A COMPARISON OF THE RESULTS OF SURGERY AND OF RADIATION IN THE TREATMENT OF CANCER OF THE CERVIX

An Analysis of 200 Cases Subjected to Radiation Treatment

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GENERAL DISCUSSION

A review of 325 cases of carcinoma of the cervix in which the patients were examined, treated, and observed personally between the years 1920 and 1929, inclusive, discloses the fact that in the cases seen in 1929 the disease was just as far advanced as in those seen in 1920, notwithstanding the numerous articles which have been written on the subject and the publicity given it by the Society for the Control of Cancer.

It has been correctly stated that for many years women have refused operation for cancer of the cervix because they felt that it was useless because of the frequent early recurrence. The extensive, successful use of radium within the past ten years should have eliminated this objection, but nevertheless the fact still remains that patients with this condition are presenting themselves too late for a cure to be accomplished. Moreover, the attempt to treat these advanced cases with radium has had a tendency to bring this method into disrepute because the pain with which the late stages of the disease are attended is believed by the laity to be due to a radium burn. For this reason many patients refuse radium treatment.

In most cases thorough questioning reveals the fact that the patient did consult a physician from four to six months before the disease was recognized and proper treatment instituted. If a patient consults her family physician because of some supposed menstrual disorder, he must assume the responsibility and convince himself by a thorough examination that there is or is not an existing pathologic condition; and if there is, the patient should be treated promptly. Consultation without proper examination leaves the patient with a false sense of security which leads to a delay of several months.

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Investigation has also disclosed the fact that simple hysterectomy for carcinoma of the cervix is still in vogue in many smaller localities, whereas in most of the larger towns and clinics throughout the country it is generally conceded that radium and X-ray are the preferred methods of treatment. It would seem that ease of communication through medical meetings and journals in the present age should have accomplished more than it has during the past ten years.

I think it quite safe to assume that the major controversy regarding the relative merits of surgical and radiation treatment for cancer of the cervix is settled. It is generally agreed that surgery is excellent treatment for early cases, but these are so few as to be almost disregarded. It is also quite fair to say that radiation will cure as many of the early cases as will surgery, without any mortality or morbidity.

Before the Medical Society of the State of New York in 1920, Reuben Peterson presented a paper on "Radical Abdominal Operation for Carcinoma of the Cervix" in which he reported that 40.09 per cent of his patients who were operated upon were permanently cured. However, he operated upon only 60 of 380 patients. In reality, 18 patients, or 4.7 per cent of the whole number, were cured. Fourteen died as the immediate result of operation. In view of present-day statistics, it is quite clear that if this group of 380 patients had been treated with radiation, the percentage of cures would have been considerably higher.

Wertheim, who developed the radical operation for carcinoma of the cervix and whose experience is greater perhaps than that of any other surgeon, found an operability of 48 per cent and was able to effect a five-year cure in 18.04 per cent. This means that out of 100 patients seen, 48 were operated upon. Allowing for a minimum mortality of 12 per cent, 42 patients would survive operation. Eighteen per cent of these patients were cured, which in reality means nine out of the original 100 cases.

Norris, professor of gynecology at the University of Pennsylvania, makes the following statement: "We prefer radiation because when carefully analyzed, the end-results of surgery are no better than if as good as those secured by radiation. In the Clark Clinic we have not submitted a case of cancer of the cervix to hysterectomy for five years, and this, despite the fact that Dr. Clark was one of the pioneers in the radical operation."

Crossen states that his general plan of treatment of cancer of the cervix is to give a heavy dose of radium and follow this with deep x-ray therapy.

Kelly says: "On account of the numerous distressing recurrences even in the hopeful group (carefully selected cases of cancer of the cervix) there is a growing

inclination to decline operation in favor of radiation." This statement from a man having such a large surgical experience should carry a great deal of weight.

