

# 79-005



**GYNECOLOGIC ONCOLOGY GROUP • HEADQUARTERS**  
P.O. BOX 60 • PHILADELPHIA, PENNSYLVANIA 19105 • 215-829-6030

GYNECOLOGIC ONCOLOGY GROUP

NAV1.954707.002

PROTOCOL GOG #7743

(34)

A RANDOMIZED STUDY OF ADRIAMYCIN AS AN ADJUVANT  
AFTER SURGERY AND RADIATION THERAPY IN  
PATIENTS WITH HIGH RISK ENDOMETRIAL CARCINOMA  
STAGE I AND OCCULT STAGE II

STUDY CO-CHAIRMEN: SANFORD SALL, M.D.  
NEW YORK MEDICAL COLLEGE  
DEPARTMENT OF OBSTETRICS AND GYNECOLOGY  
1249 FIFTH AVENUE AND 106TH STREET  
NEW YORK, NEW YORK 10029

212-805-7033  
212-831-0444

DAVID LEVY, M.D.  
UNIVERSITY OF ALABAMA MEDICAL CENTER  
DEPARTMENT OF RADIATION ONCOLOGY  
UNIVERSITY STATION  
BIRMINGHAM, ALABAMA 35294

205-924-2760

C. PAUL MORROW, M.D.  
UNIVERSITY OF SO. CALIF. MED. CTR. AT L.A.  
WOMEN'S HOSPITAL - UNIT II - ROOM 908  
LOS ANGELES, CALIFORNIA 90033

213-226-3401

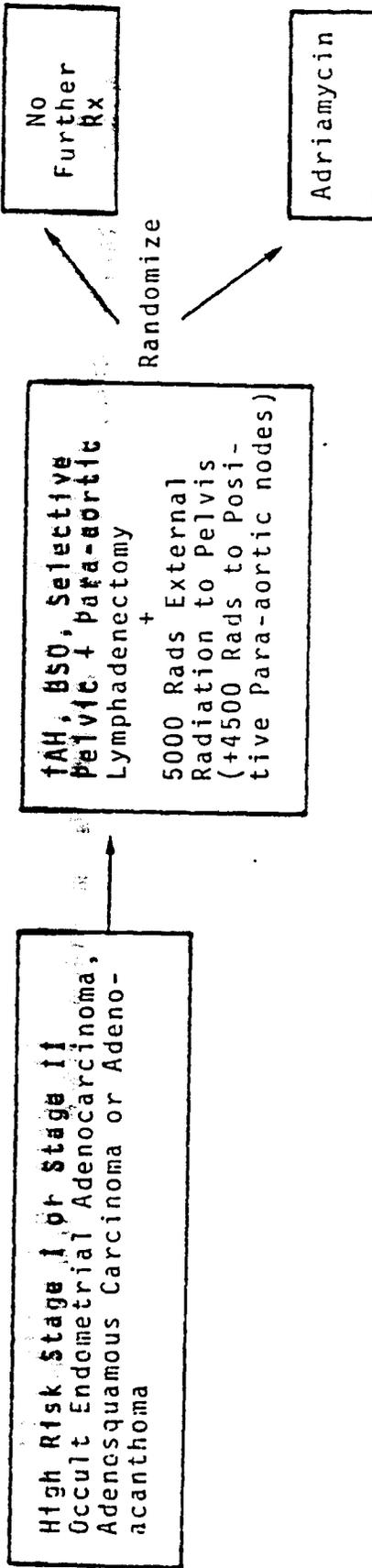
ACTIVATED - NOVEMBER 14, 1977

HEADQUARTERED AT DEPARTMENT OF OBSTETRICS AND GYNECOLOGY • JEFFERSON MEDICAL COLLEGE

ENCLOSURE (14)

A RANDOMIZED STUDY OF ADRIAMYCIN AS AN  
ADJUVANT AFTER SURGERY AND RADIATION THERAPY IN  
PATIENTS WITH HIGH RISK ENDOMETRIAL CARCINOMA  
STAGE I AND OCCULT STAGE II

SCHEMA



## OBJECTIVES

1. Study differences in morbidity and patient survival as functions of various tumor growth patterns as well as treatment in the high risk Stage I and, optionally, high risk Stage II occult\* endometrial carcinoma.

