THE PALLIATIVE TREATMENT OF INOPERABLE CARCINOMA OF THE CERVIX BY MEANS OF RADION

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The various palliative treatments formerly employed in cases of inoperable carcinoma of the cervix have proved so unsatisfactory that any improvement should be hailed with joy by the profession. Reports of the success of radium treatment, therefore, deserve attention and investigation, since these reports have appeared in the last few years with such frequency that the method may now be considered firmly established. The technique and application, the range of usefulness, the permanency of the relief, the histological changes taking place, and the process by which the rays produce their effects are, however, questions which are still unsettled; and the purpose of this article is to contribute to the various phases of the subject not yet cleared up, and to put on record sundry interesting observations made during the treatment of a small but varied series of cases.

Under ordinary circumstances, it would be unwise to report such a series of cases at so early a stage of treatment; but as no claim is made that permanent results have been obtained, it has been thought permissible to describe the early palliative effects, without attempting to predict whether the improvement is more than temporary.

The writer has treated twelve cases of carcinoma of the cervix in the gynecological wards of Mt. Sinai Hospital, eleven on the service of Dr. Joseph Brettauer, and one on that of Dr. H. N.
Vineberg. He takes this occasion to thank Dr. Brettauer and Dr. Vineberg for putting the cases at his disposal. Two patients withdrew from treatment and were lost sight of after two radiations each, before the result could be observed. His technical experience has been enlarged by the treatment of fourteen other patients, including those suffering from vulvar, rectal, gastric, laryngeal, etc., conditions; these, however, will not be referred to, as they do not bear directly upon the subject discussed in this paper.

_Radium employed._ Through the kindness of Dr. Francis Carter Wood, radium bromide, equaling 130 mgm. of pure radium, was placed at the disposal of the writer. The radium was distributed in four glass tubes containing respectively 83, 20, 17, and 10 mgm. The length of the largest tube (28.7 mm.) at times made awkward its application within the vagina. In most instances, 120 mgm. were used; in some cases, only 47 mgm. were employed.

**TECHNICAL**

_Screening._ As it is essential that the soft alpha and beta rays be removed by filtration, brass or lead was interposed between the glass radium container and the tissues. These metal filters in turn generate soft secondary rays which are as destructive to the tissues as the soft primary rays, but the secondary rays are readily absorbed by para rubber, gauze, or paper.

_Preparation of radium carrier._ The radium was arranged differently in each case, depending upon the site of the lesion, the size of the growth, and the dimensions of the vagina.

1. If 47 mgm. only were used, the three naked glass tubes of 10, 17, and 20 mgm. were placed in a hollow lead cup attached to a handle. The opening was covered with a lid of brass, 1 to 1.5 mm. thick, which was fastened with a layer of adhesive plaster, and the cup was inclosed in a small bag of rubber, 1 mm. thick (fig. 1). The use of the lead cup was suggested to the writer by Dr. Howard A. Kelly of Baltimore, who employs it in the treatment of cervical carcinoma. The cup has the advantage that the rays are cut out in every direction but one,
Fig. 1. Instrumentarium Used for Radium Application to Uterus, Cervix and Vagina

A, Hollow lead cup on handle, showing brass cover attached with adhesive plaster and thrown back. Hollow used to contain the radium. B and D, Brass container for 17 and 10 mgm. capsules of radium. C, Thinner walled lead cup without cover. E, Brass containers in tandem arrangement for radiation of corpus carcinoma. F, Numerous layers of lead foil which are used to protect healthy parts.
and that the attending nurse is able to change the direction of the rays without disturbing the patient. It is most useful in carcinomata of small size where concentration of the rays is desired.

2. For large cauliflower growths, especially such as were accompanied by diffuse downward infiltration of the vaginal walls, the following arrangement was found to be most advantageous: The 83 mgm. tube was inclosed in a brass capsule, 1.5 mm.
thick, which was screwed to a handle. Around the periphery of this tube the three other tubes were placed in a similar container, but without handles. They were secured to the central tube with strips of adhesive plaster, surrounded with a rubber bag, and introduced as one (fig. 2). If, for example, the anterior vaginal wall be infiltrated, but the rectovaginal septum be unaffected, one side of the carrier may be additionally screened by four to eight thicknesses of lead foil, applied inside the rubber filter. If the lead protector be placed facing the rectum, this viscus is protected from unnecessary radiation, while the affected anterior wall receives a larger quantity of radiation.

