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Use of radiation in the treatment of cervical carcinoma

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THE USE OF RADIATION IN THE TREATMENT OF CERVICAL CARCINOMA

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INTRODUCTION

The most important danger to the uterine cervix is cancer. Carcinoma of the cervix is second in frequency only to breast cancer among the neoplasms causing cancer deaths in females in the United States. (29)

Considerable progress has been made in understanding the spread of cancers of the uterine cervix since the Weitheim operation was devised and the first radium treatments given at the beginning of the century. The relationship of the zones of effectiveness of internal radium therapy and external radiation to the routes of spread of carcinomas of the cervix is well known. (10)

These main routes of cancer spread are along the vaginal mucosa, into the myometrium of the lower uterine segment, and from there to the fundus. Then it spreads into the network of lymphatics of the paracervical areas and on to the parametria and the pelvic wall lymphatics.

Cervical cancer may assume varied forms in its spread, and the complications which may result from this requires an adaptation of therapy to meet conditions, once treatment is begun. (11)

The purpose of this study on the use of radiation in the treatment of cervical cancer is to survey the results of medical

literature on this topic and to show the results of radiation treatment on cases of cervical cancer treated at the University of Nebraska College of Medicine.

HISTORY

The principles of the treatment of squamous cell carcinoma of the cervix with irradiation has changed little since 1922. The use of radiant energy in the treatment of cancer of the cervix followed only two years after Becquerel inadvertently produced his self-inflicted atomic energy burn by carrying a tube of radium in his vest pocket. Cancer of the cervix was the first of the internal cancers to be successfully treated by radium, probably due to its favorable anatomic position centered within the pelvis.

As time passed an American physician, Margaret Cleaves, treated a patient with cancer of the cervix using radium, in 1903. Later in 1907, Dominici (Laboratoire Biologigue du Radium) in Paris announced his principles of filtered radiation. Radium therapy then was developed principally in Stockholm and Paris. By 1922 radiation therapy was a practical and useful agent in cancer therapy, following the introduction of external X-Ray as a supplement to radium, in 1918.

By 1929 the Radiumhemmet in Stockholm had adopted the combined therapy in the management of most cervical cancer. But in Germany during and following World War I, the Germans were unable to acquire radium for medical use and thus their efforts turned

toward roentgen radiation. Seitz and Wintz, using improved apparatus of greater voltage and employing filtration in their studies of irradiation of the pelvis by crossfiring through multiple portals, published (1920) an early account encouraging results in the treatment of advanced cervical cancer.

In the 1930's the 400 KV, 500 KV and 800 KV units became available. Higher doses were hence given to the pelvic walls. By using these doses and more efficient techniques, survival rates were further improved. Since World War II two new roentgen ray generators, cobalt 60 units and 15 to 25 MEV betatrons, have been used extensively in the management of cancers of the uterine cervix. (10)

BACKGROUND INFORMATION

The ultimate aim of radiotherapy of cancer of the cervix is to eradicate the primary disease and its extension into the surrounding tissues. At the same time any injurious effects on the viability and function of the other pelvic structures must be minimized.

The effects of radiation are multiple. One of these is the cellular changes occurring, as first seen in the dividing nucleus. The nucleus assumes abnormal forms and there is an arrest of division of the nucleus. An indirect effect of radiation on the tumor is due to the response of the stroma and blood vessels. (11)

Anemic patients and patients with local and systemic infections do not tolerate irradiation as well as do normal individuals. Thus the tumor response in these persons is not as satisfactory. (33)

The patient receiving radiotherapy should be on a high protein, high calorie diet, increasing radiation tolerance.

STAGES AND SUBSTAGES

Cervical carcinoma is divided and subdivided within four stages. Stage I represents local disease confined to the cervix. Stage II cases are subdivided into Stage II-A and II-B in order to determine which cases are suitable for primary intracavitary radium therapy. In Stage II-A the disease is limited to the upper two thirds of the vagina and there may be minimal involvement of the parametria. In Stage II-B there is involvement of the lateral parametria and cancer extension almost to the pelvic wall, but there is still tumor free space between the tumor and the pelvic wall.