## BACKGROUND AND RATIONALE

Adenocarcinoma of the endometrium is the most common gynecologic cancer. In 75% of the cases, the tumor is clinically confined to the uterus at the time of diagnosis (FIGO Stage I) and the gross 5-year survival rate is in the range of 75 to 80%<sup>1-5</sup>. While many treatment methods are in vogue, most utilize a combination of surgery and irradiation. It is not known which plan will produce the best cure rate with the least morbidity. The role of radiotherapy in the prevention of vault recurrences has been well established but the indications for pelvic irradiation remain controversial<sup>6</sup>.

The treatment of most malignancies is based on an understanding of the natural history of the disease spread and identification of risk factors for regional and distant metastases. It is well known that prognosis in endometrial cancer decreases with histologic dedifferentiation, extra-uterine extension and myometrial penetration<sup>3,7,8,9</sup>. Lewis, Stallworthy and Cowdell<sup>10</sup> reported a significant risk of pelvic node involvement in Stage I endometrial adenocarcinoma related to histologic grade and muscle invasion. This study did not address the risk of aortic node spread, traditionally accepted as the primary metastatic route.

Because of the paucity of surgical-pathologic data regarding the distribution of extrauterine spread in clinical Stage I endometrial adenocarcinoma, a limited study was undertaken by the GOG to define the pattern of nodal involvement. The preliminary results of this investigation are presented in Tables I and II.

Myometrial Invasion					
Grade	Endometrium Only (%)	Inner 1/3	Middle 1/3	Outer 1/3	Total
1	1/56 (1.8)	0/26 (0.0)	0/4 (0.0)	1/3 (33.3)	2/09 (2.2)
2	1/21 (4.8)	2/41 (4.9)	1/6 (16.7)	4/11 (36.4)	0/79 (10.1)
3	0/3 (0.0)	5/16 (31.2)	1/5 (20)	7/14 (50.0)	13/38 (34.2)
Total	2/80 (2.5)	7/83 (8.4)	2/15 (13.3)	12/78 (42.9)	23/206 (11.2)

Table I  
Stage I Endometrial Adenocarcinoma and  
Pelvic Node Metastases - Data from GOG  
Pilot Study (P-1)

Myometrial Invasion					
Grade	Endometrium Only (%)	Inner 1/3	Middle 1/3	Outer 1/3	Total
1	1/56 (1.8)	0/26 (0.0)	0/4 (0.0)	0/3 (0.0)	1/89 (1.1)
2	0/21 (0.0)	0/41 (0.0)	1/6 (16.7)	3/11 (27.3)	4/79 (5.1)
3	0/3 (0.0)	6/16 (37.5)	0/5 (0.0)	5/14 (35.7)	11/38 (29.0)
Total	1/80 (1.2)	6/83 (7.2)	1/15 (6.7)	8/28 (28.6)	16/206 (7.8)

Table II  
Stage I Endometrial Adenocarcinoma and  
Aortic Node Metastases - Data from GOG  
Pilot Study (P-1)

\*Stage II occult - Microscopic evidence of cervical involvement but no gross clinical involvement as defined for this GOG Protocol. (See Appendix I for FIGO Staging)

pelvic node metastases occur with increasing frequency as the grade and degree of myometrial invasion advance but appear to be very uncommon in Grade I lesions with cervical penetration. Aortic node involvement follows a similar pattern but occurs less often. Furthermore, only two study patients with aortic node disease had negative pelvic nodes supporting the concept of primary pelvic lymphatic spread.

Since the data referred to above was evaluated, the number of patients in Pilot Study 2-1 has increased to 250. Of these, 11.5% had positive pelvic nodes and 8% had positive para-aortic nodes. The group of 250 patients have been analyzed for the incidence of complications. All received radiation therapy. Complications from the combination of surgery and radiation therapy totaled 12. These consisted of the following: one death due to pulmonary embolus, 7 lymphocysts associated with the failure to use drainage (following the introduction of adequate drainage, no further lymphocysts were encountered), 3 patients developed thrombophlebitis and one had an evisceration.

