



# GYNECOLOGIC ONCOLOGY GROUP • HEADQUARTERS

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PROTOCOL GOG #85

SWOG #B695

A RANDOMIZED COMPARISON OF HYDROXYUREA  
VERSUS 5-FU INFUSION AND BOLUS CISPLATIN AS AN ADJUNCT TO  
RADIATION THERAPY IN PATIENTS WITH STAGES II-B, III AND IV-A  
CARCINOMA OF THE CERVIX AND NEGATIVE PARA-AORTIC NODES

(PHASE III)

(GOG CATEGORY I - SIX CREDITS/ENTRY)

PROTOCOL FORMAT: GOG

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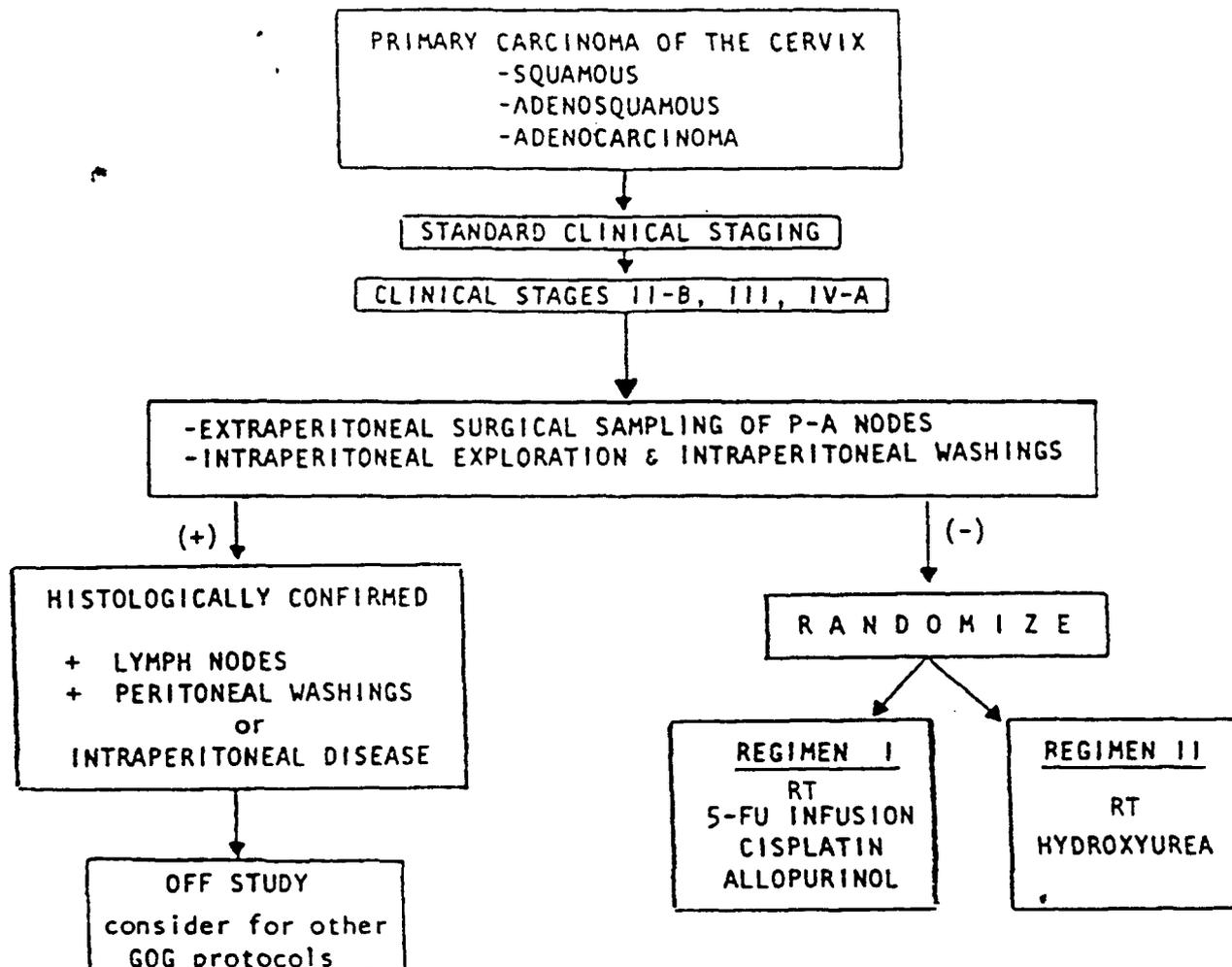
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A PROGRAM OF THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