A survey of the literature (7) shows that the incidence of involvement of the pelvic wall lymph nodes is less than 25 per cent in Stage I and Stage II-A, around 40 to 50 per cent in Stage II-B, and above 60 per cent in Stage III cases.

The emphasis should be on the local disease which can be encompassed within the intracavitary radium therapy zone of adequate dosage in Stage I and Stage II-A. From Stage II-B on the disease is beyond the reach of intracavitary radium therapy. (11)

Stage III cases are also subdivided. Stage III-A represents a condition where only one pelvic wall is involved and Stage III-B includes those cases with both pelvic walls, or one pelvic wall and the lower one third of the vagina, involved. These Stage III-B cases have frozen or near-frozen pelves. Their prognosis is significantly worse than those patients of Stage III-A.

The Stage IV cases are subdivided into those in which the disease is limited to the pelvis, and those in which there is distant metastases. Radical radiation therapy is still indicated in Stage IV cases without distant metastases.

The following tables were compiled to show the treatment policies in two different conditions. Table I shows policies for carcinoma of the uterine cervix used in one institution; Table II summarizes treatment policies for Primary Carcinoma of the Cervical Stump.

TABLE I

Policy of Treatment in Carcinomas of the Uterine Cervix

Stage	Treatment	Exceptions
I	8,000-12,000 mgh in 2-4 insertions in 2-4 weeks, and 3,000-4,000 rads to parametria and pelvic walls **	If lesion is large, 2,000-4,000 rads are given first to the whole pelvis in order to secure optimal geometric conditions for intracavitary radium therapy.
II-A	Same as Stage I	Same as Stage I
II-B	4,000 rads to the whole pelvis in 4 weeks with telecobalt followed by 4,500-6,555 mgh in 2 insertions in 2 weeks.	For some selected cases of particularly infiltrative stony hard squamous cell carcinomas in Stage II-A, less whole-pelvis radiation may be given in order to give more local radium therapy. A hysterectomy is performed in the large endocervical squamous cell carcinoma if regression is slow.
III-A	5,000 rads to the whole pelvis in 6 weeks with the telecobalt followed by 4,000-6500 mgh in one insertion.	Same as Stage II-B
III-B	6,000 rads to the whole pelvis in 7 weeks with telecobalt occasionally with additional 2,000-3,000 mgh of radium.	
IV	Palliative.	Same as Stage III-B when no distant metastases.

**In cases of associated pregnancy, or up to 1 year postpartum, 4,000 rads are given to the whole pelvis because of increased probability of metastatic disease in the pelvic wall lymph nodes.

TABLE II

Policy of Treatment of Primary Cancer of the Cervical Stump

Stage	Treatment
I.	1. 72 hour radium applications 2. 3500 r trans vag. X-Ray (140 KV Al HVL) or if canal not located. Needle implant 6000 r.
II early	1. 2000 r to entire pelvis in two weeks (10 RX) 2. 4800 hr. radium application 3. 3500 r trans vag. (140 KV 3mm Al HVL) 4. 2000 r to parametrium
II advanced III	1. 2000 r to entire pelvis in two weeks 2. 48 hour radium application ** 3. 2000 r to entire pelvis in two weeks 4. 48 hour radium application **May substitute 400 r T.V. for the two radium applications: 140 KV 3mm Al HVL
IV	4000 - 6000 r Entire pelvis (lateral ports in part)

There have been many different techniques and applicators developed for intracavitary radium, but the technique and applicator per se are far less important than adherence to principles which have demonstrated their merit by favorable results over the years. (32)

The dose to the parametria and pelvic wall depends upon the total milligram hours, the location of radium within the pelvis, and the respective loading of the tandem and colpostats. The main contributor to the pelvic wall lymph nodes from the intracavitary radium system is the uterine radium because of the

central location. The contribution of the vaginal radiation depends upon the location of the radium. This varies with age, size of tumor, and distortion caused by disease. With high location within the pelvis the contribution to the obturator lymph nodes is approximately 1,000 r for each 4,400 mgh. The contribution to the hypogastric and external iliac lymph nodes is approximately half of that delivered to the obturator lymph nodes. (11)

Doses to Point A and B are calculated for the patients from tables. Point A refers to a point 2 cm lateral to the cervical canal and 2 cm from the mucosa of the lateral fornex and corresponds to the paracervical tissue. Point B corresponds to the pelvic wall and the obturator lymph nodes. It is on the same level as Point A and 5 cm lateral to the uterine canal. The limiting tolerance is measured at Point A with the intention of delivering the maximum possible dose to Point B. External radiation is calculated for the mid-pelvic tumor dose.