Schwartz<sup>11</sup>, Lewis<sup>10</sup>, and Dobbie<sup>12</sup> had reported a total of 25 cases of endometrial carcinoma who had positive pelvic nodes and were eligible for 5-year follow-up. Ten of these (40%) were alive at the 5-year interval. It seems reasonable to accept, then, that the risk of spread to the parametrium and the pelvic wall nodes in Grades 2 and 3 endometrial adenocarcinoma is significant and that extension of the treatment field to encompass these areas will be beneficial to some patients.

In this country, radiotherapy for endometrial carcinoma has been generally given preoperatively with the concept of preventing tumor spread at the time of surgery and to utilize the cervical and endometrial cavities as radium carriers. Graham,<sup>13</sup> Shaw<sup>5</sup> and Nilsen<sup>14</sup> have reported their experience with postoperative radiation and their results would certainly challenge the reputed superiority of preoperative irradiation. If the parametrium and pelvic wall are treated in all patients preoperatively, those cases who are at risk for having pelvic node metastases (myometrial invasion) may not be identifiable postoperatively. In Lewis' cooperative endometrial study, patients in the surgery-only group had a 25% incidence of deep (greater than 1/3) myometrial invasion while those in the preoperative irradiation group had an 8% incidence.<sup>15</sup> It is suggested, then, that surgery followed by irradiation tailored to the findings regarding myometrial penetration or extension to the isthmus and cervix may produce the optimum survival rate with the minimum morbidity. Since current treatment results are poorer in those endometrial cancer patients having less than well differentiated lesions, these patients can be studied as a high risk model to compare treatment plans.

The diminished cure rate of patients with cervical invasion has been variously ascribed to the probability that growth patterns of such tumors include geographic extension via the parametrial lymphatics to the pelvic nodes as well as the conventional corpus extension through vascular and lymphatic channels in the upper broad ligament.

Javert<sup>16</sup>, in 1952, demonstrated that in 46 patients with selective lymphadenectomies and 4 patients with complete lymphadenectomies, endometrial carcinoma spread to lymph nodes in 14 patients, or 28%.

Though no mention is made of cervical involvement, 13 of these 14 patients had deep myometrial penetration. Liu and Meigs<sup>17</sup>, in 1955, found that the

70% of patients with so called corpus et collum lesions had positive pelvic lymph nodes at the time of pelvic lymphadenectomy. Boronow<sup>1</sup>, however, reported positive pelvic lymph nodes in only 1 of 24 patients with corpus et collum lesions.

Thus, there is a need to study in prospective fashion the growth pattern of this disease and to formulate treatment patterns which will successfully encompass it. The treatment plans proposed in this protocol attempt to add adjunctive chemotherapy on a randomized basis to the two primary therapeutic modalities in usage. In addition, the selective node sampling (pelvic and para-aortic) should provide supplementary information of the risk of lymphatic dissemination in this disease. The randomized treatment of patients with positive nodes with chemotherapy (Adriamycin) will provide information as to its therapeutic effectiveness. Recent study by the GOG has indicated a 36% response rate in patients with recurrent endometrial cancer treated with Adriamycin.

## 1.0 PATIENT ELIGIBILITY AND EXCLUSIONS

### 3.1 Eligible

3.11 All patients with primary, previously untreated, histologically confirmed ~~invasive~~ carcinoma of the endometrium, Stage I, and Stage II occult, all grades, with one or more of the following high risk criteria are acceptable:

~~3.111 All lesions with equal to or greater than 1/2 myometrial involvement.~~

3.112 Positive pelvic and/or para-aortic nodes.

3.113 Microscopic evidence of cervical involvement but no gross clinical involvement of the cervix. (See footnote, page 1)

3.12 The following types of histologically confirmed uterine carcinoma are eligible: Adenocarcinoma, Adenoacanthoma, Adenosquamous carcinoma.

