

Treatment of Endometrial Carcinoma Stage II

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ABSTRACT

Between January 1971 and December 1980 fifteen patients diagnosed of adenocarcinoma of the endometrium, stage II seen and treated at the University of Michigan Hospitals, are reviewed. Ten patients were treated with radiation therapy alone, five received hysterectomy after radiation. The five year survival of the patients receiving radiation and surgery was 100%, although one of them died after 62 month after treatment. Of those receiving radiotherapy alone two died at 7 and 24 months after therapy. All of the patients died of distant metastasis. Radiation cystitis was observed among surgically treated patients, while proctitis was observed in 3 cases receiving radiation alone. Though the number of cases reported is small due to rarity of the disease, it appears that radiation alone could provide reasonable tumor control. Also it appears that preoperative irradiation might lead to a longer survival. One patient who survived 62 months had para-aortic node involvement.

INTRODUCTION

Carcinoma of uterine corpus is the most prevalent tumor of the female genital tract¹⁾. In 1941 Heyman and Renterwell classified endometrial carcinoma

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involving the cervix as "cancer corporis et colli uteri"²⁾, and the International Federation of Gynecology and Obstetrics adopted lesions of corpus et collum as stage II, endometrial carcinoma³⁾.

The management of such tumors has included a wide variety of treatment programs including either radiation therapy alone or combined with surgery. Thus radiation therapy given in the form of external beam or radium, or a combination of the two approaches and surgical excision have been reported by various oncologists, Bruckman, Homesley and Kottmeier (1977).^{4~6)} The treatment delivered at Mayo Clinic reviewed by Malkasian was basically total hysterectomy and bilateral salpingo-oophorectomy with postoperative radiation added on an individualized basis.⁷⁾

Rutledge⁸⁾ reviewed the role of radical hysterectomy in adenocarcinoma of the endometrium and concluded that the combination of conservative hysterectomy and irradiation was of greater usefulness in the majority of cases.

The purpose of this report is to evaluate the treatment plan, results and prognosis of fifteen patients with endometrial carcinoma who have received various combinations of treatment at the University of Michigan Hospitals during the decade of 1971 through 1980. The survival rate, local recurrence and complications subsequent to the treatments given to these cases will be analyzed.

MATERIALS AND METHODS

During the decade beginning with January of 1971 and ending at the end of December of 1980, twenty patients with Stage II adenocarcinoma of

the endometrium, were treated by radical irradiation, with or without surgical intervention at the University of Michigan Hospitals. All patients were referred from the Gynecology Oncology Service of the University Hospital, following presentation of the case at the weekly Gynecology-Radiation Therapy-Pathology Conference. The definition of cervical involvement (stage II) was based on fractional curettage, which demonstrated the presence of malignant tissue along with normal endocervical glands. Patients with the following conditions were excluded from this study: 1) Presence of malignant cells floating in the endocervical curettage material. 2) Histologically evidence of surgical involvement of the cervix in patients originally staged as I.

All patients received routine pretreatment work-ups, including chest X-ray, intravenous pyelogram, barium enema, cystoscopy and sigmoidoscopy, in addition to a complete pelvic examination, blood counts, urine analysis and blood chemistries. All the pathology specimens were reviewed by one of the authors (N.K.) and 17 of 20 cases were proven to be clinical and histological stage II endometrial carcinoma. Complete follow-up information was available except in two patients. Two patients were lost to follow-up at 26 months and 42 months. Both were alive without evidence of disease at that time. Thus, fifteen patients will be included in this review. There were thirteen white, one black and one unrecorded race.

The average age was 60 years, ranging from 26 to 82 years. Eleven patients were postmenopausal, whereas four were premenopausal. Vaginal bleeding was their chief complaint. Common me-

dical problems in these patients included histories of hypertension (10), diabetes (2), obesity problems (5), cardiovascular diseases (3), alcoholism (1) and urinary stress incontinence (1). There were two patients who had taken estrogen previously. One patient (#7) was found to have a concomitant, primary endometroid carcinoma of the ovary.

Histologic findings were made up of adenocarcinoma (74%), adeno-squamous cell carcinoma (13%) and adenoacanthoma (13%). Adenocarcinomas with benign squamous components were classified as adenoacanthoma. Adenocarcinomas with malignant squamous cells were recorded as adeno-squamous carcinoma. Their distribution according to grade and histology is shown in Table 1.