G. G. Ward, Woman's Hospital of New York, makes this statement: "The morbidity results of the radical operation — fistula, thrombosis, suppuration, etc.— are not to be forgotten." He believes that in the very early stages of the disease, surgery will effect as many cures as will radium, but only at the expense of high primary mortality and greater morbidity. He has not performed an operation for carcinoma of the cervix since 1920.

Lynch, of the University of California, remarks: "Surgery should be restricted rather than developed, since it is amply proved that the results of radium and x-ray in the treatment of borderline cases far surpass those of surgery, and most of the cases fall in this group."

W. J. Mayo states: "Cancer of the cervix in the earliest stages is certainly as well treated by radium as by hysterectomy, and in the advanced cases where hysterectomy is not possible, radiotherapy will occasionally yield splendid local results; even though metastatic processes later appear without local recurrence, the benefit is as lasting as could be produced by the knife."

The opinions of these eminent men cannot be disregarded and it is reasonable to say that until some better treatment is discovered, radiation therapy is the best treatment for cancer of the cervix.

Etiology and Prophylaxis

The etiology of cancer of the cervix (or of any other part of the body) is not known, and it is not within the scope of this paper to discuss the various theories that have been advanced regarding it. We can only analyze as thoroughly as possible the conditions existing in the area in which cancer has become engrafted. The established relationship between chronic irritation and cancer gives hope that better obstetric care and surgical prophylaxis in the treatment of ulcers and tears will reduce the incidence of cancer of the cervix.

In a series of 5,000 cases studied by Graves, in which cervical repair had been done, only four patients later developed malignancy. While these figures have not been checked with an equally large series of cases, they furnish sufficient proof that repair operations, properly performed, are a most effective prophylaxis against cancer of the cervix. However, advanced cases will continue to be seen, and greater efforts must be made to improve the present methods of treatment.

Diagnosis

Pain, hemorrhage, and an odorous discharge are undoubtedly symptoms of carcinoma of the cervix, but generally of a hopeless case. Therefore, the condition must be recognized before these symptoms appear. Any deviation from the normal menstrual cycle

must be investigated and any discharge must be accounted for. The simplicity of the equipment for the pelvic examination, the fact that the cervix is easily accessible for inspection, and bearing in mind the fact that any discharge is pathologic, should render the diagnosis of carcinoma of the cervix a very simple matter for every physician. In case of doubt, we feel certain that biopsy does no harm.

Classification

Anyone who has treated a large group of cases is at once impressed by the varied, individual differences in resistance to cervical cancer, but as Burnam points out, "Neither the nature of normal body defenses nor knowledge as to how to amplify them is at hand."

Broders developed a method of evaluation of histologic malignancy by which the prognosis of a case can be expressed on a numerical basis, dividing the cases into four groups according to the degree of cellular differentiation, the mortality rising correspondingly to the decrease in differentiation. The one drawback to this method is that this sort of work is necessarily subject to personal equation, and is difficult to standardize, just as a certain type of operation is difficult to standardize. Direct, personal contact with Broders would be necessary in order to develop a precise duplication of his method.

Stimulated by the excellent work of Broders, a tremendous amount of investigation is being carried on for the purpose of determining whether there is any definite relationship between the histologic structure of a carcinoma and its malignancy, and to try to deduce from this finding the best form of treatment for the particular type of condition in question, and to determine the prognosis.

Martzloff has carried on investigations relating to the predominant type of cell present, and from a study of 387 cases he concludes that the histomorphology of the predominant types of cells in epidermoid cancer of the cervix is important, as it indicates the relative malignancy of a given tumor. From his study he proved that the spinal cell type of cancer is the least malignant, the transitional cell type the next in order of increasing malignancy, and the fat spindle cell type, the most malignant of all. However, we know that pathologists frequently differ as to the classification of an individual cell. Hueper objects to Martzloff's method on the ground that the evaluation of histologic malignancy based on only one factor is incomplete and incorrect. He believes that a carcinoma is not sufficiently characterized by the cell type alone; the amount of anaplasia must also be taken into consideration.