3. In crater-like carcinomata, extending up into the cervix and involving the parametria, the arrangement was slightly varied, the long central tube being advanced 1 to 2 cm. in front of the three smaller tubes. This permitted the introduction of the projecting tube within the cervix, the smaller tubes at the same time radiating the vaginal portion and fornices (fig. 3).

Introduction of the carrier. The radium is introduced under guidance of sight, after the vaginal walls are separated with spades or retractors. Unless the carrier is to be introduced within the cervical canal, a layer of gauze about 0.5 cm. in thickness is interposed between the growth and the carrier. The carrier, fastened to the handle, is pushed firmly against the gauze, and then the vagina is tightly packed with gauze, so that its walls are separated as far as possible from the radium. The handle is secured to the vulva with strips of adhesive plaster, exactly as a permanent catheter is fixed in position. A dressing and T binder complete the operation. Patients who suffer pain are given a liberal injection of morphine to keep them quiet and comfortable.

Length of application. It is rarely possible to introduce the radium for more than eighteen to twenty-four hours at one session, because the patient must remain quiet during the treatment. An application of 120 mgm. for twenty-four hours gave the large dosage of 2880 mgmhrs. (milligram hours). A considerable part of the radiation, however, is absorbed by the 1.5 mm. of brass or 0.5 to 2 mm. of lead, the 1 to 3 mm. of
rubber, and the gauze, all of which are interposed between the radium and the tissues.

*Frequency of application.* The frequency of application depends largely upon the local conditions, the amount of reaction

(pain, rectal and bladder tenesmus, change in body weight, symptoms of absorption or toxemia), etc. In general, the following method has proved most satisfactory to the writer, but individual preference and experience will suggest wide

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*Fig. 3. Central Applicator Advanced to Permit Introduction Within Vaginal Canal, the Latter Containers Radiating the Portio*
variations. The further advanced the growth, the larger the initial dose indicated. The second treatment should be given seven to ten days after the first; the third treatment, fourteen days after the second. If improvement becomes apparent (cessation of pain, hemorrhage, and foul discharge, shrinkage and cleansing of the cancer surface), the next two treatments should be given at intervals of three weeks in diminishing dosage. For the first series 5000 to 6000 mgmhrs. are sufficient; and, thereafter, one treatment each month for two or more months completes the primary treatment. The patient should present herself for examination at least once in four weeks, in order that general appearance, general health, local conditions, and weight, may be observed. Should recurrence manifest itself, a new series of radiations may be undertaken.

**CLINICAL**

*Local effects of radiation.* In every case so far treated a distinct amelioration of pain was observed within two weeks after the second radiation. Coincidentally, the bleeding diminished or disappeared, and the foul discharge become odorless and serous in character. In the earlier cases treated, because of insufficient filtration, very annoying rectal and vesical tenesmus was complained of, usually most marked on the third and tenth day after the beginning of the treatment. Severer rectal tenesmus developed in these cases as late as the third month. Since the practice of distending the vagina with gauze has been adopted, these unpleasant symptoms have either not appeared or have been very mild in character.

Between the third and fifth week after the beginning of the treatment, the cervix was observed to contract and shrink, assuming a characteristic senile size and conformation. The interior of the cervix and, sometimes, the vaginal portion were covered with a densely adherent, thick, yellow white, “bacon-like” exudate, which persisted for months. The thickening of the parametria and vaginal infiltration (much of which is usually of an inflammatory nature) gradually diminished. At
a later date (after three to six months) the parametria again became more rigid (scar tissue?).

General effects of radiation. With the disappearance of the pain, bleeding, and discharge, the patient's general condition rapidly improved. In several instances (large, sloughy growths), a mild toxic condition, not marked by rise of temperature and transient in duration, was observed. In most cases, a rapid increase in weight was noted. Several of the patients appear to enjoy perfect health at present; in several others, a progressive loss of weight and strength and undefined pains and malaise are noted after a period of several months of well-being. In one of these, an enlarged nodular liver signifies hepatic metastases; in two others, in spite of the deterioration of health, no physical signs as yet denote recurrence.