Seventy three percent of the patients had uteri that sounded to be more than 8cm in length. Their average sounding was 9cm, ranging from 7cm to 12cm. All patients have been followed for a minimum two years. The maximum follow-up was 10 years. The patients were treated with a variety of radiation therapy techniques (Table 2). Ten patients received radiation therapy alone. External irradiation was delivered five days a week by Co 60 AP-PA parallel opposing fields, which had an average size of 15×15cm with a daily dose of 180 cGy. The total dose ranged from 2000 cGy to 4000 cGy in 2 to 4 weeks (Fig. 1). When 2000 cGy of external beam irradiation was given, two intracavitary radium applications (including Heyman capsules, tandem and ovoides (Fig. 2a, 2b, 3a, 3b), followed by a boost of external irradiation to the pelvic side walls was given. If the total pelvic dose was 4000 cGy a single intracavitary application of

Table 1. Distribution of Histologic Grade in Endometrial CA, Stage II

Histologic Grade	Adeno Carcinoma	Adeno Squamous Carcinoma	Adeno Acanthoma
Grade I	3	—	—
Grade II	4	—	1
Grade III	4	2	1

Table 2. Case Histories, Treatment and Follow up of the Patients with CA of Endometrium, Stage II

Patient No./Age/Race	Treatment				Status of Primary Site/Site Metastasis	Complication	Status After Treatment
	Radiation	Surgery	Radiation	Dose(cGy)			
1 66 W	1) Ext. 2) IC 2x 3) Boost	None	1980 cGy 7,400 mghrs	A: 9330 U: 5000	Controlled	None	DI-30months (MI)
2 44 W	1) Ext. 2) IC 2x 3) Boost	None	1980 cGy 7,540 mghrs	A: 9400 U: 5000	Controlled	None	NED+120months
3 55 B	1) Ext. 2) IC 2x 3) Boost	None	1400 cGy 7,300 mghrs	A:9170 U:5000	Uncontrolled/ Perit. & Liver	Proctitis	DOD-24months
4 76 W	1) Ext. 2) IC 2x 3) Boost	None	1980 cGy 9,400 mghrs	A: 9350 U: 5000	Controlled	None	DI-44months (MI)
5 56 W	1) Ext. 2) IC 2x 3) Boost	None	1980 cGy 6,320 mghrs	A: 9410 U: 4725	Controlled	Proctitis	NED+46months
6 82 W	1) Ext. 2) IC 2x 3) Boost	None	1980 cGy 7,300 mghrs	A: 9200 U: 5000	Controlled	None	NED+86months
7 72 W	1) Ext. 2) IC 2x 3) Boost	None	1980 7,300 mghrs	A: 9500 U: 5000	Controlled	Proctitis	NED+25months
8 60 W	1) Ext. 2) IC 1x	None	4140 cGy 3,850 mghrs	A: 8650 U: 5000	Uncontrolled /Abdomen	Intestinal obstruction	DOD-7 months
9 66 W	1) Ext. 2) IC 1x	None	5040 cGy 5,200 mghrs	A: 9130 U: 5400	Controlled	None	NED+50 months
10 46 W	1) Ext. 2) IC 2x	None	3960 CGy 7,237 mghrs	A: 9050 U: 4500	Controlled	None	NED+66 months
11 70 W	1) Ext. 2) IC 1x	TAH & BSO	3960 4,000 mghrs	A: 7960 U: 4900	Controlled	Cystitis	NED+36months
12 63 W	1) Ext. 2) IC 1x	TAH & BSO	3960 cGy 4,900 mghrs	A: 7960 U: 4500	Controlled	None	NED+63months
13 77 ?	1) Ext. 2) IC 2x 3) Boost	TAH & BSO	1980 cGy 7,200 mghrs	A: 9420 U: 5000	Controlled	None	NED+51 months
14 26 W	1) IC	RH & PLD	5,800 mghrs	A: 4000	Controlled	Cystitis	NED+56 months
15 42 W	1) IC 1x 2) Ext rad to PA	RH & PLD	4,410 mghrs	A: 4405	Uncontrolled /PA: 5000 liver, lung	None Peritonium,	DOD-62 months

Abbreviations

A-A point
U-pelvic brim
cGy-centi gray
DOD-death with disease
DI-death with intercurrent disease
NED-no evidence of disease
MI-myocardiac infarction

Ext.-external radiation
IC-intracavitary radiation
TAH-total abdominal hyterectomy
BSO-bilateral salpingo-oophorectomy
RH-radical hysterectomy
PLD-pelvic lymph node dissection
PA-paraaorta