Hueper has developed a technic of evaluation of histologic malignancy based on twenty factors which are recognized as being characteristic of differentiation and

anaplasia, and which are evaluated on a percentage basis. The sum of these results translated into numerical values he calls "histologic malignancy index" or "histologic malignogram." He believes that this method is freed to a large extent from the influence of personal experience and interpretation through the introduction of well-defined standards, so that a duplication by other workers is made possible. This is an elaborate piece of work and undoubtedly will go far toward solving the problem, but again, for routine work, it probably is not practical. However, it is to be hoped that from all these investigations will come eventually a simple formula which will help the clinician to classify his cases more intelligently and thereby improve his end-results. So far we have not attempted to grade our malignant cases.

Merely the classification of the malignancy according to histologic structure does not, however, tell the story of the end-result. It is important also for the clinician to classify his cases according to the extent of the disease. A Grade 1 malignancy with wide extension would not be expected to have the same chance of cure or of palliation that a Grade 3 or 4 would have, if it were absolutely confined to the cervix.

An effort is being made to standardize the many classifications of malignancies which are in use at the present time. Some clinicians classify them merely as operable, borderline, or advanced; others divide them into four groups and some into five groups. For working purposes, we believe that the classification into four groups made by the American College of Surgeons is quite practical, except in regard to the question as to whether or not the broad ligaments are involved. Very frequently it is impossible to decide whether the condition is inflammatory or whether it is malignant. The case of recurrent carcinoma of the cervix after hysterectomy (complete or supravaginal) should also be segregated from the primary cases.

Rationale and Technic of Radium Therapy

For practical purposes, the simple idea that radiation is a means of destroying cancer cells without too much injury to the normal cells is a good working hypothesis, but by reason of our accumulating knowledge of the physics of radiation, and of the biologic effects of radiation, we are being led to a better understanding of its action. In brief, radium has a threefold action on malignant tissue. It affects (1) the cancer cells, (2) the connective tissue, and (3) the blood and lymph vessels. The action on the cancer cell is shown microscopically by swelling and vacuolization of the protoplasm and by shrinking of the nuclei. This is followed by phagocytosis and absorption and replacement by a homogeneous connective tissue. This contracts and affects the lymphatic and smaller blood vessels and starves the growth.

There is not sufficient time to enumerate the varieties of technic which have been used since radium therapy was instituted nor to mention all the men who have contributed to the advancement of our present knowledge. Suffice it to say that there are two entirely different schools of thought in regard to the method of treatment. In one the opinion is that it is best to give large massive doses in a short space of time, preferably in one, or at most, two sittings. The other is that it is preferable to give very small doses over a longer period of time. I believe that most of the large clinics in this country favor the former opinion, while the latter group is led by Regaud of the Radium Institute of Paris. This difference of opinion will undoubtedly be settled before many years, after the results of both methods are compared. Standardization of radium dosage for uterine cancer is impractical, dosage and technic must vary with the character and location of the involvement.

The technic followed in the Cleveland Clinic has varied very little during the past ten years, the only change being that since we have had a larger amount of radium available, we are giving larger doses over a shorter period of time, and we try to give the complete dose at one sitting, whereas previously the total amount of radiation was given in two doses. The average dose given in our earlier cases was 4200 mg. hours distributed evenly in and against the cervix. In our later cases, since we have combined radium with high voltage X-ray, the average dose is about 3600 mg. hours. Our standard screen is made of brass, one and one-half mm. in thickness, and this is encased in a rubber tube 3 mm. thick. At the present time we place a tube in the fundus as well as in the cervix, because in our earlier cases we found frequently that a patient would be free from symptoms for a year or so and then suddenly have bleeding and discharge, and examination would reveal a large undermined cavity at the upper end of the vagina due to the fact that the radium had not been placed high enough in the cervical canal. From this finding we are led to believe that an anesthetic is necessary in order to estimate the extent of the growth, and also to place the radium accurately in proximity to the growth. It is sometimes impossible, even when the patient is under an anesthetic, to place a tube of radium high in the cervical canal.