Applicability of the treatment. (a) To advanced cases. Up to date, no case has been refused treatment. As will be noted from the histories, two cases had been given up as hopeless, after repeated local cauterizations (thermocaustery) had proved even temporarily ineffective. One patient had had two operations (hysterectomy and secondary operation for recurrence) followed by local recurrence in the vaginal vault. In several instances, the recto- and vesicovaginal septa were involved. One patient with fracture of the humerus (x-ray diagnosis: "pathological fracture of the humerus, suspicious of metastatic involvement") is now under treatment.

The writer sees no contraindication to the treatment of even the most advanced cases. Even if no permanent relief is afforded, prompt cessation of pain, bleeding, and discharge can be obtained. A more merciful death from internal metastases or cachexia may then be anticipated. Only where carcinomatous perforation into the bladder or rectum is imminent, will radiation, by hastening the disintegration of the carcinomatous tissue, favor cloaca formation.

(b) To early cases. The operable cases of carcinoma of the cervix which have come under the writer's observation during the last ten years have been few in number (23). The final results of the radical operation, except in the hands of a few operators who control a large material, have been discouraging.
In the light of the experience of others and of the two cases reported below (cases 4 and 5), the writer feels inclined to advise, at least tentatively, that operable cases be subjected to a short preliminary treatment by radiation, followed by an abdominal total hysterectomy and salpingo-oophorectomy without excision of the parametria. It is, however, not justifiable, in the present state of our knowledge, to rely solely upon radium treatment in operable cases, unless the patient is an exceptionally poor risk (excessive obesity, severe cardiac, pulmonary, or renal disease), because there is as yet not sufficient evidence that a permanent cure can be produced by radium.

The preliminary radium treatment should be vigorous and short in duration. "Sterilization" of the growth should be sought, but the operation should be undertaken before the parametrial scar tissue formation, which regularly follows radiation, has had time to advance too far. In case 4, seven weeks elapsed between the beginning of treatment and the hysterectomy. The pelvic connective tissues were found to be so hard, contracted, and board-like, that the ureters could not be identified or pushed away from the uterine arteries. The operation consequently proved most difficult, and a transient ureterovaginal fistula subsequently developed.

Case 5 was, therefore, operated upon nine days after the beginning of radiation, and no such technical difficulties were encountered. On the other hand, microscopical examination of the carcinoma showed very few cytological changes, although the normal appearance of the cells did not necessarily exclude inhibition of cell division, the checking of division being the mode of action of radium on cells (fig. 11).

In view of these observations, the writer is inclined to advise preliminary radiation extending over a period of three weeks (three exposures of about 2000, 1200, and 800 mgm. hours each) followed within two to three days by hysterectomy. It appears inadvisable to operate before the lapse of three weeks, because the growth has not been sufficiently cleansed from a bacteriological point of view. Four weeks after operation, radium treatment should be resumed (at least three treatments at four weeks intervals).
HISTOLOGICAL

In every case a specimen was excised from the growth before the treatment was inaugurated. Usually a small specimen was removed before each subsequent radiation so that the cytological process could be followed from beginning to end. Toward the close of the treatments, however, difficulty is experienced in obtaining sufficient material, as the cervix becomes small, hard, and covered with a necrotic layer of detritus.

Figures 4, 5, 6, and 7 are photomicrographs of sections obtained from specimens taken at intervals during the course of treatment from Case 6. Figure 4 shows untreated squamous-cell carcinoma, figure 5, beginning nuclear alterations in the cancer cells; figure 6, far advanced cellular degeneration and vacuolation; figure 7, the final stage in which cell detritus, fibrin, and amorphous material predominate.

The first cellular changes are noted about ten days after the initial treatment. Rapid disintegration of the surface of the growth does not become apparent before three weeks have elapsed.

From observations made upon readily accessible carcinomata (massive carcinomata of the vulva, two cases), it has become evident that 1 to 1.5 cm. is about the maximum depth of cancer tissue at which the rays of 120 mgm. of radium exert their effect. Beyond this distance, the cancer cells appeared to be unaltered, even after four or five prolonged exposures. This, of course, does not preclude the possibility that large quantities of radium, 500 to 1000 mgm., may perhaps exert a far deeper action. The majority of those who employ radium in pelvic disease, however, appear to agree that from 50 to 100 mgm. is the optimum amount to use.

