Attachment ③ Factsheet Human Experimentation 156

Prognostic Importance of the Intracavitary Radium Arrangement in the Treatment of Carcinoma of the Uterine Cervix[1]

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ABSTRACT—In many patients, it is not feasible to apply a combination of tandem and colpostat in the treatment of carcinoma of the cervix uteri, *e.g.*, in elderly patients or in instances of residual disease in fornices and vaginal walls or shrinkage of the vaginal vault. The authors have employed a long tandem with a protruding source into the upper vagina; the effects of these respective modalities upon prognosis are compared.

INDEX TERMS: Cervix, Cancer, radiotherapy • Uterus, Cancer, radiotherapy • Vagina, cancer

Radiology 95:175–180, April 1970

RECURRENCE of invasive carcinoma of the cervix uteri following radiotherapy has usually been found to be the result of a less than ideal application of radium (10); for this reason, the treatment technique should be modified or other modalities added when optimal placement of a standard radium applicator is not possible (3, 5). External irradiation followed by intracavitary application of radioactive sources has been employed for all stages of invasive carcinoma of the cervix uteri seen at this institution (1, 2).

Although the standard applicator consists of a combination of tandem and colpostat, such a placement is not always feasible. If the vaginal canal is narrow, as in elderly patients, or if there is residual disease in fornices and vaginal walls or shrinkage of the vaginal vault, the colpostat will not remain in the proper position. In such cases, a long tandem with a protruding source into the upper vagina is used. This report concerns the two different modalities of radium applicators used in our institution, and particularly the influence that each has had upon prognosis.

MATERIAL

A total of 737 cases of invasive carcinoma of the cervix uteri were seen at the I. González Martínez Hospital in San Juan from January 1958 to December 1962. Of this number, 202 cases were excluded from this analysis. Forty-two patients were not treated, either because their general condition was too poor to justify treatment or because the patient refused treatment at this institution or left for treatment elsewhere. Fifteen patients were initially treated by surgery elsewhere and were referred to our department because of persistent or recurrent tumor. Nineteen cases were classified as carcinoma of the cervical stump. The remaining 126 patients were excluded for a number of reasons, as explained in TABLE I.

External Irradiation: The 535 remaining patients were treated with external irradiation followed by intracavitary curietherapy. An exposure of 4,000 R, calculated at the midplane of the pelvis, was administered over a period of six weeks by means of anterior and posterior fields (18 × 12 cm) plus sciatic fields (8 × 10 cm) at

[1] From the Radiotherapy and Cancer Division of the Puerto Rico Nuclear Center, the Radiotherapy Department of the I. González Martínez Oncologic Hospital, and the University of Puerto Rico School of Medicine, San Juan, Puerto Rico. Presented at the Fifty-fifth Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, Ill., Nov. 30–Dec. 5, 1969.

This investigation was supported in part by Public Health Service Grant T1 CA 5169-05. sjh

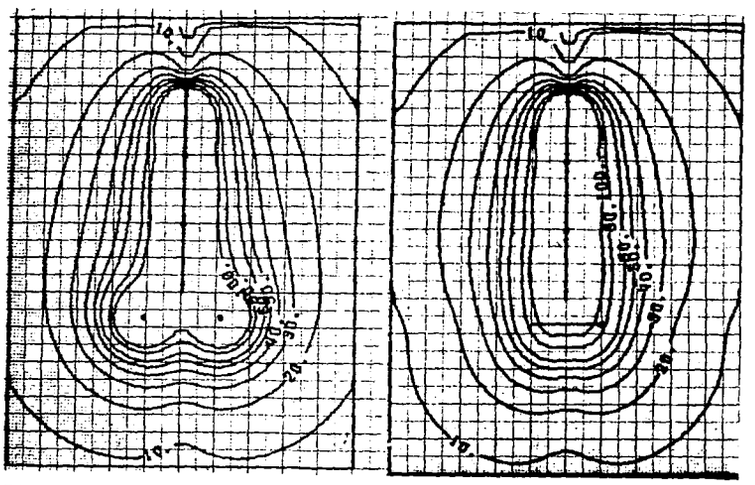

Fig. 1. Dose-rate distribution around a tandem and colpostat radium applicator in coronal (left) and sagittal (right) sections through the pelvis.