In addition to the radium tubes placed in the fundus and cervix, two or three tubes are placed against the cervix and these are held in place by packing the vagina tightly with gauze. If the growth is of the cauliflower variety, it is frequently curetted away or radium needles are placed in it. A catheter is then placed in the bladder to keep it empty and therefore as far away as possible from the radium.

Care should be taken in transferring the patient from the table to the cart and from the cart to the bed. We believe that bending and twisting of the patient during the transfer will dislocate the vaginal tube and may account for bladder and rectal symptoms. The best method is to place the cart alongside the table and slide the patient on to the cart by a sheet, and from the cart to the bed in the same manner, so that the position of the patient is unchanged throughout the procedure. We have not used gold seeds in the treatment of any of these primary cases, but they are of great value in the treatment of recurrences, because their action is more or less localized. Large, heavily filtered doses frequently are harmful in the treatment of recurrence. We have not had any experience in placing gold seeds in the broad ligaments by laparotomy.

We have tried numerous remedies for radium sickness but none is entirely satisfactory. Many patients have no sickness even after large doses of radium. In some cases the sickness is due not to radium but to the anesthetic or to the morphine which is given for pain or discomfort.

The majority of the patients are able to leave the hospital the day following treatment unless they live some distance away. They are instructed not to be too active and to take a douche once or twice daily. They are given an appointment to return in three or four weeks for high voltage X-ray therapy which is administered by Dr. Portmann. The treatment is given in four or five doses over a period of four or five days. In 1925, we gave the X-ray treatment in two doses on the days immediately following the radium treatments, but we soon found that this method did not give satisfactory results, for statistics show that in that year the duration of life after radium treatment was greatly reduced and the patients led a very miserable existence on account of rectal and bladder symptoms.

After patients have been treated we make an effort to have them return at monthly intervals for three months, and after that, every three months during the following year. If local recurrences develop, they are treated with seed implantation. If the recurrence is deep, X-ray therapy is repeated, with marked relief for a time. In cases in which there is no ureteral involvement, but pain is referred down the legs, we plan in the future to do a chordotomy, just as a gasserian ganglion operation is done for relief of pain in cases of extensive malignant disease of the face.

We have always taken the stand that surgery following apparent cure by radium therapy is not only unnecessary but is frequently

disastrous, and many surgeons who employed this procedure from five to ten years ago have now abandoned it. Neither should radiation be relied upon to offset the disaster of an incomplete operation.

Complications

The chief complications in the treatment of carcinoma of the cervix by radium are hemorrhage, symptoms referable to the rectum and bladder, and fistulae (urinary and fecal).

Hemorrhage may be due to the natural progress of the disease or to ulceration caused by the radium. We believe the former is the usual cause. In the most serious cases packing and transfusion are sufficient to control the hemorrhage.

Bladder and rectal symptoms are of two types — early and late — and it is quite important that they should be recognized. It is reasonable to assume that if a sufficient dose of radium is given to cure carcinoma of the cervix, it will also be sufficient to produce an erythema to the rectum or bladder. Very often this erythema is slight and passes unnoticed unless the patient is questioned. If it it is severe, it is evidenced by a slight burning sensation and a desire to go to stool or to void somewhat more frequently than usual. In the mild cases, the condition usually clears up in ten days or two weeks, but in the severe cases from four to six weeks may be required. It is in this latter group that the late rectal and bladder complications develop, usually six or eight months after the initial radiation treatment. These late symptoms are frequently mistaken for a recurrence of the carcinoma, and if the patient is treated for recurrence, irreparable damage will result. A clue to the true state of affairs is found in the fact that the symptoms are out of all proportion to the findings. There is severe pain and tenesmus and the stool contains considerable blood and mucus. Digital examination causes greater pain than in the case of recurrence. The patient is not cachectic. Proctoscopic examination reveals a puckered up scar or small ulcer at about the level of the cervix with telangiectasis and considerable redness of the mucosa. The condition may be compared to an overtreated area on the skin which is healed by the formation of scar tissue through which fine vessels may be seen to course. In the rectum the scarring is subject to trauma and infection with subsequent ulceration which causes the late symptoms.