The uterus removed from case 4, after eight radiations had been given, was cut in interrupted serial sections. In only two minute areas were spots suggestive of degenerating carcinoma cells found. Figure 8 shows the carcinoma before treatment, and figure 9 the suggestive areas; this section was at a level well above the fornix at a distance of at least 3 or 4 cm. from the tip of the cervix.
FIG. 4. M. M., JUNE 6, 1916
Squamous-cell carcinoma before treatment.

FIG. 5. M. M., JUNE 14, 1916
Same eight days after 1000 mgmhrs. of radiation. Note swelling of cells; enlargement and diffuse staining of nuclei.
Same seventeen days after beginning of treatment, 900 additional mgmhrs. having been given. Note vacuolation of cells and increase in number of poorly staining nuclei.

Same twenty-seven days after beginning of treatment, 4200 mgmhrs. of radiation. Note purulent exudate containing an occasional degenerating cancer cell.
INOPERABLE CARCINOMA OF THE CERVIX

FIG. 8. P. G., FEBRUARY 11, 1916
Squamous-cell carcinoma in close proximity to cervical glands, before treatment.

FIG. 9. P. G., APRIL 3, 1916
Section from uterus removed per abdomen, seven weeks after beginning of treatment (five radiations aggregating 4600 mgmhrs.). The entire uterus was cut and examined. The sole suspicious spots found are the two areas shown in the photomicrograph.
In view of the fact that the direct action upon cancer cells of the 120 mgm. of radium, as applied by the writer, does not manifest itself—when judged by histological criteria—beyond a distance of 1 to 1.5 cm., and yet at least temporary curative effects are observed over far wider areas in the region of the cervix, the writer is led to conclude that some other local factor must come into play. This local factor, in the case of cervical carcinoma, is probably supplied by the large quantity of connective tissue (parametria) which radiates from the cervix in all directions. Under the influence of the rays the connective tissue contracts, hardens, and perhaps proliferates. As a result, the lymphatics and smaller blood vessels are permanently blocked, and the dense scar produces a condition of "starvation" of the growth, a condition which has, at times, been obtained by surgical means (ligation of the internal iliac arteries). Further study is necessary and additional proof must be adduced before this suggestion can be accepted as more than a working hypothesis.

Histologically, carcinoma cells may appear normal and active, while biologically their growth and mitotic activity may either be inhibited or dead. This is especially true if the carcinomatous tissue is removed within eight to ten days after radiation. Figure 10 shows a sagittal section of the uterus removed in case 5 ten days after the first radiation had been given. The cells, when viewed with a high power (fig. 11) appear to be unchanged. Yet, though the vagina was cut across very close to the growth, no tendency to local recurrence was observed in the four weeks elapsing between operation and resumption of treatment.

Many further observations of interest and value can doubtless be made by close and persistent scrutiny of local excisions obtained during the course of treatment and of operative specimens obtained after preliminary radiation.

The following conclusions are warranted in the present state of our knowledge:

1. Radium is our best palliative measure in inoperable carcinoma of the cervix.

2. Far advanced cases may be treated with radium.
FIG. 10. F. W.

Sagittal section of the cervix of uterus removed nine days after the first radiation. Microscopically the cells appear unchanged and macroscopically the cervix looks infected and sloughy.

FIG. 11. F. W., May 1, 1916

Section from cervix of uterus removed per abdomen nine days after beginning of radiation (two radiations aggregating 2900 mgmhrs.). The cancer cells (1 cm. from the surface) as yet show no changes, though their power of multiplication may be inhibited or destroyed. Higher power of figure 10.
3. Radium not only rapidly relieves the pain, hemorrhage, and discharge, but indirectly also improves the general health and condition.

4. The minimum quantity of radium substance needed is 50 mgm.

5. "Border line" cases or operable cases should be submitted to operation after a short preliminary course of radiation. Good primary results may then be expected from simple total hysterectomy.

6. Operated cases should be subjected to postoperative, prophylactic radiation, beginning not later than four weeks after operation.