CANCEROCIDAL AND TOLERANCE DOSES

The ability to cure a cancer effectively by radiation without the destruction of the patient or her tissues is entirely dependent upon the ability to deliver to the cancerous area a sufficient dose of irradiation which kills the cancer and yet spares the normal tissue in the tumor area. So many variables modify the response in any one situation that a wide biological range is used in expressing this cancerocidal dose. Also the time over

which the dose is given is important because of dose of 5000 r in 24 hours would cause tissue necrosis, but when given over a much longer period of 20 days, it would probably cause cancer regression without severe reactions. Another variable other than the time dose relationship is the sensitivity of the tumor to radiation.

In the absence of obvious overt infection, the dose of choice is 8000 r delivered to Point A over a period of five weeks. (33,35) It is generally conceded that full irradiation by intracavitary sources to the entire pelvis is not practical because of the limitations dictated by the tolerances of the central structures. Thus to obtain cancerocidal dosages to the lateral pelvis, supplemented therapy to the lateral areas is necessary.

Iso curves are used in determining the dose rate being delivered to specific points. However, problems may occur due to anatomical deviations such as: the displacement farther or closer to the sources, of the bladder and rectum; or the unusual position or malposition of the applicator due to the tumor. The use of immediate localizaing films in the operating room serves as a good precaution.

Thus an important contribution to the radio therapy is the introduction of direct measuring devices for monitoring the dose rate being delivered to specific points. The scintillation probe counter is an excellent practical tool for this purpose. (33)

The limiting factors of external radiation are the skin tolerance, minimized with rotational or multiple skin ports; and the rectum. The orthovoltage X-Ray machine, cobalt teletherapy unit, Van de Graaff unit and the betatron, are available at the present time for supplemental radiotherapy.

The cobalt teletherapy unit is used for most supplemental therapy in this hospital at the University of Nebraska. The dosages reaching the midparametrial areas are increased without increasing the skin dosage with the cobalt unit, as compared with dosages of the orthovoltage X-Ray machine.

COMPLICATIONS OF RADIOTHERAPY

All radiation which is delivered to the pelvis for the treatment of cervical cancer causes residual damage to some degree to all pelvic organs and structures. The extent of the damage varies from an insufficient amount to cause clinical symptoms, to an amount sufficient to cause permanent loss of functions.

The small intestine is extremely sensitive to radiation and accounts for the major incidence of radiation sickness; however, the etiology of this illness cannot be accounted for entirely by this intestinal radiation. The skin, small intestines, large intestine, bladder, ureters, uterus, vagina, bone and ovaries may be involved and may lead to complications.

Generally the radiation injuries heal spontaneously if given enough time. Biopsies of pathologic areas subsequent to therapy should be delayed because radiated tissue is incapable of withstanding and combating infection.

SUPER LETHALITY AND RADIO-RESISTANCE

Super lethality is used to describe the condition in which the cancer lesion worsened after large doses of radiotherapy. The decrease in favorable results in Stage I lesions with an increase in gamma radiation is explained by the fact that the major portion of the cancer lies within the limits of safe tolerance of therapeutic radiation dosage; and when additional radiation is given, complications secondary to excessive radiation arise and survival does not increase as might have been expected. With later stages the major portion of the cancer is located in an area receiving less than a cancerocidal dose and an increase in dose will significantly increase the survival and will overshadow the secondary complications resulting from the radiation exceeding the safe-tolerance level.

Radio-resistance in reference to cervical cancer is really the relative resistance or insensitivity of tissue to the effects of radiation. Any tissue, normal or malignant, can be destroyed by radiation if the exposure is long enough. Thus the cancer is radio-resistant if it does not respond to the amount of radiation

that is safe to apply.

