe rectal and/or bladder complications were not different in the two groups. We may conclude that the administration of external irradiation in three-fractions-per-week instead of the usual five-fractions does not increase the normal tissue reactions. The authors are aware of the fact that other centers have used larger individual fractions (200 to 250 rads) for their daily fractionation with weekly doses of as much as 1000 rads; these doses have not been tolerated by our patients. Regardless of the preliminary nature of this report, one can observe a consistent tendency to a more favorable outcome in the cases treated with three-fractions-per-week.

One disturbing finding in this study is the fact that our overall results during the time of this study in the treatment of carcinoma of the cervix seem to be slightly inferior to the previously achieved ones in the department. We may speculate on the possible factors causing this change in survival. Among the possible reasons, we have the fact that at the time of the study we were taking cytology smears before, during, and after irradiation by scraping the cervix; at the same time that we were taking

Table X. Distribution of time interval from exterior irradiation to curietherapy (179 cases)

	3/week	5/week
0-6 days	18 (18%)	16 (20%)
7-13 days	26 (26%)	26 (32%)
14-20 days	26 (26%)	26 (32%)
21 days and over	28 (28%)	13 (16%)

Table XI. Carcinoma of the cervix uteri<sup>1</sup>. Two-year survival by stage and socio-economic status

Stage	Indigent			Non indigent <sup>2</sup>		
	No.	Survival	%	No.	Survival	%
I	36	34	94	9	8	89
IIA	42	35	83	8	8	100
IIB	39	27	69	11	10	91
III	36	20	56	2	1	—
IV	5	4	80	1	0	—
Total	158	120	76	31	27	87

<sup>1</sup> Cases treated with cobalt teletherapy and curietherapy.

<sup>2</sup> Including 17 cases not entered in the fractionation study.

biopsy specimens. Both tests were done for the study of radiation changes in the tissues. These two factors added to frequent pelvic examinations may have affected the prognosis. Both, the biopsy procedure and frequent palpation of cervix tumors have been implicated by KOTTMEIER [6] and GLUCKSMANN [5] as possible factors leading to infection and poor prognosis.

An analysis of post-treatment distant metastases constituting the initial manifestation of active neoplastic disease, revealed a 4% frequency in the 1958-61 group of cases, 4% in the test cases and 7% in the patients treated with five-fractions-per-week. The observed small difference between the test cases and the controls is not statistically significant.

Besides the specific knowledge derived from this study, we have learned a number of facts related to the operation of clinical trials and the randomization of patients. Needless to say, a number of subjective factors influenced this study. The random choice of treatment category should be made in a way that clinicians' bias is excluded; at the present time this is done in our bio-statistician's office. Cases should be randomized by stage and, ideally, by socio-economic status.

When we analyzed this study, we found that the clinicians had influenced the choice of dose in a number of cases. For example, some cases were given as much as 5000 R in the mid-pelvis for their external radiotherapy and the curietherapy exposures in a few patients exceeded 4000; in others this was slightly below 4000 R. Yet, an analysis of the survival in these cases with higher or lower doses did not show difference in survival from the rest of the group. In a number of cases the reasons for

administering a larger external dose of irradiations were: little tumor regression at the end of therapy, the case had an adenocarcinoma, or no curietherapy seemed feasible.

In choosing our total doses we have not corrected for decreased fractionation. BOTSTEIN [2] has suggested that we should lower the dose from 10 to 15% when changing from a daily to a three-time-per-week fractionation. FLEMING and WIERNICK [4] have suggested a reduction from 15 to 20% when changing from daily to three-per-week fractionation. Fowler, irradiating pig skin, needed a reduction of 20% when a change is made from 21 fractions to 9 fractions for 28 days total time. We did not choose to reduce our dose in view of the fact that our results prior to the study period had revealed an incidence of complications of less than 3%. However, our experience in this study has shown that the complications were as high as 10% with both techniques. This may have been due to the non-study factors discussed previously.

#### *Conclusion*

A random prospective study of fractionation of external irradiation of 200 cases of carcinoma of the cervix with a minimal follow-up period of two years has been presented. Both the test cases and the controls received the same weekly and total doses of external irradiation and this was followed by a standard curietherapy application, which had produced satisfactory five years results. The only difference in the two groups was that the test cases received their irradiation in three-fractions-per-week *versus* five-fractions-per-week in the controls.

The preliminary results of this study suggest a more favorable situation regarding completeness of treatment and survival, when the stated weekly dose is delivered in three-fractions *versus* the conventional fractionation; this is more notable in the advanced cases. The complication rate and distant metastases were not significantly different in the two groups.

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