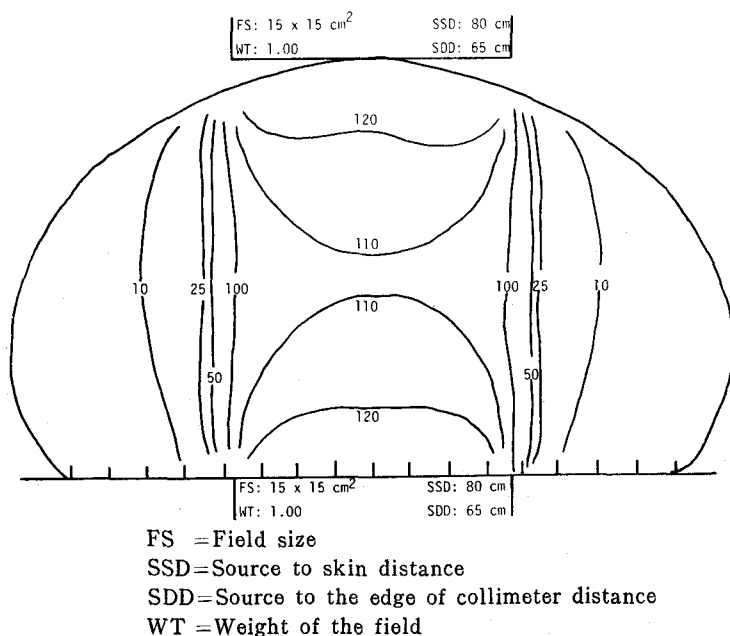


Fig. 1. Dose distribution for carcinoma of the endometrium stage II with two opposing cobalt 60 beams.

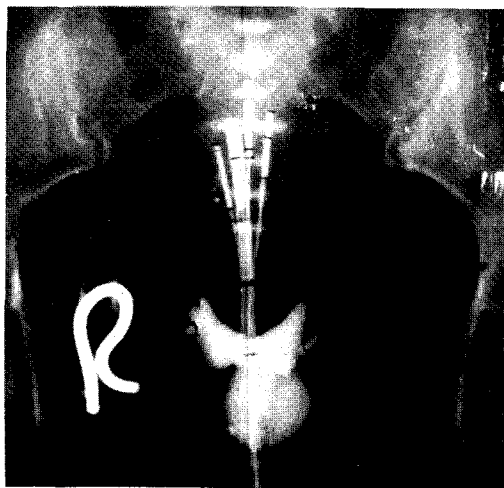


Fig. 2a. Anterior-posterior radiograph showing; Heyman capsules, tandem and ovoids.

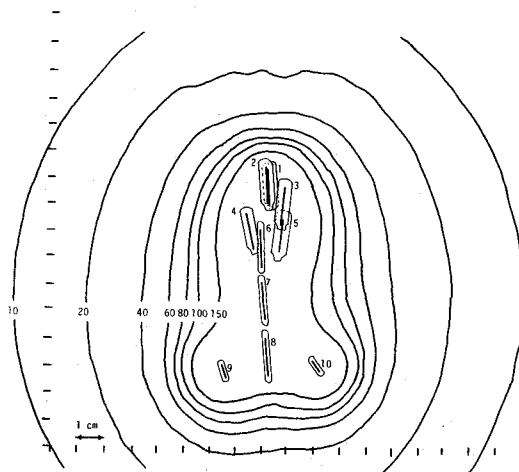


Fig. 2b. Dose/rate distribution (rads/hour) on a coronal plane (parallel to uterine canal)

Ra 224 was used.

An average dose of 9040 cGy (range 8700 to 9500 cGy) to point A and average dose of 4930 cGy (range 4500 to 5000 cGy) to the pelvic brim were delivered. The remaining five patients were treated with preoperative irradiation followed by surgery as part of the initial treatment planning. Three patients had a total abdominal hysterectomy, and

bilateral salpingo-oophorectomy (TAH-BSO). Two had radical hysterectomy (RH) and pelvic lymph node dissection (PLD). For those who had RH, only intracavitary radium treatment was given. One patient (#15) with para-aortic node involvement at the time of radical hysterectomy subsequently received additional post-operative, para-aortic irradiation, total dose 5000 cGy in five



Fig. 3a. Lateral radiograph showing; Heyman capsules, tandem and ovoids.

