

MIXED MESODERMAL SARCOMA OF THE UTERUS*

By PHILIP J. DiSAIA, M.D.,† JOSEPH R. CASTRO, M.D.,‡
and FELIX N. RUTLEDGE, M.D.

HOUSTON, TEXAS

MIXED mesodermal sarcoma of the uterus is a relatively rare tumor that is associated with a grave prognosis. Sternberg *et al.*,⁵ for instance, reported 21 cases, all succumbing to the disease. In 1966 Edwards² reported a 42 per cent 2 year survival in a selected group of patients who were treated at the M. D. Anderson Hospital and Tumor Institute at Houston, Texas with preoperative radium therapy followed by hysterectomy.

This paper enlarges on that report by analyzing the treatment techniques and results on all patients seen at our hospital with this diagnosis during the period from March 1944 through December 1969, including a recent group of patients treated with preoperative whole pelvis irradiation, radium insertion and hysterectomy.

CLINICAL MATERIAL

From March 1944 through December 1969, 101 patients with mixed mesodermal sarcoma of the uterus were seen at the M. D. Anderson Hospital. Follow-up information is available on 94 patients including 19 patients who in early years received no treatment because of far advanced disease. Thus, 75 patients are available for analysis of treatment techniques.

The age range of 31 to 85 years with an average of 59.9 years is comparable with other reported age incidences.^{1,3,4,7} Seventy-five of the 94 patients were in the fifth, sixth, or seventh decades of life when the diagnosis was made, as shown in Figure 1.

Twelve per cent of the patients in our series were nulliparous, while 30 per cent

were Negroid, suggesting a higher incidence than in Caucasians (Table 1).

Careful review of the history of the 94 patients revealed that none of the patients had received either pelvic irradiation or intracavitary radium prior to the diagnosis of mixed mesodermal sarcoma of the uterus; thus, preliminary irradiation is probably not significant in the etiology of this lesion.

The interval between the onset of symptoms and the diagnosis was relatively short, usually less than 5 months.

Postmenopausal bleeding was the dominant presenting symptom. Abdominal pain and distention were experienced by a very small percentage of the patients. Other complaints included watery vaginal discharge, anorexia with weight loss, dysuria, and/or edema.

The association of obesity, diabetes and hypertension in the patients with this

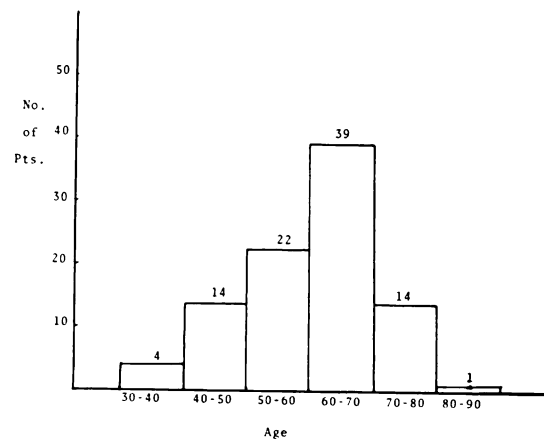


FIG. 1. Age distribution.

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From the Department of Surgery, Section of Gynecology, The University of Texas, M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas.

† Present Address: Section of Gynecologic Oncology, Los Angeles County—University of Southern California Medical Center, Los Angeles, California.

‡ Present Address: Section of Radiation Oncology, University of California Medical Center, San Francisco, California.

malignancy was high (Table 1). Thirty-eight patients (40 per cent) were diabetic at the time of diagnosis, 43 patients (45 per cent) had a diagnosis of obesity, and hypertension was seen in 23 patients for an incidence of 24 per cent of the total group.

CLINICAL GROUPING

Since the extent of disease is usually of prognostic significance in gynecologic malignancies, a clinical-surgical classification was established as follows:

Group I: Disease confined to corpus uteri.

Group II: Extension to cervix, vagina and/or parametrium.

Group III: Extension outside pelvis.

Physical examination, radiographic findings and/or surgical findings were utilized in this classification scheme; unfortunately, depth of myometrial invasion was not sufficiently frequently recorded to be of consistent value.