### 3.2 Ineligible

3.201 Patients with Stage I and II disease not evidencing the high risk criteria as defined above.

3.202 Borderline carcinoma termed "probably malignant".

3.203 Histologic types other than Adenocarcinoma, Adenoacanthoma, or Adenosquamous carcinoma.

3.204 Patients whose circumstances will not permit completion of the study or the required follow-up.

- 3.205 Patients with recurrent Stage I and II lesions of the uterine corpus.
- 3.206 Patients who for any reason were previously treated with pelvic irradiation, or chemotherapy.
- 3.207 Patients with inadequate hematologic indices: Granulocytes < 2000/ $\mu$ l and platelets < 100,000/ $\mu$ l.
- 3.208 Patients with septicemia or with severe infection.
- 3.209 Patients with past or concomitant cancer other than skin cancer (except melanoma).
- 3.210 Patients with abnormal EKG or prior heart attack, angina pectoris, heart failure or arrhythmia.
- 3.211 Gross evidence of cervical involvement on pelvic examination prior to surgery. (See 3.114)

### 3.3 Exclusion Following Surgical Staging

All patients will have undergone exploratory laparotomy and patients with disease beyond the uterus, cervix and adnexa, other than those with pelvic and/or para-aortic nodal involvement, will be excluded. ~~Thus, patients who are noted to have visceral or peritoneal metastasis other than the above are not eligible for randomization.~~

## 4.0 STUDY MODALITIES

4.1 Surgical Procedure - All patients will undergo a total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective pelvic and para-aortic lymphadenectomy. Peritoneal cytology will be obtained on entering the peritoneal cavity.

### 4.11 Method of Lymphadenectomy

4.111 Pelvic Retroperitoneal Dissection - The pelvic retroperitoneal spaces are opened in the routine fashion. The common, external, and internal iliac vessels are outlined. The paravesical and pararectal spaces are opened. Any enlarged lymph nodes are identified and removed for histologic study. If no enlarged lymph nodes are identified, the lymphoid tissue overlying the lower common iliac and external iliac vessels are removed down to the inguinal ligament. The lymphoid tissue is removed from the obturator fossa anterior to the obturator nerve. A "complete" lymphadenectomy as done in early carcinoma of the cervix is not performed. It is suggested that Hemovac drains or similar retroperitoneal drainage be used following the selective lymphadenectomy.

4.112 Para-aortic Dissection - The peritoneum over the bifurcation and lower aorta is opened. Any enlarged para-aortic lymph nodes are removed if technically feasible. If no enlarged nodes are noted, the para-aortic fatpad over the aorta and vena cava is removed in toto beginning at the bifurcation of the aorta and extending toward the renal vessels. Meticulous clearance between the cava and aorta and skeletonization laterally of lumbar vessels is not required.

#### 4.2 Pathologic Evaluation

4.21 Peritoneal washings will be evaluated for malignant cells.

4.22 The uterus will be evaluated in regards to:

1. Location of tumor in uterus or cervix.
2. Depth of myometrial invasion.
3. Differentiation of tumor.
4. Size of uterus.
5. Histologic type of tumor.

4.23 The adnexae will be evaluated as to whether metastasis is present.

4.24 The lymph nodes (total number indicated) will be evaluated as to metastasis and:

1. Location of involved lymph nodes.
2. Number of involved lymph nodes.

#### 4.3 Radiotherapy

##### 4.31 Radiation Therapy for Patient With Negative Para-aortic Nodes

##### 4.311 External Radiation

Patients with negative para-aortic nodes will receive 5000 rads external beam therapy delivered homogeneously to the pelvis in 5 to 6 weeks. See Section 4.33 for dose distribution.

##### 4.312 Dose Distribution

The dose distribution of the selected techniques may deliver 160/180 rads per day to the point 7 cm lateral to the midline of the pelvis in the widest transverse diameter of the pelvis (Point "P") and at the level of the pelvic brim. In order to achieve this dose of 160/180 rads at the lateral pelvis, the dose in the midline may be as high as 190/210 rads per day. Such a dose distribution will be considered as giving 180/200 rads per day.