TABLE I: CRITERIA FOR EXCLUSION

	No. of Cases
Not treated	42 (21%)
Postsurgical status	15 (7%)
Cervical stump	19 (9%)
No radium application	68 (34%)
Radium before or during external irradiation	20 (10%)
Two or more radium applications	15 (7%)
Incomplete external irradiation	8 (4%)
Incomplete intracavitary irradiation	15 (7%)
TOTAL	202

TABLE II: REASONS FOR TANDEM ALONE

	No. of Cases
Narrow vagina	97 (51%)
Tumor infiltration of vagina and fornices	56 (29%)
Obliteration of fornices by scar tissue	21 (11%)
Stenotic ring in vagina	4 (2%)
Rectovaginal fistula	1
Laceration of vaginal wall during application of colpostat*	1
Not stated	11 (6%)
TOTAL	191

* Tandem was left in place after bleeding was controlled.

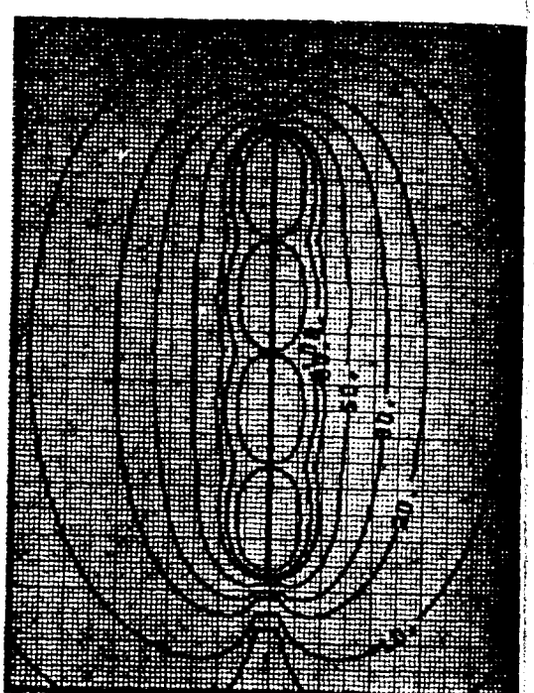

Fig. 2. Dose-rate distribution around a tandem radium applicator.

250 kVp, 2.5 mm Cu HVL, and 50 cm FSD. Since late 1958 a number of cases were treated in our El Dorado ^{60}Co unit, using 8,000 Ci, 100 cm SSD, field size 16 × 12 or 16 × 14 cm, anterior and posterior parallel opposing portals, and an exposure of 4,500 R over six weeks as calculated at the midpelvic plane.

Intracavitary Curietherapy: Our intracavitary curietherapy technique involves exposures ranging from 3,000 to 5,000 gamma roentgens calculated at point A. The majority of patients receive exposures of approximately 4,000 gamma roentgens to point A in a single application.

Our standard radium applicator consists of an intrauterine tandem arrangement

TABLE III: REASONS FOR TANDEM ALONE BY STAGE

	No. of Cases				
	Stage I	Stage II	Stage III	Stage IV	Total
Narrow vagina	1	28	54	14	97 (51%)
Tumor infiltration of vagina and fornices	...	8	41	7	56 (29%)
Obliteration of fornices	1	11	9	...	21 (11%)
Stenotic ring in vagina	...	2	2	...	4 (2%)
Rectovaginal fistula	...	...	...	1	1
Laceration of vaginal wall	...	1	...	...	1
Not stated	...	3	6	2	11 (6%)
TOTAL	2	53	112	24	191