"In our review of the cases it was found that the majority of failures of radiation as defined by local cervical persistance of cancer were due to errors in application rather than due to radioresistance." (32)

There have been many attempts to try to predict radioresistance prior to therapy. These include grading the cells, histologic changes with small amounts of radiation, RNA/DNA ratio tissue cultures, and cytological techniques. Attempts to confirm these tests have not been uniform.

RESULTS OF IRRADIATION TREATMENT AT THE UNIVERSITY OF NEBRASKA SINCE 1958

During the period from January 1, 1958, to October , 1963, 99 patients with squamous cell carcinoma of the cervix were reviewed. The ages, stages, type of treatment, and parity are important considerations. Table III which shows the distribution of ages of the University of Nebraska patients, follows:

TABLE III
Distribution by Age

	20-29	30-39	40-49	50-59	60-69	70-79	80 and over
Stage 0	11	15	8		4		
Stage I	2	10	5	2	3	3	
Stage II		4	4	4	2	1	2
Stage III			3	3	3	5	
Stage IV			1	2	1		1
Total	13	29	21	11	13	9	3

Of this group one Stage 0 was treated with radiotherapy because she was a poor surgical risk. The remainder in this Stage were treated surgically.

Summary of Stage I

In Stage I, 25 patients were studied. The types of treatment and survival rates are summarized below:

TABLE IV
Correlation of Treatment and Survival Rates in Stage I

Procedure	No. of Patients	Alive, Cancer Free After 2 Years	per cent of 2 yr. survivals
Wertheim Hysterectomy Only	10	10	100
TAH Only	2	2*	100
Vaginal Hysterectomy Only	1	1	100
Radiation and Surgery	3	1	33.3
Radiation Only	9	8	88.9
Totals	25	22	88 (average)

*One patient has recorded recurrence after 28 months.

The average dose of radiation in roentgens delivered to Point A in the 8 patients still living was 7,887 r. The dosage ranged from 4,470 r to 10,900 r. Four patients died following therapy; the average dose to Point A in this group was 6,575 r. However, 2 patients received 11,734 and 9,376 r. The patient receiving the 11,734 r had received radiation to the abdomen

for another condition. She also had had a TAH performed. Due to this prior radiotherapy, she perhaps was not as sensitive to the radiation; for the dose she received is considered quite adequate. The patient receiving the 9,376 r dose also had an anterior exenteration performed five months following the radiation therapy.

Two patients received doses too low to be cancerocidal. However, one of these patients received 2,579 r to Point A. When she died with a coronary 27 months later, no sign of disease was found. The other patient had a BUN of 40 and an anemia. The dose of 2,614 r to Point A seems very low and ineffective as treatment.

In this Stage the complications-incidence was 33 1/3%. The complications of the radiation therapy were cystitis in one patient, bowel obstruction in one patient, and proctitis in two patients. The therapy on the patient with the bowel obstruction was stopped, but in the other patients, therapy was continued.

A comparison of the complications of radiation therapy and the complications of surgery shows that there is a higher incidence with radiation. However, it must be kept in mind that surgery patients were carefully screened and had no noticeable cancer symptoms. They were patients on whom the Papanicolaou smears were done routinely and revealed abnormal smears with symptoms.

The radiation-treated patients, on the other hand, either came in with the complaint of vaginal bleeding, indicating later Stage I carcinoma, or they were poor surgical risks. It is true that the survival of the surgery patients was higher, but it must be noted that these patients were younger and in earlier Stage I conditions as compared to the radiation-treated patients. None of the pathological reports on these surgery patients showed evidence of cancer spread to the nodes, thus indicating they were a more favorable group for survival.

TABLE V
Radiation Data for Stage I

Stage I...living							
Case #	Age	Date Treated	Total mg. hr.	Pt. A r	Rectum r		Remarks
1	62	10/61	5574	5768	4172		Very obese; radium only, cystitis
2	45	7/61	6600	10900	6216		Obese
4	39	3/61	6989	10564	6700		Proctitis
5	68	6/60	4658	4470	4385		Bowel Obst.
8	52	8/61	4100	8495	6051		
10	39	5/61	2190	8016	7050		TAH and BSO prior to radiotherapy
11	30	2/61	6430	6191	3279		Wertheim 6 wks. after radium
12	56	6/59	6083	8693	7488		
Averages - - - -			7104	7887	5630		
Stage I ...died						Months Alive	Remarks
3	66	5/60	1540	2579	--	27	Died of coronary No signoof disease Hysterectomy, '47.
6	42	10/60	7035	11734	7896	26	TAH Prior Rad to Abdomen for Another condition
7	37	10/58	7916	9376	7465	11	Ant. Exenteration Sl. Proctitis
9	77	6/59	2614	2614	--	2	Anem., BUN 40
Averages			4776	6575	7680		