4.313 Treatment Volume

The volume irradiated will include the totality of the obvious disease, the whole uterus, paracervical, parametrial, and uterosacral regions, as well as the areas of the external iliac, hypogastric and obturator lymph nodes. As a minimum, this volume would have the following boundaries:

**Superior:** The upper margin of L5.

**Inferior:** The midportion of the obturator foramen, or the lowest extension of the disease with adequate margin.

**Lateral:** 1 cm beyond the lateral margins of the bony pelvic wall at the widest plane of the pelvis (this must be at least 7 cm from the midline in this plane).

4.32 Radiation Therapy for Patients With Positive Para-aortic Nodes

4.321 External Radiation

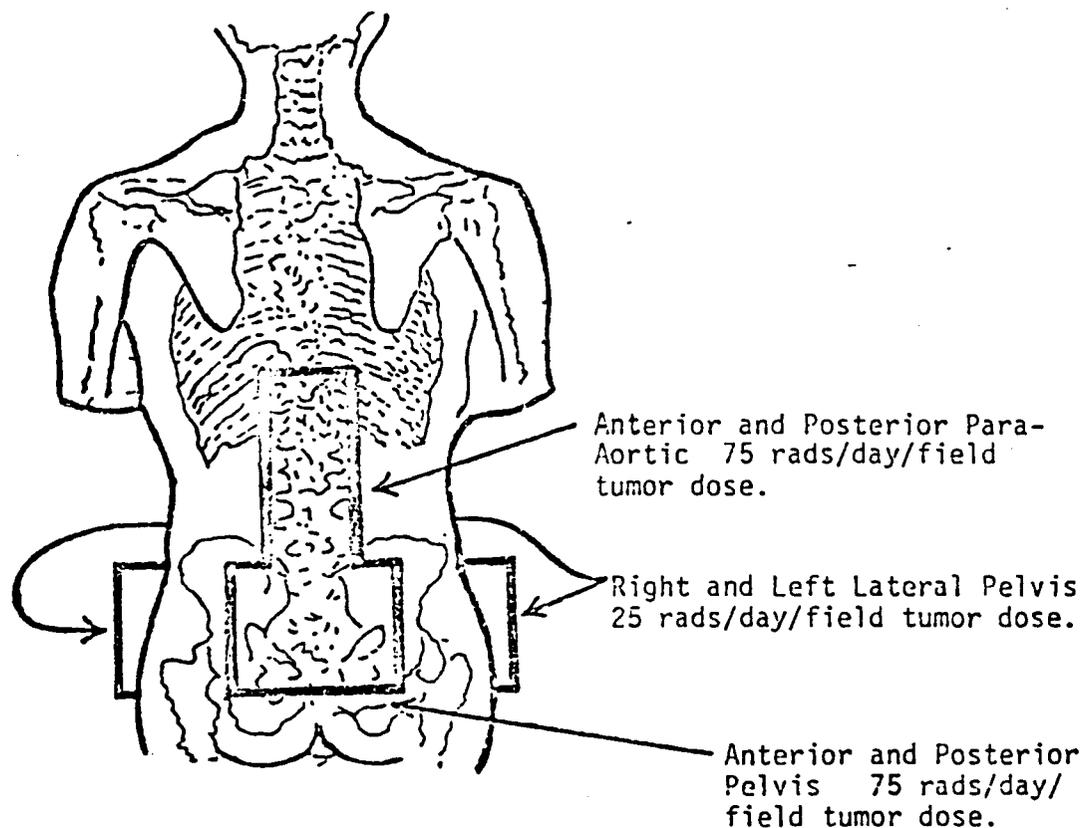
**Para-aortic Dose** -- 4500 rads

**External Pelvic Dose** -- 5000 rads

**Patients with histologically positive para-aortic nodes require the Pan-Handle technique. (See Section 4.37)**

4.32 Radiation Therapy for Patients With Positive Para-aortic Nodes - continued

4.322 Pan-Handle Technique (For Positive Para-aortic Lymph node Biopsy)



When positive histologic evidence is obtained of the uppermost common iliac (at junction of common iliac artery with aorta) or lumbar para-aortic lymph node metastases, the lymphatic drainage areas of the pelvis as well as the common iliac and lumbar para-aortic lymph nodes to the level of the diaphragm will be irradiated.