ENCLOSURE (16)

## S C H E M A

A RANDOMIZED COMPARISON OF HYDROXYUREA VS 5-FU INFUSION  
AND BOLUS CISPLATIN AS AN ADJUNCT TO RADIATION THERAPY IN PATIENTS WITH  
STAGES II-B, III and IV-A CARCINOMA OF THE CERVIX  
AND NEGATIVE PARA-AORTIC NODES, PHASE III

REGIMEN I

DAY	1	2	3	4	5	8	9	10	11	12	15	16	17	18	19	22	23	24	25	26	29	30	31	32	33		
ERT* 170 cGy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
5-FU 1000 mg/m <sup>2</sup>		x	x	x	x																		x	x	x	x	
ALLOPURINOL 300 mg		x	x	x	x																			x	x	x	x
CISPLATIN 50 mg/m <sup>2</sup>	x																									x	

REGIMEN II

ERT* 170 cGy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
HYDROXYUREA - 80 mg/kg		x		x		x		x		x		x		x		x		x		x		x		x		x

\* In addition to intracavitary therapy

## 1.0 OBJECTIVES

- 1.1 To determine whether hydroxyurea or the combination of 5-Fluorouracil and allopurinol with cisplatin is superior as a potentiator of radiation therapy in advanced cervical carcinoma.
- 1.2 To determine the relative toxicities of hydroxyurea versus the combination of 5-fluorouracil and cisplatin when given concurrently with radiation therapy.

## 2.0 BACKGROUND AND RATIONALE

Primary pelvic radiotherapy fails to control 35-90% of patients with locally advanced cervical carcinoma. Approximately two-thirds of these failures occur in the pelvis, presumably within the field of radiation.(1) It is estimated that 2,700 lives could be saved if 100% local control could be achieved.(2)

A variety of agents have been used in attempts to increase the effectiveness of radiation therapy and thus local control.(3) Hydroxyurea is one such agent so used. It inhibits the repair of radiation induced cellular damage(4) and also may induce cell synchrony.(3) GOG Protocol #4 compares standard radiation therapy to radiation therapy plus hydroxyurea.(5) This study of 104 patients with Stage III-B and IV-A squamous cell carcinoma of the cervix showed a significantly increased complete response rate, progression-free interval and survival for those patients receiving radiation and hydroxyurea. Toxicity was acceptable. GOG Protocol #56 compares the hypoxic cell sensitizer misonidazole and radiation therapy to hydroxyurea and radiation therapy. Preliminary analysis indicates that patients treated with hydroxyurea as an adjunct to radiation therapy have a longer progression free interval and significantly fewer recurrences.

Another agent that appears to increase the effectiveness of radiation therapy is 5-fluorouracil (5-FU). 5-FU has some reported activity against cervical carcinoma with an overall response rate of 20% as a single agent.(6) 5-FU also acts as a radiation sensitizer.(3,7) It selectively inhibits cells in the S-phase of the cell cycle. It also is effective in inhibiting the repair of radiation induced cell damage.(3,7,8) Because of this, 5-FU is used concurrently with or immediately following radiation therapy.(7) 5-FU has been used as a radiation sensitizer, usually with other agents, against a variety of cancers. These include anal cancer,(9) head and neck cancer(10) and esophageal cancer.(11) 5-FU also has been used as a radiation sensitizer for cervical carcinoma.(12,13) Kalra and colleagues reported a 60% complete response rate for 10 patients receiving 5-FU and mitomycin-C concurrently with a split course of radiation therapy.(12) Thomas and colleagues reported a 74% complete response rate for 27 patients receiving split course radiation therapy and two 4-day infusions of 5-FU at a dose of 1000 mg/m<sup>2</sup> plus mitomycin-C.(13) Two patients developed