7. The technique of radium treatment of cervical cancer is simple and easy to learn.

In conclusion, a word of warning must be given against the building of undue hopes upon this recent addition to our weapons in the fight against cancer. The above report of early results obtained agrees in the main with the favorable results reported by many others, and shows that radium is a wonderful palliative. Whether the final results will prove that radium can give a permanent cure of cancer is a mooted question. Judging from the limited penetrating power of the rays and the variation of resistance of different cancers, it seems probable that numerous disappointments will occur, and that in many cases positive harm will be done by enthusiasts who refuse to submit operable cancers to surgical operation.

HISTORIES


After being well for eight months, with exception of rectal tenesmus, is now losing weight and strength. No local recurrence or metastases found.

Case 3. D. E., thirty-three years old. Radical operation for carcinoma of cervix ten months before admission; reoperated for vaginal recurrence July, 1915. Since then repeated vaginal hemorrhages. Again operated December, 1915. On admission February 3, 1916, vault occupied by infiltration extending into both parametria and on right side extending almost to mucosa of rectum. No material for microscopic examination. Six radiations beginning February 3, 1916, ending July 18, total 6286 mgmhrs. At present feels and looks well, no infiltration or signs of recurrence or metastases.

Case 4. P. G., forty-two years old. Two abortions, operated at Mt. Sinai Hospital in 1912 for intraligamentous cyst, vaginal bleeding daily for three months. A red granular mass has substituted the posterior lip of the cervix infiltrating the right and posterior vaginal fornix (possibly still operable). Microscopically squamous-cell carcinoma. Five radiations beginning February 11, 1916, ending March 21, total 4629 mgmhrs. Total abdominal hysterectomy April 3, without excision of parametria. Uterus embedded in glistening white stony hard scar tissue. Uneventful convalescence except ureterovaginal fistula for four weeks. At present looks and feels well. No signs of local or general recurrence.

Uterus showed only two small microscopic areas suggestive of cancer cells.

Case 5. F. W., fifty years old; menopause three years ago, bleeds daily for eight months, has lost weight and strength. Entire cervix, especially posterior lip, is hypertrophic, uneven, bleeding freely to touch, parametria free (operable?). Microscopically squamous-cell carcinoma. Two radiations beginning April 22, 1916, ending April 28, total 2984 mgmhrs. May 1, complete hysterectomy without excision of parametria. Microscopically the carcinoma cells are unchanged (figs. 10 and 11). Three additional radiations given, beginning May 29, ending July 29, total of 8132 mgmhrs. in five sessions. At present feels and looks well. No signs of local or general recurrence.

Case 6. M. M., sixty-two years old. Eleven children, menopause fifteen years ago, foul discharge for two years, bleeding ten weeks.
Obese, emphysematous, potatrix. The cervix consists of a bulging mass, extending into left fornix and infiltrating the upper part of the recto and vesicovaginal septa. Microscopically squamous-cell carcinoma. Six radiations, total 8077 mgmhrs., beginning June 6, 1916, ending July 27. Has had severe attack of articular rheumatism. No local signs of recurrence. At present is losing weight and strength, liver enlarged and nodular.

Case 7. W. M., fifty-two years old. No pregnancies, menstruation regular until one year ago, since then meno- and metrorrhagia; lost twenty pounds in six months. Cauterized repeatedly for inoperable squamous-cell carcinoma before admission, but without relief. Crater infiltration of all vaginal walls to within 3 cm. of introitus, especially in vault, marked in vesicovaginal septum. Four radiations beginning August 16, 1916, ending October 5, total 10,905 mgmhrs. At present looks and feels well. Upper vaginal vault hard, uterus retroflexed, not freely movable. By rectum vaginal vault feels free, the right parametrium is doubtful.

Case 8. L. Z., fifty-seven years old. Ten pregnancies, menopause thirteen years ago, has been spotting eight months. Upper third of vagina infiltrated, vault rigid, cervix crater like, infiltration of vesico- and rectovaginal septum. X-ray shows pathological fracture of neck of right shoulder. Microscopically squamous-cell carcinoma. Four radiations beginning September 11, 1916, and to be continued, total to date 6070 mgmhrs. Crater (November 11) smaller, no bleeding, much improved in health. X-ray shows progress of arm lesion.