TREATMENT TECHNIQUES

Various treatment modalities and combinations thereof have been used in the treatment of these patients including: (1) hysterectomy alone; (2) hysterectomy followed by postoperative external irradiation; (3) preoperative radium followed by hysterectomy; and (4) irradiation alone where surgery was refused or contraindicated because of the extent of disease or medical problems. Recently (1966-1969) most patients received external irradiation

TABLE I

Parity	No. of Patients
Nulligravida	11
Multigravida	80
<i>Race</i>	
Caucasian	66 (70%)
Negro	28 (30%)
<i>Associated Diseases</i>	
Diabetes	38 (40%)
Hypertension	23 (24%)
Obesity	43 (45%)

TABLE II
LENGTH OF SURVIVAL OF PATIENTS
DEAD WITH DISEASE

No. of Patients	Months			
	0-12	12-24	24-36	>36
	50	11	4	4

73 per cent dead within 12 months of diagnosis.
88 per cent dead within 24 months of diagnosis

plus radium preoperatively in an attempt to give a more homogeneous dose to uterus and pelvic lymphatics. In earlier years, 19 patients were not treated, mostly because of advanced disease, although a few refused treatment.

When preoperative radium was utilized, 5,000 mg.-hours of radium were given in 2 insertions of Heyman capsules and intra-uterine tandem plus 7,000-8,000 rads vaginal mucosal dose from Fletcher colpostats. The radium insertions were separated by 2 weeks. When external irradiation was utilized, whole pelvis irradiation of 4,000 rads in 4 weeks with the 22 mev. betatron photon beam was delivered through antero-posterior-posteroanterior 15×15 cm. portals, followed by a Heyman capsule intra-uterine packing to deliver 2,500 mg.-hours. Afterloading Fletcher colpostats were also inserted to deliver 4,000 rads mucosal dose to the upper vagina. Hysterectomy and bilateral salpingo-oophorectomy followed the preoperative radium (or external irradiation) in 4-6 weeks.

RESULTS

The results are shown in Tables II-VI according to extent of disease and treatment modalities. The 24 month NED (no evidence of disease) rate is valid for analysis of treatment techniques since almost all recurrences or distant metastases occur within that time period (Table II).

Survival is directly related to the extent of disease as shown in Table III. Those patients with tumor confined to the corpus have a good chance of local control (68 per cent) and survival (53 per cent), although

TABLE III
OVER-ALL RESULTS BY EXTENT OF DISEASE

Extent of Disease	No. of Patients	NED (2 years)	Local Control (Pelvis)
Group I Corpus Alone	34	18/34 (53%)	23/34 (68%)
Group II Cervix, Vagina and/or Parametrium	35	3/35 (8.5%)	10/35 (29%)
Group III Outside Pelvis	25	0/25 (0%)	5/25 (20%)

NED= No evidence of disease.

some patients are lost because of upper abdominal disease or distant metastases. Extension of disease outside the corpus markedly lessens the outlook (Table III).

Analysis of the results as related to the various treatment modalities is made more difficult by the necessity of correlating the results with the extent of disease. The previous report by Edwards² indicated improved results when preoperative radium was utilized rather than hysterectomy alone. However, most of these patients had limited disease and, in fact, in Group I, it is difficult to show an advantage of one modality over another with the exception that some combination of surgery and radium appears preferable to either hysterectomy alone or irradiation alone (Tables IV, V, and VI).

Table VII compares the local control and survival in Groups I and II between pa-

tients who have been treated with hysterectomy or irradiation alone, in contrast to those receiving preoperative radium or external irradiation followed by hysterectomy. Patients with microscopic disease found incidentally at hysterectomy who received postoperative irradiation are not included. A statistically significant difference is not shown between preoperative radium and external irradiation. Both show an excellent rate of pelvic control, and markedly improved results over irradiation or hysterectomy alone.

DISCUSSION

The term mixed mesodermal sarcoma is appropriate because it gives some indication of the nature of the tumor, and bears relation to a similar type of tumor occurring in other organs. There appears to be no benefit in further subdividing these tumors

TABLE IV
TREATMENT PLANS IN GROUP I WITH RESULTS

Treatment	No. of Patients	NED (2 years)	Local Control
Hysterectomy Alone	5	2	2
Hysterectomy + Postoperative Irradiation	7	4	5
Preoperative Radium + Hysterectomy	12	7	10
Preoperative Irradiation + Radium + Hysterectomy	5	3	4
Irradiation Only	5	2	2
Total	34	18 (53%)	23 (70%)

TABLE V
TREATMENT PLANS IN GROUP II WITH RESULTS

Treatment	No. of Patients	NED (2 years)	Local Control
Hysterectomy Alone	5	0	0
Hysterectomy + Postoperative Irradiation	5	1	4
Preoperative Radium + Hysterectomy	1	1	1
Preoperative Irradiation + Radium + Hysterectomy	5	1	5
Irradiation Only	6	0	0
Incomplete Treatment	13	0	0
Total	35	3	10

histologically since the prognosis is similar for the entire group with the possible exception of the pure homologous type known as endometrial stromal sarcoma.