leukopenia, nine thrombocytopenia, two sigmoid strictures and there was one death due to sigmoid perforation. Most studies report using 5-FU as a 96-hour infusion at a dose of 1000 mg/m<sup>2</sup>. The advantage of this dose and schedule is that relatively standard doses of radiation therapy can be given (170 cGy/day). 5-FU infusion appears to be well tolerated in most studies. Giving the 5-FU by infusion as opposed to bolus injection seems to alter the pattern of toxicity such that stomatitis and GI toxicity are relatively more common than hematopoietic toxicity.(14,15) There is relatively little myelosuppression. The addition of allopurinol decreases toxicity, particularly stomatitis, but not at the expense of anti-tumor effect.(15,16) Allopurinol will be used in this study.

Cisplatin is an agent with known activity against cervical carcinoma. Previous GOG studies have documented response rates of 23 to 27% when used as a single agent.(17) It also appears to act as a radiation sensitizer by inhibiting the repair of potentially lethal cellular damage.(3,18) It also may act as a hypoxic cell sensitizer.(3,18) Cisplatin has been used concurrently with radiation therapy to treat head and neck(19) and bladder cancer.(20) Its use as a radiation sensitizer for cervical cancer remains to be evaluated.

In the L-1210 murine leukemia model, the combination of 5-FU, cisplatin and radiation therapy was more effective than either modality alone. The drug combination was also more effective as an adjunct to radiation than either drug when used alone as an adjunct. This study also showed that cisplatin is more effective when given prior to radiation therapy.(8)

The combination of cisplatin and 5-FU infusion has shown activity against cervical cancer(21). This regimen (dose and schedule) has been given in combination with radiation therapy with acceptable toxicity(22-24).

Preliminary data from Yordan et al support the use of 5-FU and cisplatin with radiation therapy in the treatment of cervical carcinoma. They have used these combined modalities to treat 19 patients with pelvic malignancies. Twelve of these patients had cervical carcinoma, 8 primary and 4 recurrent lesions. Seven of the eight primary patients had complete responses and two of the four recurrent lesions had complete responses. The overall response rate for patients with cervical carcinoma was 75%. The authors report acceptable morbidity.(26)

The goal of this study is to determine which adjunctive drugs (5-FU and cisplatin versus hydroxyurea) is the better potentiator of radiation therapy for cervical carcinoma.

Multiple studies, including the experience within the GOG, have confirmed that the presence of metastases to para-aortic lymph nodes is a prognostic factor of greater significance than FIGO Stage.(25) In addition, the pattern of failure in this group is vastly different, with one-half of the patients having recurrence outside the treated field. In this particular study all progression, both regional and distant, will be used as the basis for evaluation. Because a major objective of this study is to evaluate local control and survival this study will be open only to these patients with documented negative para-aortic nodes.

INTERGROUP STUDY PROPOSAL

Because of the common interest in the treatment of carcinoma of the cervix, the Southwest Oncology Group has joined with the GOG as a collaborating group.

It has been decided that the actual clinical study will be identical. Each member institution will handle entry and data submission through its respective group. Where there is overlap, the institutional representatives must themselves decide which group they will use for protocol entry and other steps.

For each group the staging procedures and requirements will be identical to that which is outlined in Appendix III & IV.

Data analysis and quality control will be handled by the GOG. In this regard, SWOG will be considered an "institution" of GOG for purposes of data flow. SWOG members will submit all data and material except those materials for rapid turnaround to the appropriate SWOG center. SWOG will then forward the data to the GOG Operations Office. Data for rapid turnaround will be submitted directly to the GOG Operations Office.

The SWOG intergroup steering committee will consist of Drs. Thipgen and Alberts, 1 radiation oncologist, 1 pathologist, 1 gyn oncologist and 1 statistician from each group.

### 3.0 PATIENT ELIGIBILITY.

#### 3.1 Eligible

- 3.11 Patients with primary, previously untreated, histologically confirmed invasive squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the uterine cervix, Stages II-B, III-A, III-B, and IV-A, with negative para-aortic nodes.
- 3.12 Patients who have had para-aortic lymphadenectomy and intraperitoneal exploration with cytologic washings, as outlined in Section 4.21 and Appendix IV.
- 3.13 Patients with adequate bone marrow function: WBC equal to or greater than 3,000/mcl; platelets equal to or greater than 100,000/mcl.
- 3.14 Patients with adequate renal function: creatinine equal to or less than 2.0 mg%.
- 3.15 Patients with adequate hepatic function: alkaline phosphatase, bilirubin and SGOT equal to or less than 2 x normal.
- 3.16 Patients who have met the pre-entry requirements specified in Section 7.0.
- 3.17 Patients who have signed an approved informed consent.