TABLE IV: REASONS FOR TANDEM APPLICATIONS BY AGE

	No. of Cases Under 50	No. of Cases 50 and Older
Narrow vagina	23 (24%)	74 (76%)
Tumor infiltration of vagina and fornices	25 (41%)	33 (59%)
Obliteration of fornices	3 (14%)	18 (86%)
Stenotic ring in vagina	...	4
Rectovaginal fistula	...	1
Laceration of vaginal wall	1	...
Not stated	2 (18%)	9 (82%)
TOTAL	52 (27%)	139 (73%)

TABLE V: TYPE OF APPLICATOR BY STAGE

Case	Tandem Alone No. of Cases	Tandem and Colpostat No. of Cases	Total No. of Cases
I	2 (4%)	52 (15%)	54 (10%)
II	53 (28%)	177 (51%)	230 (43%)
III	112 (58%)	109 (32%)	221 (41%)
IV	24 (12%)	6 (2%)	30 (6%)
TOTAL	191	344	535

with three sources containing 10 mg of radium each (or the equivalent ^{60}Co) and a vaginal colpostat with two sources of 10 mg each. The most frequently used colpostats are the Fordyce, the Silverstone, and the Ter-Pogossian types. If the vagina is narrow or if residual disease involves a significant portion of it, a long tandem with 4 or 5 sources of 10 mg each is inserted in the uterine cavity with one of the sources protruding into the vaginal vault.

The isodose patterns around the tandem and colpostat combined and around the tandem alone with our usual loadings of radium were evaluated on sagittal and coronal planes across the pelvis at the level of the internal os. Figure 1 shows the isodose pattern of the tandem and colpostat in coronal and sagittal planes, while

TABLE VI: TYPE OF APPLICATOR BY AGE

Age Group	Tandem Alone No. of Cases	Tandem and Colpostat No. of Cases	Total No. of Cases
20–29	1	8 (2%)	9 (2%)
30–39	18 (9%)	59 (17%)	77 (14%)
40–49	33 (17%)	112 (32%)	145 (27%)
50–59	44 (23%)	75 (22%)	119 (22%)
60–69	57 (30%)	68 (20%)	125 (23%)
70–79	27 (14%)	20 (6%)	47 (9%)
≥80	11 (6%)	2	13 (2%)
TOTAL	191	344	535
Oldest patient	90 yr. of age	99 yr. of age	99 yr. of age
Youngest patient	25 yr. of age	24 yr. of age	24 yr. of age
Median age	60 yr. of age	49 yr. of age	53 yr. of age

TABLE VII: RADIUM DOSE BY TYPE OF APPLICATOR

Radium Dose (gamma roentgens)	Tandem Only No. of Cases	Tandem and Colpostat No. of Cases
3,000–3,500	38 (20%)	22 (6%)
3,500–4,500	144 (75%)	239 (69%)
4,500–5,500	8 (4%)	65 (19%)
≥5,500	1	18 (5%)
TOTAL	191	344

Figure 2 shows the isodose pattern of the tandem alone.

REASONS FOR A TANDEM APPLICATION ALONE

In 191 cases, the standard technique (tandem and colpostat) was not feasible. Only a tandem was employed, for the variety of reasons shown in TABLE II. TABLE III summarizes the clinical material according to the stage of disease and the reason for employing tandem application alone. There is a preponderance of advanced stages in this group, whereas in most of the early stages it was possible to use both tandem and colpostat.