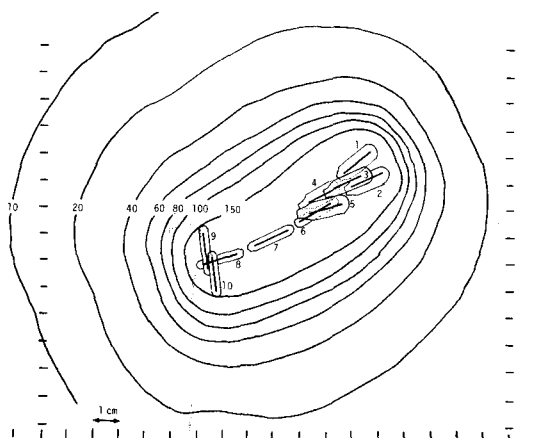


Fig. 3b. Dose rate distribution (rads/hour) on sagittal plane through the uterus.

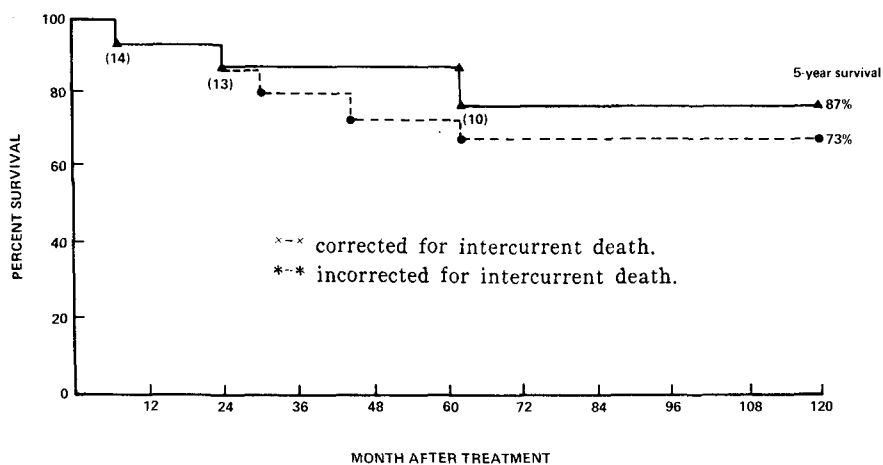


Fig. 4. Actuarial survival of endometrial carcinoma, Stage II. Numbers in parenthesis are patients at risk at the beginning of each interval.

Table 3. Review of Surgical Specimen

# Patient	Treatment Method		Pathology		Status after Treatment
	Radiation & Dose	Type of Surgery	Residual tumor	Myometrial invasion	
11	Ext. 1C 1x 3,960cGy/4,000 mghrs	TAH+BSO	negative	negative	NED+36months.
13	Ext. IC 2x Boot 1,980cGy/7,200mghrs	TAH+BSO	positive	negative	NED+51months.
14	IC 1x 5,800 mghrs	RH+PLO	negative	negative	NED+56 months.
15	IC 1x 4,410 mghrs Ext to PA 5,000 cGy	RH+PLD	negative	positive	DOD-62months
			*Para-aortic node positive		

weeks. Of these five patients treated with surgery, two patients #13 and #15 had residual tumor cells in the endometrium and myometrium. One of them (#15) had para-aortic node involvement. During the period of this study, none of the patients with stage II endometrial carcinomas were treated with surgery alone. Only one patient (#3) received chemotherapy (Melfalan), after local failure.

RESULTS

Survival;

Table 2 summarizes the methods and the results of 15 patients with Stage II endometrial carcinoma. It may be seen that two patients (#8 and #3) who received radiation alone, died of primary disease at 7 and 24 months after the initial treatment. Another patient (#15) treated with one intracavitary radium application followed by radical hysterectomy and pelvic lymph node dissection, developed metastases in the lung at 60 months and died 2 months later. It was noteworthy that this patient (#15) was found to have para-aortic node metastasis at the time of the operation and was given 5000 cGy of external radiation to para-aortic node area. The prolongation of survival of this patient was beyond our original expectations and prognosis. All of three patients died with pelvic and distant disease.

Two patients died from intercurrent disease at 30 and 44 months, respectively. At the time of their death, no evidence of recurrent disease was present.

Figure 5 records the percent survival curve after the initial treatment. The overall five year survival for the entire group was 73%, whereas survival corrected for intercurrent disease was 87%, ranging from 25 months to 120 months after diagnosis. There was no notable difference between the effects of radiation alone and those of radiation plus surgery, except for a slightly lower mortality in cases receiving surgical treatment as

well.

Review of histopathology;

As shown in table 3, a patient who had residual disease (#13) without myometrial invasion lived without evidence of disease for 51 months. However, another patient, without evidence of residual disease (#15), but who had myometrial invasion and positive para-aortic nodes, died with disease at 62 months. Of three patients who died with disease, two had moderately differentiated carcinoma and one had poorly differentiated carcinoma.