Summary of Stage II

A total of 17 patients were seen with Stage II disease. One patient refused therapy and was lost to followup in 1961. The dose of radiation is tabulated in Table VI. Thus, a total of 16 patients were treated with radiation. Nine (9) patients are living, 7 of whom were treated more than two years ago. One patient was treated less than 6 months ago and the other patient had a radical hysterectomy one year after radiation (dose to Point A was 7,000 r). The nodes were reported as negative (no evidence of carcinoma.) The last time this patient was seen, metastatic lesion to the spine was found and this was treated with radiation therapy.

The average dose to the patients still living was 8,932 r to Point A. The average dose to Point A for patients who died was 7,161 r, or a dose, which, in most instances, is less than cancerocidal. One of the deaths of these patients was following anterior exenteration. Another died with a CVA but had residual carcinoma. One of these patients had received 9,900 r to Point A but had a pelvic abscess. With this infection the radiation was probably not as effective. Another patient developed a perforated uterus following radiation and died with peritonitis, secondary to this complication. The 2 year survival rate for this group is 53%. This is considerably lower than survival statistics from Mayo Clinic. (8) Their rate for five years was 72.8%.

TABLE VI
Radiation Data for Stage II

Case No.	Age	Date Treated	Total mg. hr.	Pt. A r	Rectum r	Months Alive	Remarks
Stage II...living							
1	42	6/63	7746	9800	2350		
3	55	12/59	10416	10470	10149		Single Pul. Met. treated with irrad. nodes neg.; exenteration
5	39	3 /60	7707	10460	6650		Anemia;
7	47	9/61	5760	9077	6260		BSO 9/60;Bil. uretero sigmoidos-tomy. Hydroureter
10	48	5/60	7614	8214	7320		Mild proctitis
11	51	2/62	7078	7081	3542		Rad. Hys. 1 year after rad. Nodes and uterus neg. 11/63 spine met.
12	51	5/59	3634	5917	7210		Colitis
13	42	2/61	7471	10814	7874		Compression bladder
14	64	1/61	6984	8560	7504		BUN 21.5
Averages - - - -			7157	8932	6540		
Stage II...died							
2	35	5/60	5839	8173	6982	7	Died post. op. Exenteration
4	66	12/60	7734	9300	6780	7	Died with CVA Diabetes
6	88	7/59	6480	5384	6200	11	Uterine perf.& Peritonitis
8	75	5/58	7300	6500	6180	35	BUN 23
9	90	2/58	3500	5570	5400	17	
15	32	9/60	7564	9900	5800	10	Pelvic abscess
17	58	6/58	5220	5300	5008	22	Cordotomy
Averages - - - -			6234	7161	6050		

Summary of Stage III

A total of 14 patients were seen with Stage III disease. Only one patient is living following treatment, and she is free of disease as of 3 years and 8 months post-treatment. The average

dose to Point A in this Stage III group of patients was 6563 r with the range of 2944 r to 12,426 r. The incidence of complications is much higher in this group. Complications included: one intestinal obstruction, five ureteral obstruction, one proctitis, and two patients with severe anemia. One of these patients had a draining fistula (complication from original surgical treatment for carcinoma) two years prior to radiation.