This will be accomplished using a single large irregularly-shaped portal. This arrangement is desirable to prevent hot and cold spots at the junction of the two fields. Therefore, the anterior and posterior pelvic fields are combined with para-aortic fields to form large irregularly-shaped anterior and posterior portals. These are combined with smaller regularly-shaped lateral portals. The shape of the anterior and posterior portals has been likened to that of a "pan-handle." Hence, the technique is referred to as the "Pan-Handle" Technique.

The "handle" or para-aortic portion of the anterior and posterior portals is wide enough to adequately encompass the para-aortic lymph nodes (usually 8 cm wide) and extends from the xyphoid (superior border of T<sub>12</sub>) process to the brim of the pelvis.

The "pan" or pelvic portion extends from this point (L5-S1) to the desired inferior border, usually the mid-portion of the obturator fossa and is sufficiently wide to encompass the bony pelvis plus a 1.0 cm margin (usually 15 cm wide). The total length of the portal from the xyphoid process to the obturator fossa is normally greater than 30 cm.

Because of equipment limitations, it is necessary to extend the treatment distance range from 150 to 170 cm SSD. A daily fraction of 150 rads is to be administered to the mid-plane of the "pan-handle" fields five days each week. Both anterior and posterior "pan-handle" fields are to be treated daily (75 rads from each field). Right and left lateral portals are to be added daily only to the pelvic portion of the anterior and posterior portals. In this manner, an additional 50 rads is added to the mid-plane of the pelvis daily (25 rads boost from each lateral portal). The lateral portals will normally be about 10 cm wide and 15 to 20 cm high to encompass the desired pelvic structures. The lateral fields can be treated at 100 cm SSD.

The patient will receive 5000 rads to a homogeneous volume within the pelvis and 4500 rads to the mid-point of the parallel opposed para-aortic portions of the "pan-handle" in 5 to 8 weeks.

4.33 Radiation Sources

Radiation sources employed in these clinical trials will be x-ray generators which produce x-ray beams with a peak energy of

1 MEV or more or Cobalt 60 irradiators. Radiation output of the unit must be adequate to permit employment of a TSD or SSD of 80 cm or more. For patients with AP/PA pelvic diameters in excess of 25 cm and/or lateral pelvic diameters in excess of 30 cm, equipment with capability exceeding 4 MEV must be used.

- 4.34 Beam verification films (port) will be obtained and submitted to the GOG Headquarters with the patient's records. (See Section 10,191)
- 4.35 The Radiologic Physics Center, under the sponsorship of the American Association of Physicists in Medicine, will supervise the dosimetry control for this clinical trial. To participate in the trial, the institutions must demonstrate the ability to achieve an accuracy of  $\pm 3\%$  in measuring the output of their sources and  $\pm 5\%$  in delivering the prescribed dose.

#### 4.4 Chemotherapy Treatment

##### 4.41 ADRIAMYCIN (Doxorubicin Hydrochloride) - NSC 123127

##### 4.411 Drug Formulation, Storage and Procurement

Adriamycin is supplied in vials of 10 mg or 50 mg of freeze-dried doxorubicin hydrochloride and lactose USP as a lyophilized powder which is stored at room temperature away from light. Reconstitution is by solution in normal saline to a concentration of 2 mg/ml. The solution may be stored for 24 hours at room temperature or for 48 hours at 4 to 10°C protected from sunlight. Refrigeration is recommended.

- 4.412 Administration: Injection may be performed by bolus double-needle technique or via a freely running intravenous infusion of 5% dextrose in distilled water or normal saline. Extravasation should not be permitted.
- 4.413 Supplier: Adria Labs., Wilmington, Delaware.
- 4.414 Toxicity: Major adverse effects include reversible hematologic depression (primarily leukopenia, although anemia and thrombocytopenia occur), vomiting, alopecia, diarrhea and stomatitis.

Cardiac toxicity is dose related and can be avoided by limiting the total dose to 400 mg/M<sup>2</sup>.

Local necrosis and thrombophlebitis can be minimized by careful administration.

Hepatic dysfunction requires dose reduction or discontinuation.