TABLE VIII: FIVE-YEAR SURVIVAL BY STAGE, TYPE OF APPLICATOR, AND RADIUM DOSE*

Stage	3,000–3,500 R No. of Cases	3,500–4,500 R No. of Cases	4,500–5,500 R No. of Cases	≥5,500 R No. of Cases	Total No. of Cases
			Tandem only		
I	...	2/2	...	...	2/2
II	3/4(75%)	26/48(54%)	1/1	...	30/53(57%)
III	8/24(33%)	28/82(34%)	0/6	...	36/112(32%)
IV	2/10(20%)	2/12(17%)	0/1	1/1	5/24(21%)
TOTAL	13/38(34%)	58/144(40%)	1/8(12%)	1/1	73/191(38%)
			Tandem and colpostat		
I	2/3(67%)	33/39(85%)	6/8(75%)	2/2	43/52(83%)
II	6/8(75%)	83/126(66%)	24/35(68%)	5/8(62%)	118/177(67%)
III	3/10(30%)	33/72(46%)	8/19(42%)	3/8(38%)	47/109(43%)
IV	0/1	0/2	0/3	...	0/6
TOTAL	11/22(50%)	149/239(62%)†	38/65(58%)	10/18(56%)	208/344(60%)

* Dose given in gamma roentgens.
† Includes 6 patients lost and considered dead.

The age of the patients is correlated with the reasons for tandem application alone in TABLE IV. Most of the patients in whom proper placement of a colpostat was not possible and in whom we were forced to use a tandem only because of a narrow vagina, residual tumor infiltration, or fornix obliteration were older than fifty years of age.

STAGE OF THE DISEASE

Most of our cases were in an advanced stage of the disease at the time of diagnosis, and only 10 per cent of the 535 cases analyzed were in Stage I. TABLE V shows the distribution of the material according to the stage of the disease and the type of arrangement used for the intracavitary radium therapy.

AGE

The age distribution of the 535 cases analyzed is given in TABLE VI, correlated with the type of radium applicator used. Patients who had a tandem alone are in the oldest age groups, while only 26 per cent were under the age of fifty years.

Of the patients receiving the standard application, 51 per cent were younger than fifty years of age. The youngest patient in our study group was twenty-four years old; the oldest, ninety-nine years of age. The median age for the entire group of 535 patients was fifty-three years; it was sixty years for those who had a tandem alone and forty-nine years for the group w tandem and colpostat.

RADIUM DOSE

Following a dose of 4,500 R at the m plane of the pelvis by whole-pelvis irrad tion, we considered the optimal radi dose in our cases to be 4,000 R to point In patients in poor general condition, when high readings in the rectum w registered on the gamma meter with radium in place, the dose to point A w limited to between 3,000 and 3,500 However, in cases with a considera amount of residual disease after exter irradiation, the dose to point A was rai to 5,000 R if the rectal dose rate was at acceptable level. Table VII shows relationship between the radium dose a the type of applicator used. Most of patients given doses greater than 4,500 had a considerable amount of residual ease in the cervix following whole-pelvi radiation.

RESULTS

The five-year survival rate for the en group and its relation to the stag disease, radium dose, and the type o plicator used is shown in TABLE V Patients who received an optimal ra dose within the range of 3,500 to 4,5 had the best five-year survival rate in e group: 40 per cent among patients w tandem alone and 62 per cent a

patients with both tandem and colpostat. Comparison of the results obtained in the various dose groups above 3,500 R in cases with both tandem and colpostat shows no appreciable difference corresponding to the stage of the disease. The number of cases given more than 3,500 R in the group using only the tandem is too small to reach a similar conclusion.

Comparing the five-year results of the tandem/colpostat group and the group with a tandem alone, there appears to be no difference in the survival rate seen among patients given doses of 3,000 to 3,500 R. There is some difference in the survival rates of Stage II patients in the 3,500–4,500 R dose range, and likewise in Stage III cases; however, these differences are not statistically significant. While better results were obtained in patients with both tandem and colpostat, it should be recognized that these patients were clinically expected to have a better survival rate. For this reason, the better results *per se* cannot be attributed to the radium arrangement alone.

COMPLICATIONS

The overall incidence of significant complications (cystitis, proctitis, intestinal obstruction, and fistula) was 4 per cent. Complications were present in 10 of 191 patients (5 per cent) in the group treated with a tandem application alone and in 13 of 344 cases (4 per cent) in the group treated with the tandem/colpostat combination. The risk of complication was higher when the dose delivered was greater than 4,500 R in patients with a tandem application alone or greater than 5,500 R with the standard technique.