#### 3.2 Ineligible

- 3.21 Patients with recurrent, invasive carcinoma of the uterine cervix regardless of previous treatment, or cancers other than squamous cell, adenosquamous, or adenocarcinoma.
- 3.22 Patients who cannot be or have not been adequately clinically staged.
- 3.23 Patients who for any reason have previously been treated with pelvic irradiation or have received cytotoxic chemotherapy.
- 3.24 Patients with septicemia or severe infection.
- 3.25 Patients with circumstances that will not permit completion of the study or required follow-up.
- 3.26 Patients with GOG Performance Grade of 4.
- 3.27 Patients with past or concomitant malignancy other than skin (excluding melanoma).
- 3.28 Patients with histologically confirmed cancer involving the para-aortic lymph nodes, intraperitoneal disease, or positive intraperitoneal cytology.
- 3.29 Patients who have not had surgical exploration as outlined in Section 4.2.

#### 4.0 STUDY MODALITIES

All eligible patients with invasive squamous cell, adenocarcinoma, or adenosquamous carcinoma of the cervix, Stages II-B, III-A, III-B, and IV-A will undergo clinical staging as permitted by the FIGO rules (Appendix III). All patients will undergo surgical staging to include extraperitoneal sampling of the para-aortic lymph nodes, peritoneal cytology and intraperitoneal exploration.

All patients with cancer confined to the pelvis will receive pelvic irradiation and will be randomly assigned to receive either concomitant 5-FU and cisplatin or hydroxyurea. Patients with disease outside the pelvis are not eligible for this protocol. They may be eligible for other GOG protocols.

#### 4.1 Preoperative Clinical Staging

##### 4.11 Standard Clinical Staging

Patients will have a chest x-ray and an intravenous pyelogram prior to therapy. Pelvic examination will be performed under anesthesia as permitted under FIGO rules, to determine the clinical stage of their cancer (Appendix III). An abdominal pelvic CAT scan with intravenous contrast may be used in place of the intravenous pyelogram.

#### 4.2 Surgical Procedures

##### 4.21 Para-Aortic Lymphadenectomy

Must be accomplished by a retroperitoneal approach. See Appendix IV for content of procedure. (Pelvic lymphadenectomy is not a requirement of this protocol).

##### Intraperitoneal Exploration

Will be carried out after biopsies of para-aortic lymph nodes. Cytologic washings of the peritoneal cavity must be obtained. Inspection of all intraperitoneal organs for evidence of metastases must be done. Any suspicious areas should be biopsied if possible.

#### 4.3 Radiotherapy Procedures

Radiation therapy must be started within 6 weeks post surgery. The radiation therapy is the same for both regimens.

#### 4.31 Radiotherapy for Stage II-B

##### 4.311 External Irradiation

Patients with Stage II-B lesions will receive 4080 cGy external beam therapy delivered homogeneously to the pelvis in 24 fractions. This may not complete external beam radiation. See Section 4.322, parametrial boost.

##### 4.312 Intracavitary Therapy

Following the completion of external beam therapy, the patient will receive 4000 cGy to Point "A" by intracavitary implant with radium or its equivalent. The patient may receive this in one or two applications, at the discretion of the radiation therapist.

The first insertion shall not be sooner than one week following external beam therapy and no later than three weeks. If two implants are contemplated, the second implant should commence not later than two weeks after completion of the first.

Patients will receive a minimum dosage of 5500 cGy total at point B by both modalities. A parametrial boost may be utilized to accomplish this.

The total elapsed time for completion of external and intracavitary therapy shall not exceed ten weeks.

#### 4.32 Radiotherapy for Stages III-A, III-B, IV-A

##### 4.321 External Irradiation

Patients staged as having Stage III-A, III-B and IV-A disease will receive 5100 cGy delivered homogeneously to the pelvis in 30 fractions. The whole pelvis should receive no more than 5100 cGy.