The same is true in the case of late bladder symptoms. Cystoscopic examination will reveal an area of intense redness and sometimes ulceration. We have observed several cases of this type over a period of months, and a few over a period of two years.

Occasionally the urinary salts will be found deposited in the slough in the bladder and stones will be formed.

For the rectal symptoms the treatment consists of rest in bed, cleanliness of the lower bowel, and the injection of three or four ounces of warm olive oil into the rectum twice a day. Occasionally an opium suppository is necessary.

For the bladder symptoms we recommend rest, irrigation of the bladder, and the instillation of gomenol.

Some of these bladder and rectal complications may take from four to six months to clear up.

Fistula — We know that the natural progression of carcinoma of the cervix will cause a certain number of fistulae into the rectum or the bladder. In some of our earlier cases fistulae may have resulted from treatment of the carcinoma, but we feel certain that with our present-day knowledge and our improved methods of treatment, the incidence of fistula will be lower than in cases in which the patient has received no treatment at all. If the fistula appears soon after treatment we interpret it as being due to destruction from the disease. If it appears late, and there is no evidence of recurrence of the carcinoma, it is probably due either to progressive ulceration or the later complications mentioned above, and hence is the direct result of radium treatment.

The method of treatment of a fistula in the rectum must depend upon its size and the amount of inconvenience experienced by the patient. A small fistula may not require treatment. If a large fistula is present, it may be advisable to do a colostomy before attempting to repair it, and close the colostomy if and when the repair is successful.

The urinary fistula is more annoying on account of the constant flow of urine. If the fistula is small, it can easily be repaired by operation. If it is irreparable, the patient would be made more comfortable by transplantation of the ureters into the sigmoid.

End-Results

The statistics reported from the United States and abroad in regard to the end-results of treatment for carcinoma of the cervix are too numerous to be published separately, but if they are combined into one group, the following results will be shown:

Five-year cures	25 per cent
Clinical cures — three years	35 to 40 per cent
Clinical cures — less than three years	about 50 per cent

From the series of 325 cases here reported, 11 were pronounced hopeless and no treatment was advised. This decision would seem to have been justified by the fact that in these 11 cases the average duration of life was only six weeks. Twelve patients refused treatment or went elsewhere. Twenty-three patients had been treated elsewhere and referred back to the Clinic. Thus, we attempted to cure or palliate the disease in 97 per cent of our cases.

Below are shown in tabular form statistics of 241 cases of primary carcinoma of the cervix treated in the ten-year period from 1920 to 1929, inclusive.

Year	Treated	Traced	No.	Per Cent	Years	Dead	Duration of Life
			Living Over Five Years				
1920	8	8	2	25	9	6	11 months
1921	17	15	4	24	8	13	10½ months
1922	22	21	5	23	7	17	16 months
1923	26	23	5	20	6	21	17 months
1924	24	21	8	33	5	16	18 months
	97	88	24	25	5	73	14½ months
			Living — Three to Five Years				
1925	21	17	5	25	4	16	10 months
1926	30	25	9	30	3	21	13 months
	51	42	14	27½		37	11½ months
			Living — Less Than Three Years				
1927	32	26	10	31	2	22	14 months
1928	13	10	6	46	1	7	12 months
1929	48	42	35	66	−1	13	— months
	93	78	51	54		42	

It will be seen that of 97 patients treated over five years ago 25 per cent are alive and well. Patients not traced are counted as dead. The average duration of life of patients who died was fourteen and one-half months. Fourteen, or 27½ per cent are living from three to five years, and 54 per cent are alive from one to three years following treatment.

In conclusion, it is to be hoped that eventually the disease will be recognized earlier, and this, combined with our increasing knowledge of the behavior of cancer and our improved technic of treatment, will increase our curability rate.

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