The five-year survival rate in those patients with complications was 40 per cent (4/10) in the group with a tandem alone and 62 per cent (8/13) in the group with both tandem and colpostat. Five patients in the latter group had hemorrhagic cystitis. All patients with post-irradiation hemorrhagic cystitis, considered to be one complication, survived longer than five years in both groups.

DISCUSSION

Although the intracavitary application of radioactive sources remains the most effective treatment in the control of carcinoma of the uterine cervix, best survival results are obtained when intensive external irradiation is also employed for advanced stages of disease.

In a clinical trial, Paterson (8) demonstrated that external irradiation of the pelvis prior to intracavitary radium application gave better results in the treatment of carcinoma of the uterine cervix than did intracavitary radium followed by external irradiation, since external irradiation helps to reduce the tumor to a size which can be more effectively irradiated by the intracavitary radioactive source. The need to supplement the intracavitary dosage with external irradiation, even in early stages of the disease, is based upon well-documented data. Numerous sources indicate that 13 per cent of the lymph nodes are involved in Stage I, 31 per cent in Stage II, and 41 per cent in Stage III (7). These nodes can be controlled by external irradiation, as has been reported by Decker *et al.* (4) and Rutledge *et al.* (9). These authors found less node involvement coupled with evidence of sterilization of metastatic lymph nodes in the pelvis in a series of lymphadenectomies performed following radical radiotherapy to the pelvis.

The present techniques of intracavitary application of radioactive sources in the treatment of carcinoma of the uterine cervix are modifications of two fundamental methods, the Paris and Stockholm techniques. A number of specially designed applicators for intracavitary treatment have been described, all of them consisting of two fundamental parts; (*a*) the intrauterine component, which is of utmost importance for dosage to the paracervical tissue and the area of regional lymph nodes, and (*b*) the vaginal component, which contributes mainly to the dosage in the paravaginal region. This latter part of the applicator provides the maximum dose to the rectum (6).

In most cases it is possible to utilize a

tandem and a colpostat, but frequently the configuration of the vaginal canal does not allow the correct placement of a standard applicator. The overall results in these cases were less favorable than in the group in which a standard arrangement was feasible; however, patients employing the tandem alone were older and the stages of disease more advanced than in the group using a combination of tandem and colpostat.

When the optimal placement of a standard application is not feasible, the treatment techniques should be carefully evaluated and modified to render the maximum benefit. Additional external irradiation or other intracavitary or interstitial radium arrangement, or a combination of irradiation and surgery, may improve the results in such cases.

SUMMARY

External irradiation followed by a standard (tandem and colpostat) radium application is the treatment of choice for invasive carcinoma of the cervix uteri in this department. A significant percentage of cases are not suitable for a good placement of the colpostat, so that only a tandem is left in place, most commonly in older patients and in those with advanced stages of disease.

The radium dose at point A was 3,500 to 4,500 R after complete external irradiation in the majority of cases. The five-year survival rate was 38 per cent for patients who had the tandem alone and 60 per cent for patients with the standard technique. A small group of patients received a radium dose in the range of 3,000 to 3,500 R; of these, the five-year survival rate was 34 per cent for patients with the tandem alone and 50 per cent for patients treated with both tandem and colpostat.

The frequency of complications was similar in both groups: 5 per cent in patients with the tandem alone and 4 per cent in patients treated with the standard technique. Of the patients with complications, the 7 who had hemorrhagic cystitis survived longer than five years, *i.e.*, this complication does not worsen prognosis.

The results obtained with external irradiation followed by standard radium application are considered quite satisfactory; further evaluation and perfection of the intracavitary treatment techniques in the nonstandard group may improve treatment results still further.

ACKNOWLEDGMENT: The authors express their sincere gratitude to Mrs. Raquel Reyes, Executive Secretary of the Radiotherapy and Cancer Division, for her unselfish dedication to the elaboration of the tables and manuscript of this and other reports.

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