There are various theories of origin of these tumors,^{2,5} but probably they arise from the epithelial stroma of the endometrium, cervix or upper vagina, occurring in children as sarcoma botryoides or in adults as mixed mesodermal sarcoma of the endometrium. The tumor tissue appears primitive and its pluripotential capabilities may explain the diversity of the histologic picture. Although the epithelial components in these tumors are limited to those of the female genital system, this is certainly not true of the sarcomatous elements. Sup-

porting the argument of the origin from epithelial stroma is the observation that these tumors characteristically arise in epithelial areas, never deep within the organ.

These growths may be silent for some time with gradual enlargement until they present as a pedunculated growth extending through the os into the vagina. Concomitant with the growth of this neoplasm to involve the cervix and vagina is a progressive distention of the endometrial cavity and invasion of the myometrium.

Many of our patients have had pelvic control of tumor through combined irradiation and hysterectomy only to recur with disease in the upper abdomen. Distant

TABLE VI
TREATMENT PLANS IN GROUP III WITH RESULTS

Treatment	No. of Patients	NED (2 years)	Local Control
Hysterectomy Alone	5	0	2
Hysterectomy + Postoperative Irradiation	4	0	1
Preoperative Radium + Hysterectomy	1	0	1
Preoperative Irradiation + Radium + Hysterectomy	2	0	1
Irradiation Only	7	0	0
Incomplete Treatment	6	0	0
Total	25	0	5

TABLE VII
SURVIVAL AND LOCAL CONTROL
BY TREATMENT MODALITIES
(Groups I and II only)

	NED	Pelvic Control
Hysterectomy Alone	2/10	2/10
External Irradiation Alone	2/11	2/11
Preoperative Radium and Hysterectomy	8/13	11/13
Preoperative External Irradiation, Radium and Hysterectomy	4/10	9/10

metastases can also occur, although the usual mechanism of death is intraabdominal disease. Indeed pulmonary metastases were seen by chest roentgenograms and/or autopsy in only 14 of the 94 patients (15 per cent).

We have previously suggested the value of preoperative radium prior to hysterectomy in selected patients.² More recently, on theoretical grounds, it seemed logical to deliver a more homogeneous dose of external irradiation to the primary tumor and pelvic lymphatics followed by Heyman packing and/or intrauterine tandem insertion with vaginal radium. A hysterectomy and bilateral salpingo-oophorectomy was done 6 weeks later. Although the results when correlated with the extent of disease do not show any statistically significant advantage of this mode of therapy over preoperative radium plus hysterectomy, it is our distinct clinical impression that the latter group treated with external irradiation have generally been patients with more extensive disease and larger uteri than those treated prior to 1965 by preoperative radium and hysterectomy. In recent years these patients with large uteri who have been treated using external radiotherapy, radium and hysterectomy technique have had an improved rate of local control (65-75 per cent in Groups I and II). Further improvement in survival rates might result from combination of irradiation and surgery with chemotherapy.

Patients in whom microscopic disease is discovered incidentally at the time of hysterectomy who receive postoperative irradiation have an excellent outlook, but the good results are chiefly related to the limited extent of disease rather than to the efficacy of the treatment modality.

CONCLUSIONS

1. Mixed mesodermal sarcoma of the uterus remains a devastating disease with a guarded prognosis.
2. Both local control and survival are chiefly related to the extent of disease.
3. The combination of irradiation and hysterectomy appears to be superior to either irradiation or hysterectomy alone.
4. External irradiation, single Heyman packing followed by hysterectomy and bilateral salpingo-oophorectomy offer the best chance of local pelvic control of the tumor and long-term survival.

Felix N. Rutledge, M.D.
Department of Surgery
Section of Gynecology
The University of Texas
M. D. Anderson Hospital
and Tumor Institute at Houston
Houston, Texas 77025

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