If no intracavitary brachytherapy is planned, the patient must receive 6120 cGy of external teletherapy delivered to the described tumor.

##### 4.322 Intracavitary Therapy

Following the completion of external beam therapy, the patient should receive intracavitary therapy.

If the patient received, or is to receive, 5100 cGy external pelvic teletherapy and an intracavitary implant is contemplated, the dosage will be 3000 cGy to Point "A" from the intracavitary source.

The first insertion shall be instituted not later than two weeks after completion of the external beam therapy.

If two implants are contemplated, the second implant should commence not later than two weeks after completion of the first.

Point "B" shall receive a minimum dosage of 6000 cGy total by both modalities. A parametrial boost may be utilized to accomplish this.

The total elapsed time for completion of external and intracavitary therapy shall not exceed ten weeks.

#### 4.33 Dose Distribution

The patient should be treated with AP and PA parallel ports with each port being treated each day. A four field box technique with parallel opposed AP/PA two opposing lateral fields may be used. Dose distribution across treatment volume should not vary more than 5% from recommended dose.

#### 4.34 Radiation Sources

Radiation sources employed in these clinical trials will be x-ray generators which produce x-ray beams with a photon energy of 4 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.

Simulator localization films and verification films taken on the treatment machine will be necessary in all cases. Standard 3 1/2 x 4" polaroid pictures of all treatment portals with the patient in the treatment position are recommended.

Intracavitary radiation may be delivered by radium, cesium, or cobalt sources in standard or commonly used applicators provided that acceptable dosimetry can be determined. Interstitial therapy is not acceptable for this protocol.

#### 4.35 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 (must be at least 7 cm from the midline in this plane).

- 4.36 Beam verification films will be obtained and submitted with the patient's records.

Orthogonal dosimetry films will be taken following the intracavitary insertion, and the films and calculations submitted to the GOG Operations Office with the patient's records.

- 4.37 Rapid Turnaround

The American College of Radiology will review pretreatment films, calculations, and plan of treatment within one week. The following information will be needed for this review:

- Stage of Disease
- Plan of treatment (dose prescription)
- Initial calculations
- One copy each of simulator and verification films

- 4.38 Radiation Therapy Quality Control and Documentation

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 institution 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 Required Pathology Material and Data

Representative stained slides showing documentation of invasive cancer, as well as a slide for each additional positive site and a dictated pathology report from the participating institution. The pathologists must specify type and pattern of invasion, location of lesion, greatest depth of invasion (if available), and histologic grade and type.

The surgeon must dictate, preferably in the introductory paragraph of the operative note, the measurements of the size of the lesion in two dimensions, location of the lesion, extension of the lesion into the parametrial areas, bladder, or rectum, clinical status of the pelvic lymph nodes and groin lymph nodes, clinical status of supraclavicular nodes.

Within the body of the operative note the limits of dissection should be clearly stated. All nodes removed should be carefully described as to their location.

4.5 Chemotherapy4.51 Fluorouracil (5-Fluorouracil, 5-FU) NSC #19893

See Appendix VII.

4.52 Allopurinol

See Appendix VIII.

4.53 Cisplatin (cis-diamminedichloroplatinum, Platinol®)  
NSC #119875

See Appendix IX.

4.54 Hydroxyurea (Hydrea®) NSC #32065

See Appendix X.

## 5.0 PATIENT ENTRY/RANDOMIZATION AND TREATMENT PLAN

Patients who have fulfilled the eligibility requirements in Section 3.0 will be stratified on the variable

- (1) Stage II-B
- (2) Stage III
- (3) Stage IV-A

and will be randomized to one of the treatment regimens outlined in Section 5.2.

### GOG Institutions:

An original, signed Form HHS-596, indicating prior approval by the institution's Human Rights or Clinical Trials Committee for participation in this study must be forwarded to the GOG Operations Office before patient entries onto the study will be accepted. In addition, a copy of the informed consent being used (if it differs from the suggested form appended to the protocol) or a letter from the Principal Investigator stating that the suggested form is being used, must accompany the HHS-596.

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