TABLE VII
Radiation Data for Stage III

Case No.	Age	Date Treated	Total mg. hr.	Pt. A r	Rectum r	Months Alive	Remarks
Stage III...living							
1	75	4/60	6266	7080	6062		
Stage III...died							
2	47	2/61	7033	12426	12208	30	Partial bowel obst. Hydronephritis
3	72	5/58	----	4290	4110	9	Anemia
4	51	9/58	4681	4734	6251	37	Parametritis; Ureter obstruction
5	65	11/60	3059	4464	3820	32	Obst. ureter
6	65	1/59	6932	6455	7764	2	Diag. 2 yrs. prior; Hys. 2 yrs. prior; Abscess
7	77	12/58	4016	4367	3809	2	Hydronephrosis BUN 25-30
8	49	6/60	6940	9142	6443	40	Met. to Skin
9	73	10/61	----	8600	8600	2	3000 r radiation prior for draining fistula
10	73	3/60	5430	3675	3258	8	Proctitis, anemia Hematemisis, diverticulitis--stopped treat.
11	45	4/59	5355	9124	6512	11	Uretero obst. anemia BUN 25
12	67	2/60	1440	2944	2000	3	
13	56	5/60	6322	6463	4198	12	Refused further ext. radiation; anemia
14	58	8/59	6545	8633	7881	6	Bronchiogenic Ca
Averages---			5250	6563	5912		

Summary of Stage IV

A total of five patients were seen with Stage IV disease. Two patients were treated with radiation in this group. One was treated with an anterior exenteration yielding apparent success. One patient refused therapy and the other patient died before therapy could be started. The radiation therapy in these patients was palliative because there was metastases in the lung in one patient and the other patient had received prior radiation. The patient with lung metastases received a 7000 r mid-pelvic dose.

The survival rates for Stage III and IV are very poor and 0% for Stage IV radiation therapy; however, the number of patients is too small to be significant.

RESULTS OF DIAGNOSTIC STUDIES

Metastatic surveys were done on all Stage II and Stage IV patients. All Stage II cases were negative and four out of the five Stage IV's were negative in the X-Ray studies done on this group. The intravenous pyelogram was the most consistent abnormal finding with either an obstructed ureter or a non-functioning kidney on one side. Seven IVP's were done on patients with Stage I disease and three were abnormal. According to one author, the abnormal findings on pretreatment pyelograms diminish the chance of the patient surviving one year by approximately 50%. (31)

In this study conducted at the University of Nebraska, there was a high number of patients in the 22-29 age group and two

of these patients had invasive carcinoma. One of these patients with invasive carcinoma had been followed closely with Papanicolaou smears and after three dysplastic smears in a six month period, a cone was done showing invasive squamous cell carcinoma. The high number of patients in the lower age groups is probably due to the type of patients seen. Most of the patients were from the lower economic groups and many have been pregnant several times in their teens.

Two year survivals were calculated for the various stages. Survival statistics are reported as five year cures, traditionally. However, for evaluating results of treatment, data based on survival without evidence of disease two years after treatment for cancer of the cervix are also considered reliable. (33) Eighty-five per cent of the patients with persistent cancer show evidence of persistence within two years.

Between the second and fifth years subsequent to therapy, only 10% of the patients treated for cervical cancer demonstrate persistence of the cancer for the first time; and if the limitations of the data are kept in mind, it is possible to evaluate adequately the results of treatment at various periods.

It is of interest the percentages of blood types in this study. In this group of patients, 79 of the 99 had their blood typed and 46.7% were O, 49.4% were A, 2.5% were AB, and 1.3% were B. Of note is the low number of type B, but because the

study is small, this may be of little significance.

A study was done by Garriga (14) on the relations of blood group to radiation response. Groups A and B responded in a very similar manner and when compared to group O, the latter had a significantly better response to radiation therapy.

CONCLUSIONS

1. The primary treatment for invasive cervical carcinoma at the University of Nebraska Hospital has been intracavitary radium supplemented with external radiation. The exception would be a few highly favorable Stage I's and especially those in the younger age groups where castration is not desirable.
2. Surgery is apparently more effective in Stage I, but the patients were favorably selected whereas the patients with radiotherapy were not selected and had later Stage I disease.
3. Salvage rates are low in the Stage II, III, and IV groups and also in the patients in whom the initial treatment was inadequate.
4. Many failures of radiation are due to errors in application rather than due to radioresistance.
5. The status of the urinary tract markedly influences the survival rates.
6. Earlier diagnosis through public education and more routine pelvic examinations combined with Papanicolaou smears at regular intervals promise the most immediate early diagnosis, thus benefiting the patient with this disease.

7. Carcinoma of the cervix is a curable disease when detected in its earliest stages.

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