Complications;

During the follow-up period, two patients developed radiation cystitis and three patients radiation proctitis. The two patients with cystitis developed the symptoms approximately 15 months after hysterectomy. The three patients with proctitis showed the first symptoms between 15 to 24 months, after radical irradiation. None of these patients needed an aggressive management for complications.

DISCUSSION

It would have been desirable to have a large number of cases than our fifteen patients studied in this review. However, the present results do augment the previous publications in which even smaller cases of stage II adenocarcinoma of endometrium were evaluated (Fayos)⁹. In light of the generally negative consensus involving the presence of positive para-aortic nodes, the long term survival of our patient #15 who died at 62 months after the initial treatment is of interest. While this finding could be regarded as adding still another controversial evidence to the issue of para-aortic radiotherapy, it provides another clue that para-aortic irradiation can be clearly beneficial, and therefor should be considered in radiation therapy regimens of advanced cases.

It is noteworthy that a combination of radiotherapy and simple hysterectomy has been reported

to yield superior results (Tak)¹⁰², as well as that a pre-operative radiotherapy using external pelvic irradiation and intracavitary application is better than post-operative radiotherapy. This is possibly due to the fact that the method allows to obtain an ideal dose distribution and to irradiate a minimal volume of the bowel which might result in adhesions in pelvis post-operatively (Tak)¹⁰³. However Abayomi et al, reported the results of radiation therapy alone in 66 cases of endometrial carcinomas because of medical contraindications to surgery¹¹³. Local control was achieved and three year actuarial survival was 78% for stage I and Stage II.

Berman reported that actuarial survival was the best for the group of patients treated with radiation therapy alone¹²³. Our study suggests that a combined approach might give a little better results. The five year relapse-free survival was 100% (none of 5 died) in radiation and surgery group and 75% in radiation alone group (2 out of 8 died). This is supported by a previous report by Kottmeier (1977) who obtained 52.8% of 5 year survival with radiation alone, whereas a combination of radiation and surgery produced a 5 year survival rate of 83 %⁶³.

In 1973 Kottmeier summarized the results from 52 institutions reporting 5 years survival statistics of 70% for patients with stage I disease and 47.4 % for patients with stage II disease, respectively¹³³. Another review by Rutledge in 1974 combining results from 205 stage II patients, reported 5 year survival figures of 51%⁸³. Fayos reported that the overall five year survival of 294 cases of endometrium carcinoma was 79%⁸³. His report on 5 year survivals with respect to stages I, II and III were 83%, 91% and 40%, respectively⁹³. Bruckman also reported 83% relapse free, actual 5 year survival of stage II carcinomas of the endometrium when they were treated with external irradiation 4000 cGy, intracavitary irradiation 4000 mghrs, and surgery (TSH+BSO)⁴³.

Similarly Greenberg, et. al reviewed 34 patients with stage II endometrial carcinoma. Nineteen

patients were treated by standard irradiation therapy techniques using two intracavitary applications and external radiation. The remaining patients were treated by a wide variety of treatment programs. It was found that there was excellent local control and no significant difference between the two groups¹⁴³.

Because of the varied conditions under which treatments are given, a comparison of different treatment modalities is difficult. However, our data along with those from others suggest that a significant proportion of patients treated with radiation therapy alone due to poor operative risk, could achieve good prognosis.

It is of interest and perhaps significant that those who had radiation alone developed proctitis, while those receiving radiation and surgery showed cystitis. This might reflect the irritative effect of surgery on irradiated bladder. Though the numbers are small to make any conclusions. For this reason, future case histories involving radiation and surgery, which will undoubtedly continue inasmuch as the combination appears to give better results in selected cases, will have to be carefully reviewed. Any further consistency in cystitis developments after combined radio-surgical therapy should be closely monitored.

SUMMARY

Fifteen patients carcinoma of the endometrium, stage II treated at the University of Michigan Hospitals during a ten year period between 1971 and 1980 are evaluated. Of the fifteen patients given radiation therapy five received hysterectomy after radiation. The five year survival of the patients receiving radiation and surgery was 100% although one of them died after 62 month after treatment. Of those receiving radiotherapy alone two died at 7 and 24 months after therapy. All of them died of distant metastasis. Transitional cystitis was observed among surgically treated patients, while proctitis was observed in 3 cases receiving radiation alone. Though the number of

cases reported is small due to rarity of the disease, it appears that radiation alone provides reasonable tumor control. Also it appears that radiotherapy followed by hysterectomy might lead to a longer survival after radiation. One patient who survived 62 months postoperatively had para-aortic lymph node metastases.

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